211. *Preliminary Syntheses in the Morphine Series. Part III.* Michael Condensations with 2-Arylcyclohex-2-enones and Cyclisation of the Products to Octahydrophenanthrene Derivatives.*

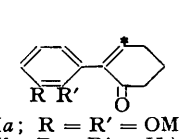
By David Ginsburg and Raphael Pappo.

Products formed by Michael condensation of 2-aryl*cyclo*hex-2-enones with compounds containing reactive methylene groups are described. The transformation of these products into various octahydrophenanthrene derivatives has been studied.

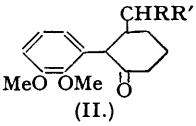
In Part II of this series (*J.*, 1951, 516) the preparation of 2-aryl*cyclo*hex-2-enones was described. For their further conversion into pharmacologically active compounds related to morphine, it was necessary to substitute 2-(2 : 3-dimethoxyphenyl)*cyclo*hex-2-enone (I*a*) at position 3 (marked *) with a radical which would form the 9 : 10-bridge in the desired phenanthrene system and still retain reactive groups on which further transformations could be based.

* A preliminary report covering part of the material contained in this communication is being published : Pappo and Ginsburg, *Bull. Res. Council Israel*, 1951, **1**, in the press.

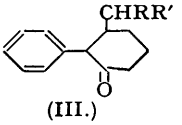
A satisfactory solution of this problem lies in the observation that 2-(2 : 3-dimethoxyphenyl)-*cyclo*hex-2-enone undergoes Michael condensation with compounds containing reactive methylene groups, giving high yields of adducts of type (II), *e.g.*, (II; R = CO_2Et or CN, R′ = CO_2Et) with ethyl malonate and ethyl cyanoacetate, respectively. A compound such as (II; R = NO_2, R′ = CO_2Me) is obviously a precursor of an octahydrophenanthrene carrying an amino-group in the 10- and a keto-group in the 4-position (IV). 2-Phenyl*cyclo*hex-2-enone (I*b*) was used as a model substance in the study of this condensation.



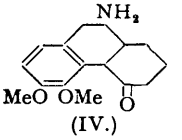
(I*a*; R = R′ = OMe.)
(I*b*; R = R′ = H.)



(II.)



(III.)



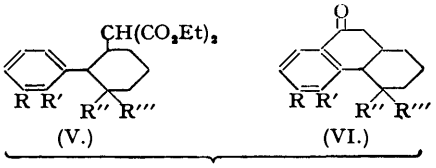
(IV.)

Only compounds containing a reactive methylene group condensed with the 2-aryl*cyclo*hex-2-enones. Attempted condensation with compounds containing a methine group, such as the ethyl diethoxymethylmalonate or phthalimidomalonate, failed, although compounds of this type are known to take part in Michael condensations in other cases (cf. the use of ethyl acetamido- and formamido-malonate in syntheses of amino-acids; Albertson and Archer, *J. Amer. Chem. Soc.*, 1945, **67**, 2043; Snyder, Shekleton, and Lewis, *ibid.*; p. 310; Galat, *ibid.*, 1947, **69**, 965). These failures may perhaps be attributed to the presence of the bulky 2-aryl groups. Such " steric hindrance " of the Michael condensation is not without analogy. Thus, Turner and Voitle (*ibid.*, 1950, **72**, 4166, where also previous literature is cited) have shown that 1-acetyl-2-methyl*cyclo*hexene does not undergo Michael condensation with *cyclo*hexanone, and Woods (*ibid.*, 1947, **69**, 2551; cf. Koelsch, *ibid.*, 1945, **67**, 569) has recorded an analogous observation for 5 : 5-dimethyl-3-phenyl*cyclo*hex-2-enone.

The progress of the Michael condensation can be followed qualitatively by treating one drop of the reaction liquid with 2 : 4-dinitrophenylhydrazine solution : the 2 : 4-dinitrophenylhydrazone of the αβ-unsaturated starting material is red or orange-red, that of the end-product yellow to orange.

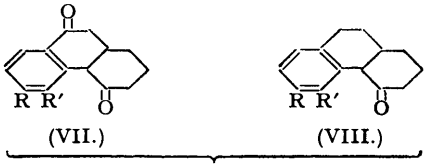
The Michael condensation products obtained with ethyl malonate have been systematically investigated with a view to determining conditions for the cyclisation to octahydrophenanthrene derivatives.

(i) Malonic esters (II and III; R = R′ = CO_2Et), or their ketals, were reduced by the Clemmensen method to malonic esters of type (V*a* and *b*), and the latter were hydrolysed and cyclised by means of zinc chloride in acetic acid–acetic anhydride (but not by hydrogen fluoride) to yield, through simultaneous half-decarboxylation, the corresponding 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-9-ketophenanthrenes (VI*a* and *b*). Equally, Clemmensen reduction of 3-keto-2-phenyl*cyclo*hexylacetic acid which was available from (III; R = R′ = CO_2Et) led to the corresponding known *trans*-2-phenyl*cyclo*hexylacetic acid which could easily be cyclised to Cook's *trans*-octahydroketophenanthrene (VI*b*), m. p. 95° (Cook, Hewett, and Robinson, *J.*, 1939, 168; cf. Linstead *et al.*, *J. Amer. Chem. Soc.*, 1942, **64**, 2014).



(V.) (VI.)

a; R = R′ = OMe; R″ = R‴ = H.
b; R = R′ = R″ = R‴ = H.
c; R = R′ = OMe; R″ = OH; R‴ = H.



(VII.) (VIII.)

a; R = R′ = OMe.
b; R = R′ = H.

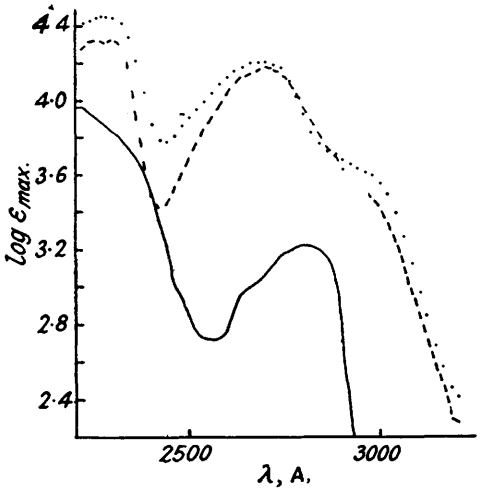
(ii) Hydrogenation of (II; R = R′ = CO_2Et) in presence of Adams's catalyst gave the corresponding carbinol, which, on hydrolysis and cyclisation as in (i) was converted into the 4-acetoxy-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-9-keto-5 : 6-dimethoxyphenanthrene (acetate of VI*c*).

(iii) When the carbonyl group in (II, III; R = R′ = CO_2Et) was blocked by formation of the ketal with ethylene glycol (Salmi, *Ber.*, 1938, **71**, 1803; cf. Sulzbacher, Bergmann, and Pariser, *J. Amer. Chem. Soc.*, 1948, **70**, 2827) or with ethyl orthoformate, the ester groups could be

subjected to alkaline hydrolysis and the free acid cyclised. By hydrolysis of the ketal groups, compounds (VII*a* and *b*) were then obtained. This detour proved necessary in this case when it became apparent that compounds of types (II) and (III) are unstable to alkali, the Michael condensation being reversed.

The two carbonyl groups in a compound such as (VII*a* or *b*) differ greatly in reactivity. Thus, the 4-keto-group could be selectively converted into a ketal and catalytic reduction attacked preferentially the 9-carbonyl group, reducing it to a methylene group (as in VIII*a* and *b*). Significant differences in the rate of formation of ketals between arylaliphatic and alicyclic ketones have been observed before (acetophenone is much less reactive than 2-methyl*cyclo*hexanone; Sulzbacher, Bergmann, and Pariser, *loc. cit.*), and the complete de-oxygenation of carbonyl groups conjugated with aromatic nuclei by catalytically activated hydrogen is not uncommon (cf. Horning and Reisner, *J. Amer. Chem. Soc.*, 1949, **71**, 1036; Linstead, Whetstone and Levine, *ibid.*, 1942, **64**, 2014).

The ultra-violet spectra illustrate this difference between the two carbonyl groups rather strikingly (see figure). The 9-ketone (VI*a*) and the 4-(ethylene glycol) ketal of the corresponding 4 : 9-diketone (VII*a*) have identical spectra which resemble that of 3 : 4-dimethoxybenzoic acid (Hirshberg, Lavie, and E. Bergmann, *J.*, 1951, in the press). The wave-length of the first band reflects the interference with resonance, exerted by the " *ortho*-substituent " to the 9-carbonyl



Ultra-violet absorption, in isooctane, *of:*

– – – – – –, 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-9-*keto*-5 : 6-*dimethoxyphenanthrene;*
. . . . . ., 4-(*ethylene glycol*) *ketal of* 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4 : 9-*diketo*-5 : 6-*dimethoxyphenanthrene;*
————, 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4-*keto*-5 : 6-*dimethoxyphenanthrene.*

group (cf., for the spectrum of 3 : 4-dimethoxyacetophenone, Tasaki, *Chem. Zentr.*, 1927, II, 1949). 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-Octahydro-4-keto-5 : 6-dimethoxyphenanthrene (VIII*a*) has only one band of lower intensity; its extinction coefficient, however, is much higher than that of a normal aliphatic ketone, probably owing to superposition, on the carbonyl band, of the absorption of the veratrole system which absorbs approximately at the same wave-length as non-aromatic, non-conjugated ketones (for the spectrum of veratrole, cf. Savard, *Bull. Soc. chim.*, 1928, **43**, 1073; Kiss *et al.*, *ibid.*, 1949, 275; Wolf and Herold, *Z. physikal. Chem.*, 1931, *B*, **13**, 201. For the spectrum of 2-phenyl*cyclo*hexanone, cf. Bachmann and Wick, *J. Amer. Chem. Soc.*, 1950, **72**, 3388, and Alpen, Kumler, and Strait, *ibid.*, 1950, **72**, 4558, who also give a theoretical interpretation of this type of spectrum).

The following table summarises these results; it indicates, incidentally, that in the cases of (VI*a*) and the ketal of (VII*a*), the solvent has little effect on the absorption of these—highly substituted—compounds.

As far as our experience shows, the Michael condensation and subsequent cyclisation leads to only one of the possible isomers—presumably of analogous configuration in all cases. Even (II; R = CN, R′ = CO_2Et) resulted in 90% yield although in this compound there is an

additional—however, easily enolised—asymmetric carbon atom in the side chain. It should, of course, be borne in mind that the alkaline medium necessary for the Michael condensation may well cause isomerisation of $C_{(12)}$ so that the configuration of the product isolated does not necessarily reflect the steric mechanism of the addition reaction. As judged by the formation

Ultra-violet absorption.

Compound.	Solvent.	$\lambda_{max.}$	log $\varepsilon_{max.}$	$\lambda_{max.}$	log $\varepsilon_{max.}$
(VI*a*)	*iso*Octane	2700	4·18	2300	4·34
,, ...	Dioxan	2720	4·11	2320	4·26
,, ...	Ethanol (anhyd.)	2780	4·10	2320	4·17
(VII*a* ketal)	*iso*Octane	2680	4·21	2270	4·45
,, ...	Dioxan	2740	4·16	2280	4·33
,, ...	Ethanol (anhyd.)	2780	4·29	2300	4·41
(VIII*a*)	*iso*Octane	2780—2880	3·21	—	—

of *trans*-octahydro-9-ketophenanthrene (VI*b*) from (III; R = R′ = CO_2Et), the two alicyclic rings in the octahydrophenanthrene ultimately isolated are locked in the *trans*-configuration.

A noteworthy case, in which the Michael condensation was used to prepare a precursor of a hydrophenanthrene derivative, is the condensation of 1-acetyl*cyclo*hexene with *cyclo*hexanone in the presence of sodamide (Rapson and Robinson, *J.*, 1935, 1285). The compound obtained, 9-keto-Δ^{10}-dodecahydrophenanthrene, may be viewed as resulting (i) from Michael condensation, followed by (ii) cyclodehydration of the adduct. Linstead *et al.* (*J.*, 1939, 842, 850; *J. Amer. Chem. Soc.*, 1942, **64**, 2003, 2009) have shown that reduction of this ketone yields a product which can be oxidised to *trans-anti-trans*-diphenic acid, and, therefore, also contains in *trans*-configuration the two rings which are hydroaromatic in the compounds described in the present communication.

Work on the stereochemistry of the new substances is now in progress with a view to obtaining the configuration prevalent in the morphine system, in which the ethanamine bridge and the hydrogen at $C_{(14)}$ are believed (but not proved) to be *cis* to each other (Grewe, *Naturwiss.*, 1946, **33**, 333; Schöpf and Pfeiffer, *Annalen*, 1930, **483**, 157).

Experimental.

(All m. p.s and b. p.s are uncorrected.)

*A. Michael Condensation with 2-Aryl*cyclo*hex-2-enones* (I).—*Ethyl* 2-(2 : 3-*dimethoxyphenyl*)-3-*keto*-cyclo*hexylmalonate* (II; R = R′ = CO_2Et). A mixture of the 2-aryl*cyclo*hex-2-enone (I) (0·1 mole), ethyl malonate (0·2 mole), and 20% sodium ethoxide solution (0·025 mole) was kept at 60° for 3 hours, then overnight at room temperature. Acetic acid (1·5 ml., 0·025 mole) was added, and the mixture diluted with ether (200 ml.). The ethereal solution was washed with water, then dried, and the solvent evaporated. Unchanged ethyl malonate was removed in a high vacuum (bath-temp. below 120° at 0·1 mm.). The remaining oil (yield, about 95%) was sufficiently pure for further transformations; in larger batches decomposition occurs on distillation but a small sample of the *ester* (II; R = R′ = CO_2Et) can be purified by distillation at 0·1 mm. (bath. temp. 220°) (Found: C, 64·4; H, 7·5. $C_{21}H_{28}O_7$ requires C, 64·3; H, 7·2%). It forms a 2 : 4-*dinitrophenylhydrazone*, yellow crystals, m. p. 117—119° (from ethanol) (Found: C, 56·7; H, 5·6; N, 10·0. $C_{27}H_{32}O_{10}N_4$ requires C, 56·6; H, 5·6; N, 9·8%).

Analogously, the following substances were prepared: *Ethyl* 3-*keto*-2-*phenyl*cyclo*hexylmalonate* (III; R = R′ = CO_2Et), an oil (Found: C, 68·6; H, 7·2. $C_{19}H_{24}O_5$ requires C, 68·7; H, 7·2%); 2 : 4-*dinitrophenylhydrazone*, yellow crystals, m. p. 119—120° (from ethanol) (Found: C, 58·5; H, 5·7; N, 11·2. $C_{25}H_{28}O_8N_4$ requires C, 58·6; H, 5·5; N, 10·9%).

Ethyl α-*cyano*-α-2-(2 : 3-*dimethoxyphenyl*)-3-*keto*cyclo*hexylacetate* (II; R = CN, R′ = CO_2Et), m. p. 95° (from butanol) (yield, 90%) (Found: C, 66·4; H, 6·2; N, 4·4. $C_{19}H_{23}O_5N$ requires C, 66·0; H, 6·7; N, 4·1%); 2 : 4-*dinitrophenylhydrazone*, yellow crystals, m. p. 176—178° (from ethanol–chloroform) (Found: C, 56·9; H, 5·3; N, 13·4. $C_{25}H_{27}O_8N_5$ requires C, 57·1; H, 5·1; N, 13·3%).

Methyl 2-(2 : 3-*dimethoxyphenyl*)-3-*keto*cyclo*hexylmalonate*, an oil (97%) (Found: C, 62·1; H, 6·5. $C_{19}H_{24}O_7$ requires C, 62·6; H, 6·6%); 2 : 4-*dinitrophenylhydrazone*, orange crystals, m. p. 162—163° (from ethyl acetate–ethanol) (Found: C, 55·0; H, 5·4; N, 10·9. $C_{25}H_{28}O_{10}N_4$ requires C, 55·1; H, 5·2; N, 10·3%).

Methyl α-*cyano*-α-2-(2 : 3-*dimethoxyphenyl*)-3-*keto*cyclo*hexylacetate*, m. p. 114° (from butanol) (95%) (Found: C, 65·3; H, 6·2; N, 4·6. $C_{18}H_{21}O_5N$ requires C, 65·3; H, 6·3; N, 4·2%); 2 : 4-*dinitrophenylhydrazone*, yellow crystals, m. p. 167° (from ethanol–chloroform) (Found: C, 56·2; H, 5·0; N, 13·7. $C_{24}H_{25}O_8N_5$ requires C, 56·4; H, 4·9; N, 13·7%).

Methyl α-*cyano*-α-(3-*keto*-2-*phenyl*cyclo*hexyl*)*acetate*, m. p. 86—87° (from butanol) (Found: C, 70·4; H, 6·2; N, 5·1. $C_{16}H_{17}O_3N$ requires C, 70·8; H, 6·3; N, 5·2%); 2 : 4-*dinitrophenylhydrazone*, yellow crystals, m. p. 155—157° (from ethanol–ethyl acetate) (Found: C, 58·4; H, 4·6; N, 15·8. $C_{22}H_{21}O_6N_5$ requires C, 58·5; H, 4·6; N, 15·5%).

3-*Nitromethyl*-2-*phenyl*cyclo*hexanone* (III; R = NO_2, R′ = H). A mixture of 2-phenyl*cyclo*-hex-2-enone (0·1 mole), nitromethane (0·2 mole), and a 30% methanolic solution of Triton B methoxide

(equivalent to 0·025 mole) was kept at 60° for 3 hours and then at room temperature overnight. Acetic acid (0·025 mole) was added, followed by ether (200 ml.), whereupon the *product* crystallised in 80% yield. It showed a m. p. of 126·5—127·5° (from dioxan–ethanol) (Found: C, 67·0; H, 6·6; N, 6·1. $C_{13}H_{15}O_3N$ requires C, 66·9; H, 6·4; N, 6·0%) and gave a 2 : 4-*dinitrophenylhydrazone*, yellow crystals, m. p. 155—157° (from ethanol–chloroform) (Found: C, 55·1; H, 4·4; N, 16·8. $C_{19}H_{19}O_6N_5$ requires C, 55·2; H, 4·6; N, 16·9%).

When sodium methoxide was used as condensing agent, a slightly less pure product was formed in 80% yield.

Methyl 2-(2 : 3-*dimethoxyphenyl*)-3-*keto*cyclo*hexyl-α-nitroacetate* (II; R = NO_2, R′ = CO_2Me). The condensation, using methyl nitroacetate (0·2 mole), was carried out as above for 12 hours at 60°. The ethereal solution of the product was washed with water and dilute sodium hydrogen carbonate solution, which removed most of the unchanged ester; the balance was distilled off in a high vacuum. The oily residue (90%) was sufficiently pure for further transformations. Similarly was obtained methyl 3-keto-2-phenyl*cyclo*hexyl-α-nitroacetate (III; R = NO_2, R′ = CO_2Me) (90%), an oil.

The last two adducts were reduced to the corresponding amino-esters, and then hydrolysed to the amino-acids. Their further transformations will be reported later.

B. Cyclisation of the Michael Adducts: Method (i).—trans-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*Octahydro*-9-*ketophenanthrene* (VI*b*). (*a*) A mixture of ethyl 3-keto-2-phenyl*cyclo*hexylmalonate (III; R = R′ = CO_2Et) (10 g.), anhydrous ethanol (30 g.), ethyl orthoformate (30 g.), and toluene-*p*-sulphonic acid (0·1 g.) was refluxed for 4 hours. The solution was cooled, neutralised with sodium methoxide, and concentrated *in vacuo* (water-pump). The residual oil was refluxed with 50% aqueous potassium hydroxide solution (20 ml.) for 4 hours. The solution was diluted with water, neutralised with hydrochloric acid to slightly alkaline reaction (pH *ca.* 8), and extracted with ether to remove unhydrolysed ester and some phenolic material. It was then acidified with excess of hydrochloric acid and kept for 1 hour (for completion of the hydrolysis of the acetal grouping), and the oil which separated was taken up in ether. By removal of the solvent, 7·5 g. of crude, oily 3-keto-2-phenyl*cyclo*hexylmalonic acid were obtained. It was not possible to isolate the ketal of this acid.

(*b*) Clemmensen reduction (Martin's modification, *J. Amer. Chem. Soc.*, 1936, **58**, 1438). The crude malonic acid (3·5 g.) and amalgamated zinc wool (7 g.) were added to a mixture of water (5 ml.), concentrated hydrochloric acid (12 ml.), and toluene (7 ml.), and the whole was refluxed for 48 hours with addition of concentrated hydrochloric acid (3·5 ml.) at 6-hour intervals. The product was then extracted with benzene, the benzene solution washed with water, and the solvent evaporated off. The oily solid was recrystallised from dilute acetic acid and *trans*-2-phenyl*cyclo*hexylacetic acid, m. p. 110°, obtained (2·8 g.) (Found: C, 77·4; H, 8·6. Calc. for $C_{14}H_{18}O_2$: C, 77·1; H, 8·3%) (Linstead *et al.*, *J. Amer. Chem. Soc.*, 1942, **64**, 2019, report m. p. 113·5—114·5°). The acid could be further purified by distillation in a high vacuum.

(*c*) Cyclisation. The crude product (2 g.) of the Clemmensen reduction in concentrated sulphuric acid was heated on the steam-bath for 10 minutes (Cook, Hewett, and Lawrence, *J.*, 1936, 71), poured on ice, and extracted with ether. The extract was washed with dilute sodium carbonate solution, then dried, and the solvent removed. The residue (1·7 g.) crystallised and melted at 92—95°. After recrystallisation from ethanol, 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-9-ketophenanthrene melted at 95° (Cook *et al.*, *loc. cit.*, report m. p. 95°) (Found: C, 84·3; H, 7·9. Calc. for $C_{14}H_{16}O$: C, 84·0; H, 8·0%) (yield 70%). It formed an *oxime*, m. p. 176° (from ethanol) (Cook *et al.*, *loc. cit.*, report m. p. 175—177°), and a 2 : 4-*dinitrophenylhydrazone*, orange crystals, m. p. 265° (decomp.) (precipitated from ethanol, washed with hot ethanol–ethyl acetate) (Found: N, 14·5. $C_{20}H_{20}O_4N_4$ requires N, 14·7%).

Alternatively the ester (III; R = R′ = CO_2Et) was reduced by the Clemmensen–Martin method, the product hydrolysed with aqueous potassium hydroxide, and the resultant malonic acid decarboxylated at 180—200° (10 minutes). From 15 g. of ester were thus obtained 8 g. of crude *trans*-2-phenyl-*cyclo*hexylacetic acid.

1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*Octahydro*-9-*keto*-5 : 6-*dimethoxyphenanthrene* (VI*a*). (*a*) Reduction of (II*a*): Ethyl 2-(2 : 3-dimethoxyphenyl)-3-keto*cyclo*hexylmalonate (22·5 g.) was reduced, as described above, by the Martin modification of the Clemmensen method. The crude oily residue weighed 16·5 g.

(*b*) Hydrolysis. The product (16·5 g.) was refluxed with 50% aqueous potassium hydroxide solution (35 ml.) for 4 hours, and the mixture diluted with water, extracted with ether, and acidified with hydrochloric acid. The precipitated oil was taken up in ether. Removal of the solvent yielded a semi-solid mass (15 g.) consisting of a mixture of the malonic and acetic acid derivatives. Crystallisation of 1·8 g. from ether yielded 0·8 g. of 2-(2 : 3-*dimethoxyphenyl*)cyclo*hexylmalonic acid*, m. p. 195—196° (decomp.) (Found: C, 63·6; H, 6·8. $C_{17}H_{22}O_6$ requires C, 63·3; H, 6·8%).

(*c*) Cyclisation. The crude mixture (13 g.) of acetic and malonic acid derivatives was dissolved in a mixture of glacial acetic acid (78 ml.) and acetic anhydride (52 ml.). Fused zinc chloride (1·04 g.) was added and the whole heated under reflux for 75 minutes. To the hot solution was added water (300 ml.) at a rate which maintained boiling. The oil, which separated, crystallised on storage. The solid was collected, washed with cold water, and dried. The *ketone* (VI*a*) melted at 96—97° (from aqueous–ethanol) (yield, 9·6 g., 65% from II*a*) (Found: C, 73·6; H, 8·2. $C_{16}H_{20}O_3$ requires C, 73·8; H, 7·7%), and formed a 2 : 4-*dinitrophenylhydrazone*, crimson crystals, m. p. 248° (decomp.) (from ethanol–ethyl acetate) (Found: N, 12·5. $C_{22}H_{24}O_6N_4$ requires N, 12·7%). This ketone is perhaps identical with the product, m. p. 86—89° (corr.) (dinitrophenylhydrazone, m. p. 237—238°), described by Hornung, Hornung, and Platt (*J. Amer. Chem. Soc.*, 1947, **69**, 2929).

Cyclisation of the Michael Adducts: Method (ii).—*Ethyl* 2-(2 : 3-*dimethoxyphenyl*)-3-*hydroxy*cyclo*hexylmalonate* (V*c*). The compound (II; R = R′ = CO_2Et) (10 g.) in 95% ethanol (100 ml.) was hydrogenated in the presence of Adams's catalyst (0·5 g.) at room temperature and 60 lbs./sq. in. After 3

hours, 1 mole of hydrogen had been absorbed. The catalyst was removed by filtration and the solvent removed *in vacuo*. The residual (Vc) was an oil (9·8 g.). Its *acetate*, prepared by means of glacial acetic acid, acetic anhydride, and fused zinc chloride, had m. p. 83—84° (from methyl*cyclo*hexane) (Found: C, 63·6; H, 7·6. $C_{23}H_{32}O_8$ requires C, 63·3; H, 7·3%).

1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*Octahydro*-4-*hydroxy*-9-*keto*-5 : 6-*dimethoxyphenanthrene* (VIc). (*a*) The foregoing oily hydroxy-ester (10 g.) was refluxed with 50% aqueous potassium hydroxide (30 ml.) for 1 hour. As part of the potassium salt separated out, water (75 ml.) was added and the refluxing was continued for 4 hours. The mixture was cooled and extracted with ether, and the aqueous layer just acidified with 18% hydrochloric acid and boiled for a few minutes, whereupon the oil which had separated began to crystallise. 2-(2 : 3-*Dimethoxyphenyl*)-3-*hydroxy*cyclo*hexylmalonic acid* was washed with a small volume of ice-water (6 g.) and recrystallised from dioxan–methyl*cyclo*hexane. It had m. p. 185° (decomp.) (Found: C, 59·7; H, 6·5. $C_{17}H_{22}O_7$ requires C, 60·3; H, 6·5%).

(*b*) Cyclisation. The acid (2 g.) and fused zinc chloride (0·20 g.) were added to a mixture of acetic acid (12 ml.) and acetic anhydride (10 ml.), and the whole was refluxed for 1·75 hours. The oily product obtained as above crystallised partly after being scratched (1·6 g.). Recrystallisation from ethanol gave 4-*acetoxy*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-9-*keto*-5 : 6-*dimethoxyphenanthrene* (0·7 g.), m. p. 129° (Found: C, 67·7; H, 6·9. $C_{18}H_{22}O_5$ requires C, 67·9; H, 6·9%); its 2 : 4-*dinitrophenylhydrazone* formed crimson crystals, m. p. 263° (decomp.) (from ethanol–ethyl acetate) (Found: N, 11·1. $C_{24}H_{26}O_8N_4$ requires N, 11·2%).

(*c*) Hydrolysis of the acetate. The above acetate (0·5 g.) was refluxed for 90 minutes with a mixture of 10% aqueous sodium hydroxide solution (2 ml.) and ethanol (2 ml.). After acidification and evaporation *in vacuo*, the residue was taken up in ether, and the extract washed with alkali. Trituration of the residue with methyl*cyclo*hexane gave crystals of 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4-*hydroxy*-9-*keto*-5 : 6-*dimethoxyphenanthrene* (VIc) (0·32 g.), m. p. 97·5—98° (from methyl*cyclo*hexane–benzene) (Found: C, 69·5; H, 7·3. $C_{16}H_{20}O_4$ requires C, 69·6; H, 7·3%), which gave a 2 : 4-*dinitrophenylhydrazone*, crimson crystals, m. p. 238—240° (decomp.) (from ethanol–ethyl acetate) (Found: N, 12·3. $C_{22}H_{24}O_7N_4$ requires N, 12·3%).

Cyclisation of the Michael Adducts: *Method* (iii).—1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*Octahydro*-4 : 9-*diketo*-5 : 6-*dimethoxyphenanthrene* (VIIa). (*a*) The ketal was prepared by treating ethyl 2-(2 : 3-dimethoxyphenyl)-3-keto*cyclo*hexylmalonate (10 g.) with anhydrous ethanol (30 g.), ethyl orthoformate (30 g.), and toluene-*p*-sulphonic acid (0·1 g.) as described above. After hydrolysis 2-(2 : 3-*dimethoxyphenyl*)-3-*keto*cyclo*hexylmalonic acid* crystallised as the hemihydrate after one month. It melted at 98—100° (decomp.) after recrystallisation from water, the m. p. being dependent on the rate of heating (Found: C, 58·9; H, 6·6. $C_{17}H_{20}O_7,\frac{1}{2}H_2O$ requires C, 59·1; H, 6·1%).

(*b*) Cyclisations. (i) The anhydrous 2-(2 : 3-dimethoxyphenyl)-3-keto*cyclo*hexylmalonic acid (15 g.) and fused zinc chloride (1·34 g.) were added to a mixture of glacial acetic acid (93 ml.) and acetic anhydride (65 ml.), and the whole was refluxed for 75 minutes. Water (400 ml.) was added to the hot mixture and, after cooling, the oil which separated was taken up in ether. The ethereal extract was washed with dilute sodium hydroxide solution and the solution evaporated to 30 ml. After prolonged storage, a solid, m. p. 105—110°, crystallised and was filtered off (3 g.). The remaining oil was refluxed for 90 minutes with potassium hydroxide (1·8 g.) in water (30 ml.). After 12 hours, a second crop of the above product had crystallised; it was filtered off and washed with a small amount of cold ether, and had m. p. 110° (7 g.). After recrystallisation from ethanol, the 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4 : 9-*diketo*-5 : 6-*dimethoxyphenanthrene* (VIIa) had m. p. 115° (Found: C, 70·1; H, 6·6. $C_{16}H_{18}O_4$ requires C, 70·0; H, 6·5%); it gave a *dioxime*, m. p. 210° (decomp.) (from ethanol) (Found: N, 9·2. $C_{16}H_{20}O_4N_2$ requires N, 9·2%).

(ii) 2-(2 : 3-Dimethoxyphenyl)-3-keto*cyclo*hexylmalonic acid hydrate (16 g.) was decarboxylated at 200° (10 minutes), and the resulting product dissolved in anhydrous hydrogen fluoride (50 g.). After evaporation of the hydrogen fluoride, water was added and the product extracted with ether. The extract was washed with 5% potassium hydroxide solution, then dried, and the solvent removed. The diketone (VIIa) crystallised readily, m. p. 115° (from ethanol) (yield, 90%).

(iii) The ethylene glycol ketal (see below) of 2-(2 : 3-dimethoxyphenyl)-3-keto*cyclo*hexylmalonic acid (6 g.) was decarboxylated at 190—200° (10 minutes). The crude product was heated with 80% sulphuric acid (24 ml.) on the steam-bath for 30 minutes. The mixture was poured on ice, and the solid washed with dilute aqueous ammonia, and then recrystallised from ethanol (yield, 2 g.; m. p. 115°).

1 : 2 3 : 4 : 9 : 10 : 11 : 12-*Octahydro*-4 : 9-*diketophenanthrene* (VIIb). (*a*) A mixture of ethyl 2-phenyl-3-keto*cyclo*hexylmalonate (III; R = R′ = CO_2Et) (7 g.), ethylene glycol (15 ml.), benzene (30 ml.), and toluene-*p*-sulphonic acid (0·1 g.) was refluxed for 6 hours, the water being removed azeotropically. The oily residue, obtained as above, was refluxed for 4 hours with 50% aqueous potassium hydroxide (14 g.), and the reaction product diluted with water. After acidification to pH 8, the mixture was extracted with ether, cooled, and covered with benzene (30 ml.), and an equivalent amount of hydrochloric acid was added dropwise with stirring and cooling. The ketal-acid was precipitated, but passed at once into the benzene layer. The aqueous phase was separated and extracted once more with benzene. The combined benzene extracts were dried. When scratched the (*ethylene glycol*) *ketal* of 2-phenyl-3-keto*cyclo*hexylmalonic acid crystallised (5·5 g.), m. p. 175—176° (decomp.) (from toluene–dioxan) (Found: C, 63·6; H, 6·4. $C_{17}H_{20}O_6$ requires C, 63·7; H, 6·3%).

(*b*) Cyclisation. The above ketal (10 g.) was decarboxylated at 180—200° (10 minutes). The residue was dissolved in concentrated sulphuric acid and the solution heated on the steam-bath for 10 minutes. It was then poured on ice and extracted with ether; the extract was washed with water and dilute sodium carbonate solution, then dried, and the solvent removed. The residual oily *diketone* (VIIb) crystallised on storage (5·5 g., 75%), m. p. 94—95° (from butanol) (Found: C, 78·5; H, 6·6. $C_{14}H_{14}O_2$ requires C,

78·5; H, 6·5%). It gave a *dioxime*, m. p. 235° (decomp.) (from ethanol) (Found : N, 11·9. $C_{14}H_{16}O_2N_2$ requires N, 11·5%).

*Experiments with Methyl α-Cyano-α-2-(2 : 3-dimethoxyphenyl)-3-keto*cyclo*hexylacetate.—Alkaline hydrolysis.* (*a*) This ester was converted into the *ketal* with ethylene glycol as described for (VII*b*) (yield, 80%), the product melting at 139—140° (from butanol) (Found : C, 63·8; H, 6·7; N, 4·0. $C_{20}H_{25}O_6N$ requires C, 64·0; H, 6·7; N, 3·7%). The ketal was hydrolysed by 5% hydrochloric acid at 80° (3 hours).

(*b*) Hydrolysis. The above ketal (10 g.) was refluxed with potassium hydroxide (15 g.) in butanol (50 ml.) until evolution of ammonia ceased (*ca.* 10 hours). After addition of water (50 ml.), refluxing was continued for 30 minutes. The aqueous alkaline layer was separated and the butanol layer washed once with water. The combined aqueous extracts were washed with ether, acidified to pH *ca.* 8, filtered to remove a small quantity of precipitate, and covered with benzene (100 ml.). Hydrochloric acid was added with cooling and stirring, so that the precipitate formed was immediately taken up by the benzene. The benzene extract was quickly removed, washed with water, and when scratched and cooled deposited a voluminous precipitate of the *ethylene glycol ketal* (80%) of 2-(2 : 3-dimethoxyphenyl)-3-keto*cyclo*hexylmalonic acid; this melted at 182—183° (decomp.) (from benzene–dioxan) (Found : C, 59·8; H, 5·9. $C_{19}H_{24}O_8$ requires C, 60·0; H, 6·3%). Decarboxylation was effected in quantitative yield at 190—200° in 10 minutes.

This ketal is identical with the ethylene glycol ketal of the malonic acid prepared by hydrolysis of (II; R = R′ = CO_2Et).

*Experiments with Ethyl α-Cyano-α-2-(2 : 3-dimethoxyphenyl)-3-keto*cyclo*hexylacetate.*—(*a*) *Alkaline hydrolysis.* (i) Without blocking of the carbonyl group. To this ester (II; R = CN, R′ = CO_2Et) (1 g.), in ethanol (5 ml.) was added 5% sodium hydroxide solution (30 ml.). After 24 hours, crystals of 2-(2 : 3-dimethoxyphenyl)*cyclo*hex-2-enone (I*a*), m. p. 96° (from butanol), had formed by reversal of the Michael condensation.

(ii) With blocking of the carbonyl group. The ketal from the ester (20 g.) was dissolved in ethanol (150 ml.), and a solution of potassium hydroxide (3·25 g.) in ethanol (40 ml.) added. After 3 hours at room temperature the solution, which was neutral to litmus, was concentrated *in vacuo*, water (100 ml.) was added, and some unhydrolysed starting material extracted with ether. The aqueous layer was then acidified with concentrated hydrochloric acid (10 ml.), and the oil which separated taken up in ether. The oily residue of *α-cyano-α-2-(2 : 3-dimethoxyphenyl)-3-keto-*cyclo*hexylacetic acid* crystallised after scratching (15 g.), m. p. 163—165°, decomp. at 170° (from 30% acetic acid) (Found : C, 63·9; H, 6·4; N, 4·4. $C_{17}H_{19}O_5N$ requires C, 64·3; H, 6·0; N, 4·4%).

Attempted cyclisations of the product with acetic acid–acetic anhydride–zinc chloride or with hydrogen fluoride were unsuccessful.

(*b*) *Reduction.* The ester (20 g.) in 95% ethanol (200 ml.) absorbed 1 mole of hydrogen in the presence of Adams's catalyst (0·5 g.) at room temperature and 60 lbs./sq. in. during 4 hours. The catalyst was removed by filtration and the solvent removed *in vacuo*. The oily residue was dissolved in ether, and the solution washed with dilute hydrochloric acid to remove basic material (350 mg.) Evaporation of the ether yielded the oily ethyl α-cyano-α-2-(2 : 3-dimethoxyphenyl)-3-hydroxy*cyclo*hexylacetate (18·5 g.).

Hydrolysis was effected with dilute ethanolic potassium hydroxide at room temperature as described above for the hydrolysis of the ketal. The oily product could not be cyclised with acetic acid–acetic anhydride–zinc chloride; under these conditions *α-cyano-α-3-acetoxy-2-(2 : 3-dimethoxyphenyl)*cyclo*hexylacetic acid* was obtained, m. p. 115° (from dilute acetic acid) (Found : N, 3·9. $C_{19}H_{23}O_6N$ requires N, 3·9%).

Attempted cyclisation of the acetate with anhydrous hydrogen fluoride was also unsuccessful.

C. Differences in Reactivity of the Keto-groups in (VII).—*1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-Octahydro-4-keto-5 : 6-dimethoxyphenanthrene* (VIII*a*). The diketone (VII*a*) (9 g.) in 95% ethanol (100 ml.) absorbed 2 moles of hydrogen in the presence of 5% palladium–charcoal (0·5 g.) at room temperature and 60 lbs./sq. in. during 1 hour. The catalyst was removed by filtration and the solvent removed *in vacuo*. *1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-Octahydro-4-keto-5 : 6-dimethoxyphenanthrene*, m. p. 104—105° (from ethanol), was thus obtained in nearly quantitative yield (8·5 g.) (Found : C, 73·6; H, 7·6. $C_{16}H_{20}O_3$ requires C, 73·8; H, 7·7%). This reduction could also be carried out in glacial acetic acid at 60°. The *2 : 4-dinitrophenylhydrazone*, orange crystals, had m. p. 183—184° (from ethanol–ethyl acetate) (Found : C, 60·1; H, 5·3; N, 12·6. $C_{22}H_{24}O_6N_4$ requires C, 60·0; H, 5·5; N, 12·7%), the *oxime* m. p. 148—149° (from ethanol) (Found : C, 70·4; H, 7·4; N, 5·5. $C_{16}H_{21}O_3N$ requires C, 70·0; H, 7·6; N, 5·1%), and the *semicarbazone* m. p. 219—221° (decomp.) (from ethanol) (Found : N, 13·4. $C_{17}H_{23}O_3N_3$ requires N, 13·2%).

Partial Clemmensen reduction of the diketone yielded the same product.

1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-Octahydro-4-ketophenanthrene (VIII*b*). The diketone (VII*b*) (2 g.), hydrogenated in glacial acetic acid (100 ml.) in the presence of 10% palladium–charcoal (0·2 g.) at 60—70° and 60 lbs./sq. in., absorbed 2 moles of hydrogen during 90 minutes. After removal of the catalyst and evaporation of the solvent, the *4-monoketone* was obtained as an oil (1·8 g.). On cooling it crystallised, m. p. 48—49° (from methanol) (Found : C, 84·2; H, 8·0. $C_{14}H_{16}O$ requires C, 84·0; H, 8·0%). It gave a *2 : 4-dinitrophenylhydrazone*, yellow crystals, m. p. 193—194° (from ethanol–chloroform) (Found : N, 14·5. $C_{20}H_{20}O_4N_4$ requires N, 14·7%), and a *semicarbazone*, m. p. 219° (from butanol) (Found : N, 15·8. $C_{15}H_{19}ON_3$ requires N, 16·3%).

Selective ketalisation of the 4-keto-group. (i) A mixture of the diketone (VII*a*) (7 g.), ethylene glycol (15 ml.), benzene (30 ml.), and toluene-*p*-sulphonic acid (0·2 g.) was heated for 3 hours, the water liberated being removed azeotropically. The mixture was cooled and neutralised with sodium methoxide, the benzene layer separated, and the glycol layer diluted with water and extracted with benzene. The

combined benzene extracts were washed with water and the solvent was removed *in vacuo*. The 4-(*ethylene glycol*) *ketal* crystallised immediately, m. p. 134—135° (from ethanol) (Found : C, 67·9; H, 7·0. $C_{16}H_{22}O_5$ requires C, 67·9; H, 6·9%).

(ii) The diketone (VII*b*) similarly gave a 4-(*ethylene glycol*) *ketal*, m. p. 89° (from hexane) (admixture with the diketone gave a large depression) (Found : C, 74·3; H, 7·3. $C_{16}H_{18}O_3$ requires C, 74·4; H, 7·0%).

The authors are indebted to Dr. Y. Hirshberg of this Institute for the ultra-violet-absorption data. This paper represents part of a thesis submitted by Raphael Pappo to the Hebrew University, Jerusalem, in partial fulfilment of the requirements for the degree of Ph.D.

DANIEL SIEFF RESEARCH INSTITUTE, WEIZMANN INSTITUTE OF SCIENCE,
REHOVOTH, ISRAEL. [*Received, December 1st*, 1950.]