311. *Syntheses in the Morphine Series. Part IV.* The Synthesis of* N-*Methylmorphinan.*

By David Ginsburg and Raphael Pappo.

Various methods for formation of the tetracyclic skeletal structure present in morphine from 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydrophenanthrene compounds previously described (*J.*, 1951, 938) have been investigated. *N*-Methylmorphinan has been prepared by one of these routes.

The present communication describes attempts to join $C_{(10)}$ and $C_{(12)}$ of the octahydrophenanthrene derivatives (*e.g.*, I*a* or *b*) described in Part III * by the "ethanamine" bridge, $-CH_2 \cdot CH_2 \cdot NMe-$, and thus to approach more closely to the morphine structure.

Formally, three routes are open: (*a*) introduction of an amino- or potential amino-group at $C_{(10)}$ and of an appropriate two-carbon chain at $C_{(12)}$, and junction of the two: $C_{(10)}-N + C-C-C_{12} \longrightarrow C_{(10)}-N-C-C-C_{(12)}$; (*b*) alkylation of $C_{(12)}$ by a substituent which can be converted into a two-carbon chain carrying in the β-position an amino- or potential amino-group, and introduction at $C_{(10)}$ of a halogen atom or another substituent which will react with the amino-group: $C_{(12)}-C-C-N + C_{(10)}-X \longrightarrow C_{(12)}-C-C-N-C_{(10)}$; and (*c*) introduction at $C_{(10)}$ of a substituted amino-group, the substituent being suitable for intramolecular alkalylation at $C_{(12)}$: $C_{(10)}-N-C-C-X + C_{(12)} \longrightarrow C_{(10)}-N-C-C-C_{(12)}$. So far, route (*c*) has yielded a product containing the tetracyclic system present in the morphine alkaloids. The tetracyclic nature of the cyclisation product has been proved by its conversion in a series of simple transformations into *N*-methylmorphinan (Grewe and Mondon, *Ber.*, 1948, **81**, 279).

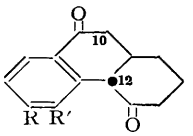
(*a*, 1) *Introduction of an Amino-group at* $C_{(10)}$.—Michael condensation of 2-aryl*cyclo*hex-2-enones with methyl nitroacetate yielded methyl 2-aryl-3-keto*cyclo*hexyl-α-nitroacetates (Part III). These were converted by high-pressure reduction in the presence of Raney nickel into the corresponding α-amino-acetates, and these were hydrolysed to the α-amino-acids (II*a* and *b*). The more readily available unmethoxylated substances were used throughout as models in developing the synthetic procedures.

The phthalimido-acid (III) formed from (II*a*) was cyclised by means of sulphuric acid to *trans*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4 : 9-diketo-10-phthalimidophenanthrene (IV). This cyclisation was possible due to the removal of the basic properties of the amino-group through the phthaloyl radical (cf. Sheehan and Frank, *J. Amer. Chem. Soc.*, 1949, **71**, 1856).

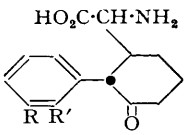
Support for the structure of (IV) was obtained through its synthesis by another route in which it was obtained in higher overall yield. The 4-ethylene glycol ketal of (I*b*) was

* Part III, *J.*, 1951, 938.

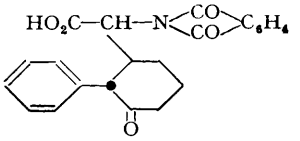
converted by means of amyl nitrite in the presence of sodium ethoxide into the 10-oximino-derivative (V), hydrogenated in the presence of 10% palladium–carbon to the 10-amino-compound (VI*a*). Hydrolysis of the 4-ethylene glycol ketal grouping in the derived 10-phthalimido-derivative gave a substance identical in melting point, mixed melting point, and infra-red absorption with (IV). Alternatively, the 10-oximino-compound could be



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



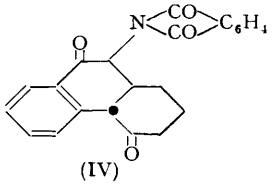
(II*a*; R = R′ = H)
(II*b*; R = R′ = OMe)



(III)

reduced catalytically in the presence of hydrochloric acid to yield the hydrochloride of the 10-amino-4 : 9-diketo-compound (VII*a*). The free base on treatment with phthalic anhydride again yielded (IV). The stereochemistry of (VII*a*) is discussed below.

Michael condensation of 2-phenyl*cyclo*hex-2-enone with ethyl or benzyl malonate on the one hand, and with methyl nitroacetate on the other, yields adducts having the *trans*-configuration (Pappo and Ginsburg, *Bull. Res. Council Israel*, 1951, **1**, No. 3, 121). That the *trans*-adduct is obtained with ethyl or benzyl malonate has been shown by conversion of the adduct into the known *trans*-2-phenyl*cyclo*hexylacetic acid (Part III, *loc. cit.*; Bachmann and Fornefeld, *J. Amer. Chem. Soc.*, 1950, **72**, 5529). That the *trans*-adduct is formed also with methyl nitroacetate (and by analogy, presumably with other donors in the Michael condensation) has been shown by the synthesis of (IV) by the two routes described. In the Experimental section an improved procedure is given for the preparation of malonate or cyanoacetate adducts in the Michael condensation. Benzyl malonate or cyanoacetate, used in place of the ethyl esters, affords more simply isolated, pure intermediates and increases the overall yield of the final products. The use of benzyl esters (cf. Bowman, *J.*, 1950, 325) was of particular importance in condensations in the dimethoxyphenyl series because acid hydrolysis of the ethyl malonate or ethyl cyanoacetate adduct in this case yielded an intractable mixture which was not further investigated. Hydrogenolysis of the benzyl ester adducts permits one to avoid the use of intermediate 4-ethylene glycol ketal derivatives. The method has proved to be of wide scope and is useful whenever basic hydrolysis of products of Michael condensation is not possible.



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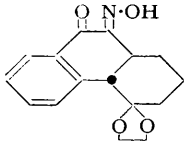

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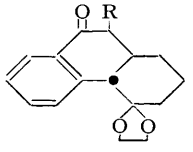
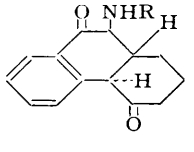


(VI*a*; R = NH_2)
(VI*b*; R = $CO{\cdot}CO_2Et$)
(VI*c*; R = CO_2Et)



(VII*a*; R = H)
(VII*b*; R = $CO{\cdot}CH_2{\cdot}$Halogen)
(VII*c*; R = $CO{\cdot}CH_2{\cdot}OAc$)

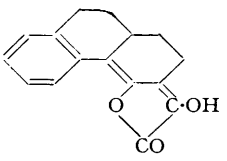
(*a*, 2) *Introduction of an Ester Group at* $C_{(10)}$.—An ester group could be introduced at $C_{(10)}$ indirectly by treatment of a compound having a carbonyl group at $C_{(9)}$ with ethyl oxalate. Decarbonylation in the presence of powdered soft glass of the 10-ethoxalyl derivative (cf. Snyder, Brooks, and Shapiro, *Org. Synth.*, Coll. Vol. II, p. 531) gave smoothly the corresponding carbethoxy-compound. The ester group is convertible into an amino-group by any of the known procedures but this approach was abandoned in favour of the simpler route (*a*, 1).

Glyoxylation at $C_{(10)}$ of the 4-ethylene glycol ketal of (I*a* or *b*) proceeded smoothly in high yield when sodium hydride was used as the condensing agent, but in extremely poor yield in the presence of sodium methoxide or ethoxide. A similar effect has been observed in the acylation of ethyl *iso*valerate (Swamer and Hauser, *J. Amer. Chem. Soc.*, 1950, **72**,

1352). In both cases the carbon atom in the β-position with respect to the carbonyl (or ester) group is highly substituted. This is probably the reason for the poor results encountered in the sodium methoxide-catalysed glyoxylation, as α-tetralones are known to condense smoothly under similar conditions with alkyl oxalates (Bachmann, Cole, and Wilds, *ibid.*, 1940, **62**, 824).

In the diketones, when the $C_{(1)}$-carbonyl group is free, sodium methoxide-catalysed glyoxylation occurs at $C_{(3)}$. *trans*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-Octahydro-4-ketophenanthrene (Part III) in the presence of sodium methoxide yielded a lactone (VIII), owing to the possibility of enolisation in the product which bears a hydrogen atom at $C_{(12)}$ (cf. Bachmann, Fujimoto, and Wick, *ibid.*, 1950, **72**, 1995). However, glyoxylation at $C_{(3)}$ of 12-2′-cyanoethyl-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4-ketophenanthrene (XI*a*) (see below), in which the $C_{(12)}$-atom is quaternary, yielded a normal glyoxylate. The difference in reactivity between the carbonyl groups in (I*b*) has been observed before (Part III). It is, therefore, not surprising that glyoxylation of (I*b*) with sodium methoxide as catalyst yielded a *mono*glyoxylate at $C_{(3)}$ which could not be isolated but formed the lactone (X) in high yield.

(*a*, 3) *Alkylation at* $C_{(12)}$.—2-Phenyl*cyclo*hexanone and 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4-ketophenanthrene were used as model substances for the study of the introduction of substituents at the tertiary carbon atom. Newman and Farbman (*ibid.*, 1944, **66**, 1550) have shown that 2-phenyl*cyclo*hexanone can be alkylated at the tertiary carbon atom (C_2) by means of methyl iodide in the presence of sodamide, and Newman and Magerlein (*ibid.*, 1947, **69**, 942) have introduced a 2-ethoxyethyl group at $C_{(2)}$ by means of 2-ethoxyethylmethanesulphonate and sodamide (see, also, Boekelheide, *ibid.*, 1950, **72**, 712). It has now been found that, equally, the 2-benzyloxyethyl group can be introduced at $C_{(2)}$ by means of 2-benzyloxyethylmethanesulphonate and sodamide. This modification is useful in view of the potential possibility of hydrogenolysis of the benzyloxy-group, a point which assumes major importance in the methoxylated compounds more closely related to morphine: the conditions under which an ethyl ether group in the alkyl side chain would be cleaved will also demethylate the aromatic methoxyl groups (Horning and Schock, *ibid.*, 1949, **71**, 1359).



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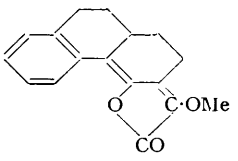

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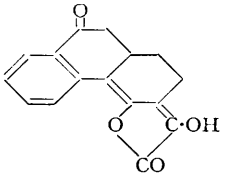
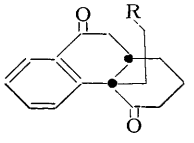


(X)



(XI*a*; R = CN)
(XI*b*; R = CO_2H)
(XI*c*; R = $CO{\cdot}NH_2$)

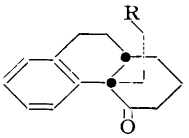
In the case of the octahydro-4-ketophenanthrene, however, the angular alkylation was not so satisfactory. The ratio of alkylation at $C_{(12)}$ and at $C_{(3)}$ varied with the nature of the alkylating reagent; several examples are given in the Experimental section. As it became further apparent that 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4-ketophenanthrene and its 5 : 6-dimethoxy-derivative and more complex analogues behave differently under identical conditions, the study of the $C_{(12)}$-alkylation of model compounds was abandoned in favour of procedures of more immediate value for further synthetical elaboration. The dissimilarity in the behaviour of the corresponding phenyl and dimethoxyphenyl analogues under a given set of experimental conditions has been observed previously (Horning and Finelli, *ibid.*, 1951, **73**, 3741). The same is true for certain phenyl and trimethoxyphenyl analogues used by a number of investigators in the elaboration of the colchicine structure (Ginsburg and Pappo, *J. Amer. Chem. Soc.*, in the press; Dr. Henry Rapoport, personal communication).

(*b*) *Cyanoethylation at* $C_{(12)}$.—Treatment of (I*b*) with acrylonitrile in the presence of benzyltrimethylammonium hydroxide (Triton B) (cf. Bruson, "Cyanoethylation," "Organic Reactions," Vol. V, Wiley, New York 1949, pp. 99—103) yielded as the major

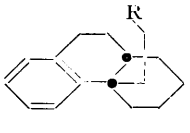
product a mono-2-cyanoethyl derivative at $C_{(12)}$ (XI*a*). The possibility of cyanoethylations having occurred at $C_{(3)}$ or $C_{(10)}$ was excluded by the observation that the reaction product yielded crystalline dibenzylidene and dipiperonylidene derivatives in high yield. Accordingly, the 4-ethylene glycol ketal of (I*b*) was unchanged when cyanoethylation was attempted under the conditions used for cyanoethylation of (I*b*). (XI*a*) was hydrolysed to the corresponding acid (XI*b*).

It was found also that the *trans*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4-ketophenanthrene with acrylonitrile in the presence of Triton B yielded mainly the *cis*-12-2′-cyanoethyl derivative (XII*a*), and a small quantity of bis-2-cyanoethyl product. That cyanoethylation occurred at $C_{(12)}$ was confirmed by the preparation of a benzylidene derivative and of a glyoxylate. Hydrolysis of (XII*a*) gave the acid (XII*b*), identical with a specimen obtained by catalytic hydrogenolysis of (XI*b*).

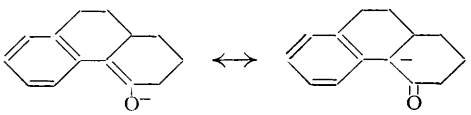
Both the structure and the steric configuration of (XI*a*) and (XII*a*) could be demonstrated directly by a simple series of transformations. *cis*-12-2′-Carboxyethyl-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4-ketophenanthrene (XII*b*) was reduced by the Huang-Minlon procedure (*ibid.*, 1946, **68**, 2487) to *cis*-12-2′-carboxyethyl-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydrophenanthrene (XIII*a*). This acid was converted into the azide, which by a Curtius rearrangement gave *cis*-12-2′-aminoethyl-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydrophenanthrene (XIII*b*). Methylation of the primary amine with formaldehyde–formic acid yielded *cis*-12-2′-dimethylaminoethyl-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydrophenanthrene (XIII*c*). The structure of this product was shown by the fact that it did not depress the melting point of a specimen of " dihydrodes-base " obtained from *N*-methylmorphinan (*cis*-junction) (Grewe and Mondon, *loc. cit.*) and kindly supplied by Professor Rudolf Grewe, but gave a large melting-point depression with the " dihydrodes-base " obtained from *N*-methyl*iso*morphinan (*trans*-junction) (Gates, Woodward, Newhall, and Künzli, *J. Amer. Chem. Soc.*, 1950, **72**, 1141) and kindly supplied by Dr. Marshall Gates.



(XII*a*; R = CN)
(XII*b*; R = CO_2H)



(XIII*a*; R = CO_2H)
(XIII*b*; R = NH_2)
(XIII*c*; R = NMe_2)



(XIV*a*) (XIV*b*)

The formation of the *cis*-12-2′-cyanoethyl derivative (XII*a*) from *trans*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4-ketophenanthrene may be explained by the fact that, as is well known, the active species of the donor in the Michael condensation is the hybrid of the enolate ion (XIV*a*) and the carbanion (XIV*b*), in either of which the steric configuration previously existing no longer obtains. Only the *cis*-12-2′-cyanoethyl product could be isolated from the reaction mixture, together with a small amount of bis-2-cyanoethyl product.

It is evident that in this case the approach of the 2-cyanoethyl moiety from the top of the molecule is hindered, so that a *cis*-relation between the hydrogen atom and the 2-cyanoethyl group is built up at the ring junction. The subtle effect exerted by the neighbouring polar groups in the present system is more pronounced than in the analogous case of methylation of 2-benzylidene-*trans*-1-decalone (Johnson, *ibid.*, 1943, **65**, 1317) or of 2-methylanilinomethylene-1-decalone (Birch and Robinson, *J.*, 1944, 501). In the last two examples mixtures of *cis*- and *trans*-9-methyl derivatives were obtained, although the *cis*-isomer predominated in the ratio of 3 : 1 (see Bergmann, Ginsburg, and Pappo, " The Michael Condensation," " Organic Reactions," in the press).

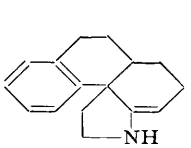
A compound such as (I*a* or *b*) is, however, of greater interest for further synthetic work and its mono-2-cyanoethyl derivative (XI*a*) was therefore investigated. The acid (XI*b*) was converted into its azide or hydrazide which were degraded by modifications of the Curtius rearrangement. In each case, the product was not the free primary amine but

the tetracyclic compound (XVI*a*) (cf. Bachmann and Fornefeld, *J. Amer. Chem. Soc.*, 1951, **73**, 51). The position of the double bond in (XVI*a*) was deduced from the infra-red absorption spectrum which showed bands at 6·06 (C=C double bond), 3·10 (NH group), and 5·95 μ (carbonyl group conjugated with the aromatic ring). With methyl sulphate, (XVI*a*) gave the *N*-methyl product (XVI*b*). This ene-amine is being studied in order to determine whether it can be utilised for further synthetic elaboration to form *N*-methylmorphinan. The pyrrolidino-compound (XV) was similarly prepared from the octahydro-4-ketophenanthrene.

The amide (XI*c*) formed from the acid chloride of (XI*b*) was treated with bromine under the conditions of the Hofmann degradation in the hope that the amine formed would be further brominated and a tetracyclic product formed in analogy with the formation of cinchoninone from *N*-bromocinchonicine (Rabe, *Ber.*, 1911, **44**, 2088). This hope has not as yet been realised.

(*c*) *Intramolecular Cyclisation of Substituted* 10-*Amino-derivatives.*—The 4-ethylene glycol ketal (VI*a*) of 10-amino-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4 : 9-diketophenanthrene was treated with halogenoacetyl chlorides (halogen = Cl, Br, or I). The 4-ethylene glycol ketals of the halogeno-amides (VII*b*) were obtained. Intramolecular alkylation of the free halogeno-amides (VII*b*) at $C_{(12)}$, in presence of various alkaline condensing agents, was unsuccessful: the chloro- and the bromo-amide were recovered unchanged; the iodo-amide apparently underwent, in part, double decomposition with sodamide to give sodium iodide and a basic amino-amide. Bromination of the bromo-amide at $C_{(12)}$, followed by attempted debromination of the resulting product with activated zinc in order to form a tetracyclic system, also failed.

The 10-amino-compound (VII*a*) and acetylglycolloyl chloride in the presence of pyridine gave the acetoxy-amide (VII*c*) in high yield. When preparation of the 4-ethylene glycol ketal of this amide was attempted, the compound unexpectedly lost the elements of acetic acid and the *cis*-diketo-lactam (XVII) was formed and isolated as its 4-ethylene glycol ketal. The infra-red spectrum of this compound was very similar to that reported by Gates *et al.* (*loc. cit.*) for the corresponding *trans*-lactam with one carbonyl group less: it showed bands at 2·95 (N–H), 5·85, 5·92 (alicyclic ketone; acetophenone-type ketone), and 6·02 μ (lactam). The mechanism of this surprising cyclisation is not clear: it will be investigated further. However, the structure of the diketolactam (XVII) was proved by Huang-Minlon reduction to the *cis*-lactam containing no carbonyl groups, though the yield was lower than that of the corresponding *trans*-lactam from the monoketo-lactam (XVIII) (Gates, personal communication). The poor yield is apparently due, in a way not very well understood, to side reactions caused by the presence of the carbonyl group at $C_{(4)}$. Analogous behaviour may be found in the Huang-Minlon reduction of 2-carboxymethyl- and 2-cyanomethyl-2-phenyl*cyclo*hexanone which yielded only phenyl*cyclo*hexane (Carton and Woods, *J. Amer. Chem. Soc.*, 1952, **74**, 5126).



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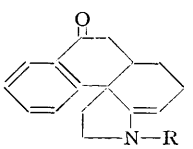
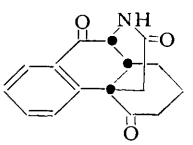


(XVI*a*; R = H)
(XVI*b*; R = Me)



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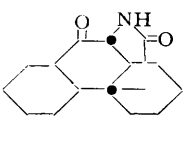

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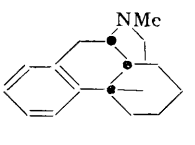

(XIX)

It was apparent that the vigorous conditions used to reduce both carbonyl groups of the diketo-lactam (XVII) caused considerable destruction by opening of the lactam ring, possibly accompanied by complete removal of the substituents in the " open " product. On reduction of the crude *cis*-lactam with lithium aluminum hydride an oily secondary amine was obtained and methylation with formaldehyde–formic acid gave *N*-methylmorphinan (XIX) identical in melting point and that of its hydrochloride with the compound described by Grewe and Mondon (*loc. cit.*). The sulphate did not depress the melting point of an authentic sample kindly supplied by Prof. R. Grewe. The micro-

infra-red spectra of the two sulphates were very kindly measured by Dr. Elkan Blout of the Polaroid Corporation and found to be identical.

Although the mechanism of the cyclisation to form the *cis*-diketo-lactam (XVII) is not clear, it is evident that inversion of configuration at $C_{(12)}$ in the acetoxy-amide (VII*c*) must have taken place. It is not possible to conceive of epimerisation at $C_{(11)}$ owing to the absence of any activating influence upon this point. We therefore deduce an important point regarding the stereochemistry of the hydrochloride of (VII*a*) obtained by catalytic reduction of the 10-oximino-derivative (V) in the presence of hydrochloric acid. Since for steric reasons the $C_{(10)}$ and $C_{(12)}$ bonds in the lactam must be *cis* (cf. Protiva and Sorm, *Coll. Czech. Chem. Comm.*, 1948, **13**, 428; *Chem. Abs.*, 1949, **43**, 1730; Cronyn, *J. Org. Chem.*, 1949, **14**, 1013; Ginsburg, *ibid.*, 1950, **15**, 1003), and since inversion at $C_{(12)}$ must occur during the cyclisation to give the steric arrangement at $C_{(10)}$, $C_{(11)}$, and $C_{(12)}$ shown in (XVII), the substituted 10-amino-group and the 11-hydrogen atom, *before cyclisation*, must be *cis* to each other. For a *trans*-junction in the octalin system under discussion, this requires that the 10-amino- or substituted 10-amino-group shall assume the equatorial conformation. It may therefore be seen that, whatever primary product of the reduction of the 10-oximino-compound (V) is formed, the stable configuration to be expected is the one in which the 10-amino-group is equatorial. Whilst this argument is plausible, one cannot completely exclude the possibility, in view of the known racemisation of acylamino-acids by hot acids, that the configuration at $C_{(10)}$ changes *during* the cyclisation. A very small amount of an isomeric amine hydrochloride was isolated from the reduction of (V), presumably differing from (VII*a*) in configuration at $C_{(10)}$.

Experiments are being continued with methoxylated analogues of some of the compounds described above with a view of accomplishing the total synthesis of morphine.

Experimental

Improved Michael Condensation Procedures : trans-3-*Keto*-2-*phenyl*cyclo*hexylacetic Acid.*—A mixture of 2-phenyl*cyclo*hex-2-enone (50 g.), benzyl malonate (150 g.), and potassium *tert.*-butoxide (prepared from 1·33 g. of potassium and 20 ml. of *tert.*-butyl alcohol) was kept at 60° for 3 hr., then overnight at room temperature. Acetic acid (2·5 ml.) was added and then ethyl acetate to a volume of 250 ml. Palladium–charcoal (10%; 13 g.) was added and the mixture was hydrogenated at room temperature at an initial pressure of 60 lb./sq. in. (1 hr.). After filtration and evaporation the residue was heated at 170—180° for 10 min. in order to effect decarboxylation of the malonic acid. The residue was dissolved in ether and extracted several times with 10% sodium carbonate solution. Acidification gave a precipitate of *trans*-3-keto-2-phenyl*cyclo*hexylacetic acid (55 g., 82% overall), m. p. 125° (from benzene). The *dibenzyl* ester of the malonic acid was crystallised from the mixture which in some runs solidified; it had m. p. 91—92° (from ethanol) (Found : C, 76·0; H, 6·3. $C_{29}H_{28}O_5$ requires C, 76·3; H, 6·2%).

trans-3-Keto-2-(2 : 3-dimethoxyphenyl)*cyclo*hexylacetic acid was obtained similarly in 88% overall yield.

trans-3-*Keto*-2-*phenyl*cyclo*hexylacetonitrile.*—2-Phenyl*cyclo*hex-2-enone (90 g.), benzyl cyanoacetate (150 g.), and potassium *tert.*-butoxide (2·32 g. of potassium; 35 ml. of *tert.*-butyl alcohol) were treated as above. trans-α-*Cyano*-3-*keto*-2-*phenyl*cyclo*hexylacetic acid*, m. p. 110—112° (from 30% acetic acid), was obtained (Found : C, 70·2; H, 5·7. $C_{15}H_{15}O_3N$ requires C, 70·0; H, 5·8%). Decarboxylation at 190—200° for 10 min. in the presence of powdered soft glass gave trans-3-*keto*-3-*phenyl*cyclo*hexylacetonitrile* (97 g., 86%), which on recrystallisation from butanol melted at 102—103° (Found : C, 78·9; H, 6·9. $C_{14}H_{15}ON$ requires C, 78·9; H, 7·0%).

α-Cyano-α-2-(2 : 3-dimethoxyphenyl)-3-keto*cyclo*hexylacetic acid, identical with the product described in Part III (*loc. cit.*), was similarly obtained, in 94% yield. The acid was decarboxylated as above. Upon evaporative distillation (bath-temp. 250°; 0·01 mm.), *trans*-2-(2 : 3-dimethoxyphenyl)-3-keto*cyclo*hexylacetonitrile was obtained as an oil (82% overall yield). The *semicarbazone* melted at 181—182° (from ethanol) (Found : N, 20·8. $C_{15}H_{18}ON_4$ requires N, 20·7%).

(*a*, 1) *Introduction of an Amino-group at* $C_{(10)}$.—trans-α-*Amino*-3-*keto*-2-*phenyl*cyclo*hexylacetic acid* (II*a*). Methyl 3-keto-2-phenyl*cyclo*hexyl-α-nitroacetate (57·5 g.) was hydrogenated in ethanol (680 ml.) at 100°/120 atm. (initial) in the presence of Raney nickel (20 g.), 94% of the theoretical amount of hydrogen being absorbed during 1 hr. The catalyst was filtered off and the filtrate concentrated (water-pump) to 300 ml. Aqueous sodium hydroxide (20%; 100 g.)

was added and the mixture kept at room temperature for 24 hr. The pH was adjusted to 5·5 with acetic acid and the precipitate was filtered. The *amino-acid* had m. p. 185—188° (from water or aqueous ethanol) (yield 50%) [Found: C, 68·2; H, 6·8; amino-N (van Slyke), 5·7. $C_{14}H_{17}O_3N$ requires C, 68·0; H, 6·9; amino-N, 5·6%].

trans-α-*Amino*-2-(2 : 3-*dimethoxyphenyl*)-3-*keto*cyclo*hexylacetic acid* (II*b*), prepared analogously, had m. p. 200—210° (decomp.) (from water) (Found: N, 4·5. $C_{16}H_{21}O_5N$ requires N, 4·6%)

trans-3-*Keto*-2-*phenyl*cyclo*hexyl*-α-*phthalimidoacetic acid* (III). The amino-acid (15 g.) and phthalic anhydride (9 g.) were heated in benzene (35 ml.) for 1 hr. The benzene was allowed to evaporate and the temperature was raised to 180—190° for 30 min. After cooling, the *phthalimido-acid* was crystallised from ethanol; it had m. p. 227° (decomp.) (yield 60%) (Found: C, 69·8; H, 5·1. $C_{22}H_{19}O_5N$ requires C, 70·0; H, 5·1%).

trans-2-(2 : 3-*Dimethoxyphenyl*)-3-*keto*cyclo*hexyl*-α-*phthalimidoacetic acid*, prepared analogously (yield 75%), had m. p. 219—220° (decomp.) (from ethanol) (Found: C, 66·1; H, 5·7. $C_{24}H_{23}O_7N$ requires C, 65·9; H, 5·3%).

Cyclisation of (III). The phthalimido-acid (III) (1 g.) was treated with concentrated sulphuric acid (5 ml.), kept on the steam-bath for 10 min., then poured on ice. The product was extracted with ether, the extract was washed with sodium hydrogen carbonate solution to remove any uncyclised acid, and the solvent was evaporated. The residue of trans-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4 : 9-*diketo*-10-*phthalimidophenanthrene* (IV) after recrystallisation from acetic acid melted at 188° (Found: C, 73·5; H, 4·4. $C_{22}H_{17}O_4N$ requires C, 73·5; H, 4·7%).

4-*Ethylene glycol ketal of* trans-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4 : 9-*diketo*-10-*oximino-phenanthrene* (V). To the 4-ethylene glycol ketal of *trans*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4 : 9-diketophenanthrene (27·4 g.) (Part III) was added a solution of sodium ethoxide (2·76 g. of sodium; 55 ml. of dry ethanol). The mixture was chilled in ice, and *n*-amyl nitrite (18·4 ml.) was added in one portion. The mixture became cherry-red and was set aside at 0° for 48 hr. with occasional shaking. Acetic acid (8 ml.) and water (100 ml.) were added and the mixture was extracted with ether. The ethereal solution was extracted several times with Claisen alkali, the extracts were acidified with acetic acid, and the oily product was taken up in ether. The *product* crystallised from the ethereal solution (17 g.). An additional crop (2·5—4 g.) was obtained after concentration of the solution. Upon recrystallisation from a large volume of ethanol, an analytical sample could be obtained, with m. p. 182—184° (decomp.; green melt) (Found: C, 66·8; H, 5·7. $C_{16}H_{17}O_4N$ requires C, 66·9; H, 5·7%). The crude crystalline material was very slightly soluble in most solvents. After being washed with ether, it was sufficiently pure to be used for further transformations.

4-*Ethylene glycol ketal of* trans-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4 : 9-*diketo*-5 : 6-*dimethoxy*-10-*oximinophenanthrene* was obtained similarly from the 4-ethylene glycol ketal of the corresponding methoxy-diketone, in 62% yield, and with m. p. 192—195° (decomp.) (from ethanol) (Found: C, 62·2; H, 5·5. $C_{18}H_{21}O_6N$ requires C, 62·2; H, 6·0%).

trans-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*Octahydro*-4 : 9-*diketo*-10-*phthalimidophenanthrene* (IV). (i) Compound (V) (6 g.), suspended in alcohol (200 ml.), was hydrogenated (10 hr.) in the presence of 10% palladium–charcoal (1 g.) at 60 lb./sq. in. (initial). The solvent was distilled off in a high vacuum (bath-temp. ≯20°). The 4-ethylene glycol ketal (VI*a*) (5·4 g.) of 10-amino-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4 : 9-diketophenanthrene was obtained as a brown oil.

When hydrochloric acid (2·2 ml.) was added to the above mixture before hydrogenation, the *hydrochloride of* trans-10-*amino*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4 : 9-*diketophenanthrene* (VII) (5·5 g.) was obtained with m. p. 228—231° (from ethanol–ether) (Found: C, 63·3; H, 6·2; Cl, 13·5. $C_{14}H_{16}O_2NCl$ requires C, 63·3; H, 6·0; Cl, 13·4%). An isomeric hydrochloride, m. p. 190—192° (from methanol), was isolated from the mother-liquor (0·1 g.) (Found: C, 63·0; H, 6·0; Cl, 13·2. $C_{14}H_{16}O_2NCl$ requires C, 63·3; H, 6·0; Cl, 13·4%).

(ii) The ketal (VI*a*) (1·9 g.) and phthalic anhydride (1·16 g.) were heated together at 170—190° for 30 min. After cooling, the glass was dissolved in acetic acid and the solution deposited crystals (2·1 g.), m. p. 217—219°, of the 4-*ethylene glycol ketal* of *trans*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4 : 9-diketo-10-phthalimidophenanthrene (Found: C, 71·6; H, 5·2. $C_{24}H_{21}O_5N$ requires C, 71·5; H, 5·2%).

(iii) The phthalimido-ketal (500 mg.) was kept in ethanol (25 ml.) containing hydrochloric acid (1 ml.) at 50—60° for 5 hr. The solvent was removed. The residue, recrystallised from acetic acid, had m. p. 187—188°. This product did not depress the m. p. of *trans*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4 : 9-diketo-10-phthalimidophenanthrene (IV) (see above).

(*a*, 2) *Introduction of an Ester Group at* $C_{(10)}$.—*4-Ethylene glycol ketal of* trans-10-*ethoxalyl*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4 : 9-*diketophenanthrene* (VI*b*). To a stirred mixture, kept at 40—45°, of the 4-ethylene glycol ketal (26 g.) of *trans*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4 : 9-diketophenanthrene, ethyl oxalate (30 g.), sodium hydride (5 g.), and dry ether (125 ml.), in an atmosphere of nitrogen, a few drops of dry ethanol were added to initiate reaction. The mixture was cooled in ice, water was added, and the solvent layer was separated and extracted with several portions of 3% sodium hydroxide solution. The combined alkaline extracts were acidified with cold dilute hydrochloric acid. The *product* (2·8 g.) had m. p. 99—102° (from ethanol) (Found : C, 67·3; H, 5·9. $C_{20}H_{22}O_6$ requires C, 67·0; H, 6·2%). When sodium methoxide was used as condensing agent the yield was 10—15%.

4-Ethylene glycol ketal of ethyl trans-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4 : 9-*diketophenanthrene*-10-*carboxylate* (VI*c*). The 10-ethoxalyl compound (10 g.) was decarbonylated by powdered soft glass at 160—170° (10 min.). The *product* (7·2 g.) had m. p. 117—118° (from aqueous methanol) (Found : C, 68·6; H, 6·4. $C_{19}H_{22}O_5$ requires C, 69·1; H, 6·7%).

Reduction of (VI*c*). Compound (VI*c*) (10 g.) in dry ethanol (100 ml.) was hydrogenated in the presence of 10% palladium–charcoal (1 g.), at 70°/60 lb./sq. in. (initial), 1 mol. of hydrogen being absorbed during 3 hr. The *4-ethylene glycol ketal* (7·1 g.) of ethyl *trans*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-9-hydroxy-4-ketophenanthrene-10-carboxylate (7·1 g.) melted at 102—103° (from heptane) (Found : C, 68·8; H, 7·1. $C_{19}H_{24}O_5$ requires C, 68·7; H, 7·3%).

Acid cleavage of (VI*c*). A mixture of (VI*c*) (1 g.), 95% ethanol (25 ml.), water (7 ml.), and concentrated hydrochloric acid (0·2 ml.) was kept at 60° for 1 hr., then overnight at room temperature. After neutralisation with solid sodium hydrogen carbonate, filtration, and dilution with water, crystals were isolated (m. p. 90°). Admixture with 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4 : 9-diketophenanthrene gave a large depression in m. p. but admixture with its 4-ethylene glycol ketal gave no depression.

The 4-ethylene glycol ketal of *trans*-10-ethoxalyl-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4 : 9-diketo-5 : 6-dimethoxyphenanthrene was obtained analogously, except that the reaction was carried out in ether–benzene, as an oil in 85% yield and was used in the next reaction without further purification.

4-Ethylene glycol ketal of ethyl trans-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4 : 9-*diketo*-5 : 6-*dimethoxyphenanthrene*-10-*carboxylate*. Decarbonylation of the ethoxalyl compound as above gave the 10-*carbethoxy*-derivative (75%), m. p. 131—132° (from ethanol) (Found : C, 64·1; H, 6·6. $C_{21}H_{26}O_7$ requires C, 64·6; H, 6·7%).

Alkaline cleavage of the 4-ethylene glycol ketal of ethyl trans-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4 : 9-*diketo*-5 : 6-*dimethoxyphenanthrene*-10-*carboxylate*. The ester (0·3 g.) was refluxed with 50% aqueous potassium hydroxide (3 ml.) for 2 hr. (cf. Bachmann, Cole, and Wilds, *J. Amer. Chem. Soc.*, 1940, **62**, 833). Water was added. The product which crystallised had m. p. 137—138°. On admixture with authentic 4-ethylene glycol ketal of *trans*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4 : 9-diketo-5 : 6-dimethoxyphenanthrene (m. p. 137—139°), it melted at 137—139°.

Lactone (VIII). A mixture of methyl oxalate (2·4 g.), sodium methoxide (1·4 g.) and benzene (10 ml.), was refluxed under nitrogen for 10 min. To this was added a solution of *trans*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4-ketophenanthrene (2 g.) in benzene (15 ml.). An orange colour developed immediately. The mixture was stirred under nitrogen at room temperature for 5 hr. A yellow suspension was obtained. This was filtered and the solid sodium salt washed with benzene and ether. The salt was insoluble in water. It was suspended in dioxan (50 ml.), and hydrochloric acid added to just neutral reaction, causing the free ester to dissolve. Sodium chloride was filtered off and water added to the filtrate. A crystalline *lactone* (VIII) (1·8 g.) was obtained, having m. p. 250° (decomp. with previous sintering) (from acetic acid) (cf. Bachmann, Fujimoto, and Wick, *loc. cit.*), insoluble in ethanol and giving no reaction with ferric chloride in ethanol but in dioxan an immediate deep red colour (Found : C, 75·4; H, 5·5. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·6%).

Lactone O-methyl ether (IX). The lactone (VIII) (1 g.) was treated with ethereal diazomethane. The lactone dissolved and the *O*-methyl ether, m. p. 146—147° (from ethanol), separated.

Lactone (X). This substance was obtained similarly from methyl oxalate (2·4 g.), sodium methoxide (1·4 g.), and *trans*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4 : 9-diketophenanthrene (2·1 g.) in benzene. In this case a cherry-red gel was obtained. The brick-red sodium salt was dissolved in water and acidified with dilute hydrochloric acid. The *lactone* (X) (1·1 g.), crystallised from methanol, had m. p. 256—257° (decomp.). The ethanolic solution gave a

negative ferric chloride test but its solution in dioxan gave a very deep red-brown colour with this reagent (Found: C, 71·9; H, 4·5. $C_{16}H_{12}O_4$ requires C, 71·6; H, 4·5%).

cis-12-2′-*Cyanoethyl*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4-*keto*-3-*methoxalylphenanthrene*. This compound was obtained similarly from methyl oxalate (1·2 g.), sodium methoxide (0·6 g.), and *cis*-12-2′-cyanoethyl-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4-ketophenanthrene (see below) (1·27 g.) in benzene. After 4 hr.' stirring under nitrogen at room temperature, an orange gel was obtained. Water was added and the benzene solution was extracted with 2% sodium hydroxide solution. Upon acidification of the alkaline extract and scratching, the oil solidified. The *product* had m. p. 131—133° (from methanol) and gave an immediate cherry-red colour with ferric chloride. The yield was 0·7 g. (quantitative, based on unrecovered material) (Found: N, 4·1. $C_{20}H_{21}O_4N$ requires N, 4·1%).

Methyl cis-12-2′-*cyanoethyl*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4-*ketophenanthrene*-3-*carboxylate* was obtained in the usual way. It had m. p. 130° (from ethanol) and gave a purple colour with ferric chloride, which developed slowly (Found: N, 4·5. $C_{19}H_{21}O_3N$ requires N, 4·5%).

(*a*, 3) *Alkylation of* 2-*Phenyl*cyclo*hexanone*.—*Model experiments*. (i) *With chloroacetonitrile*. To a refluxing suspension of sodamide (2·5 g.) in dry ether (35 ml.) was added during 1 hr. a solution of 2-phenyl*cyclo*hexanone (10 g.) in dry ether (17·5 ml.) and dry benzene (7·5 ml.). After an additional hr. of refluxing (until ammonia evolution was complete), the milky solution was cooled and a solution of chloroacetonitrile (6·1 g.) in dry ether (17·5 ml.) was added. The mixture became warm and refluxing was maintained for 3 hr. After cooling, water was added, and the organic layer was separated and washed with water and dried. After evaporation of the solvents, the residue was distilled *in vacuo*. The product (8·5 g.) was a yellow oil, b. p. 145—150°/0·4 mm., which consisted mainly of 2-*cyanomethyl*-2-*phenyl*cyclo*hexanone* (Found: C, 78·8; H, 7·2. $C_{14}H_{15}ON$ requires C, 78·8; H, 7·1%), as shown by the practically quantitative preparation of a benzylidene derivative.

2-*Keto*-1-*phenyl*cyclo*hexylacetic acid*. The above nitrile (1·4 g.) was refluxed with acetic acid (28 ml.) and concentrated hydrochloric acid (14 ml.) for 12 hr. (cf. Bachmann and Wick, *J. Amer. Chem. Soc.*, 1950, **72**, 3388). The acid isolated formed colourless needles, m. p. 133—134° (from acetic acid) (Found: C, 72·4; H, 7·0. Calc. for $C_{14}H_{16}O_3$: C, 72·4; H, 6·9%). Boekelheide (*ibid.*, 1950, **72**, 712) reports m. p. 130·5—131°.

(ii) *With ethyl iodoacetate*. Ethyl iodoacetate (18 g.) was used as the alkylating agent under similar conditions. The oily product (11 g.) boiled at 160—170°/2 mm. and formed an orange 2 : 4-*dinitrophenylhydrazone*, m. p. 163—164° (from ethanol) (Found: C, 59·8; H, 5·5. $C_{22}H_{24}O_6N_4$ requires C, 60·0; H, 5·5%). The position of the carbethoxymethyl group in this substance was not ascertained; attempted preparation of the benzylidene derivative showed that the product was a mixture of isomers apparently containing the carbethoxymethyl group in either of the two positions adjacent to the carbonyl group. Boekelheide (*loc. cit.*) reported alkylation with ethyl bromoacetate without, however, indicating the degree of possible alkylation in both positions.

(iii) *With* 2-*benzyloxyethyl methanesulphonate* (cf. Newman and Magerlein, *J. Amer. Chem. Soc.*, 1947, **69**, 943). To a stirred solution of methanesulphonyl chloride (114 g.) and ethylene glycol monobenzyl ether (137 g.) in dry ether (200 ml.) at −10° was added pyridine (112 g.) during 4 hr. The temperature was then allowed to rise and the mixture was stirred at 0° for 2 hr. Cold water was added and the product was extracted with ether, the ethereal solution was washed and dried, and the solvent was removed *in vacuo*. Small samples of the *sulphonate* could be distilled without decomposition (b. p. 120—125°/0·01 mm.) (Found: S, 13·9. $C_{10}H_{14}O_4S$ requires S, 13·8%). The material as obtained from this preparation was sufficiently pure for further work.

Alkylation was carried out as described above, with [for the same amount of 2-phenyl*cyclo*hexanone (10 g.)] 2-benzyloxyethylmethanesulphonate (16 g.) in ether (25 ml.) and benzene (25 ml.). Distillation yielded an oil consisting of practically only one isomer, 2-2′-*benzyloxyethyl*-2-*phenyl*cyclo*hexanone* (16 g.), b. p. 170—175°/0·01 mm. (Found: C, 81·5; H, 7·5. $C_{21}H_{24}O_2$ requires C, 81·8; H, 7·8%). The *semicarbazone* melted at 212—213° (from ethanol) (Found: N, 11·6. $C_{22}H_{27}O_2N_3$ requires N, 11·5%). The veratrylidene and benzylidene derivatives were prepared in nearly quantitative yield but neither crystallised.

2-2′-*Hydroxyethyl*-2-*phenyl*cyclo*hexanone*. The above benzyl ether (6·2 g.) in alcohol (50 ml.) was hydrogenated in the presence of 10% palladium charcoal (0·6 g.) at 60 lb./sq. in. (initial). One mol. of hydrogen was taken up during 2 hr. Distillation gave a colourless oily *alcohol*, b. p. 115—120°/0·05 mm. (Found: C, 77·2; H, 8·1. $C_{14}H_{18}O_2$ requires C, 77·0; 8·3%).

Alkylation of trans-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4-*ketophenanthrene*. To a refluxing suspension of sodamide (1·2 g.) in dry ether (25 ml.) and benzene (15 ml.) was added, during 1 hr., a solution of the ketone (5 g.) in ether (15 ml.) and benzene (5 ml.). The mixture was refluxed for 5 hr. (ammonia evolution). After cooling, methyl iodide (6 g.) was added. Almost immediately sodium iodide was precipitated. Refluxing was continued for 3 hr. and the product was isolated in the usual way. The product, b. p. 128—134°/0·05 mm., consisted mainly of 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4-*keto*-12-*methylphenanthrene* (Found : C, 83·9; H, 8·7. $C_{15}H_{18}O$ requires C, 84·1; H, 8·4%). The *semicarbazone* had m. p. 250—251° (from butanol) (Found : N, 15·8. $C_{16}H_{21}ON_3$ requires N, 15·5%). The 3-*benzylidene* compound, obtained in 77% yield from the oil, had m. p. 200—201° (from ethanol) (Found : C, 87·0; H, 7·6. $C_{22}H_{22}O$ requires C, 87·4; H, 7·3%).

Chloroacetonitrile and ethyl iodoacetate were also used as alkylating agents in this case but chromatography (on alumina) of the 2 : 4-dinitrophenylhydrazone mixture obtained from the reaction products showed the presence of three products in each case. These reactions were therefore not studied further.

cis-12-2′-*Cyanoethyl*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4-*ketophenanthrene* (XII*a*).—To a solution of *trans*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4-ketophenanthrene (2·8 g.) in dioxan (25 ml.) were added 30% benzyltrimethylammonium hydroxide (Triton B) (0·3 ml.) and a solution of acrylonitrile (1 g.) in dioxan (3 ml.), and the mixture was stirred for 2 hr. At the start, the temperature rose to 40°. Dilute hydrochloric acid was added, the mixture was extracted with ether, and the solvents were evaporated. The solid residue was taken up in boiling heptane and the solution was filtered to remove a small amount of bis-2-cyanoethyl adduct (0·2 g.). From the filtrate was obtained the crystalline *product*, m. p. 110—112° (from heptane or ethanol) (75%) (Found : N, 5·4. $C_{17}H_{19}ON$ requires N, 5·5%). 3 : 12-*Bis*-2′-*cyanoethyl*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydrophenanthrene* had m. p. 165—166° (from ethanol) (Found : N, 9·2. $C_{20}H_{22}ON_2$ requires N, 9·5%). Only unchanged starting material was recovered from the mother-liquor.

The adduct (XII*a*) (0·3 g.), veratraldehyde (0·25 g.), ethanol (3·4 ml.), and 15% aqueous sodium hydroxide (0·8 ml.) were kept at room temperature for 1 week. The yellow 3-*veratrylidene* derivative, recrystallised from ethanol, then from *n*-propanol, had m. p. 163—165° (yield 75%) (Found : C, 77·8; H, 6·9. $C_{26}H_{27}O_3N$ requires C, 77·8; H, 6·7%).

cis-12-2′-*Carboxyethyl*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4-*ketophenanthrene* (XII*b*).—The compound (XII*a*) (1·14 g.), acetic acid (7·5 ml.), concentrated hydrochloric acid (2·5 ml.), and water (25 ml.) were refluxed under nitrogen for 15 hr. Water was added and the *acid* was recrystallised from heptane–benzene (yield, 90%). Recrystallised finally from aqueous methanol it had m. p. 110—112° (Found : C, 75·4; H, 7·5. $C_{17}H_{20}O_3$ requires C, 75·0; H, 7·3%). The *semicarbazone* melted at 219° (decomp.) (from ethanol) (Found : N, 12·8. $C_{18}H_{23}O_3N_3$ requires N, 12·8%).

cis-12-2′-*Cyanoethyl*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4 : 9-*diketophenanthrene* (XI*a*).—Compound (I*b*) (21·4 g.) was dissolved in dioxan (100 ml.), and Triton B (30%; 1 ml.) was added. Acrylonitrile (8 ml.) in dioxan (20 ml.) was added with stirring; the temperature rose to 42°. After 2 hr. the mixture was acidified with dilute hydrochloric acid and the solvent was removed *in vacuo*. The residue was dissolved in ethanol (150 ml.). The *product* crystallised slowly [m. p. 112—113° (from ethanol); yield, 11·5 g.]. A second crop of product (2·3 g.) could be isolated from the mother-liquor (Found : C, 76·5; H, 6·4. $C_{17}H_{17}O_2N$ requires C, 76·3; H, 6·4%). The 3 : 10-*dibenzylidene* derivative, prepared in 90% yield, had m. p. 206—207° (from acetic acid) (Found : C, 84·2; H, 5·8; N, 3·1. $C_{31}H_{25}O_2N$ requires C, 84·0; H, 5·6; N, 3·2%). The 3 : 10-*dipiperonylidene* derivative melted at 230—231° (from acetic acid) (Found : N, 2·9. $C_{33}H_{25}O_6N$ requires N, 2·6%) and the 3 : 10-*diveratrylidene* derivative at 182—183° (from propanol) (Found : C, 74·5; H, 5·5; N, 2·9. $C_{35}H_{33}O_6N$ requires C, 74·6; H, 5·8; N, 2·5%).

cis-12-2′-*Carboxyethyl*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4 : 9-*diketophenanthrene* (XI*b*).—From the nitrile (XI*a*) (5·1 g.) was obtained, as described for the hydrolysis of (XII*a*), the *acid* (4·5 g.), m. p. 155° (from aqueous methanol) (Found : C, 71·6; H, 6·3. $C_{17}H_{18}O_4$ requires C, 71·3; H, 6·3%).

Reduction of (XI*b*).—Compound (XI*b*) (3 g.) was hydrogenated in acetic acid (50 ml.) in the presence of 10% palladium charcoal (0·3 g.) at 60—70°/60 lb./sq. in. (initial). Two mols. of hydrogen were absorbed during 2 hr. The product, isolated in the usual way, had m. p. 110—112° (from aqueous methanol) and proved to be identical with (XII*b*) (see above).

Huang-Minlon Reduction of (XII*b*).—The keto-acid (XII*b*) (5 g.) was refluxed with di-

ethylene glycol (50 ml.), potassium hydroxide (4 g.), and 85% hydrazine hydrate (6 ml.) for 90 min. The condenser was then removed, the temperature was raised to 195—200°, and the mixture refluxed for 5 hr. The cooled mixture was acidified with dilute hydrochloric acid. The resulting precipitate of cis-12-2′-*carboxyethyl*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydrophenanthrene* (XIII*a*), recrystallised from aqueous methanol, had m. p. 111—113° (90%) (Found : C, 79·3; H, 8·5. $C_{17}H_{22}O_2$ requires C, 79·0; H, 8·6%).

cis-12-2′-*Aminoethyl*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydrophenanthrene* (XIII*b*).—The acid (XIII*a*) (2 g.) was refluxed with thionyl chloride (10 ml.) in benzene (10 ml.) for 1 hr. Volatile material was removed *in vacuo* at <30°; benzene (5 ml.) was added and the mixture was again subjected to vacuum-distillation. The yellow residue was dissolved in acetone (10 ml.) and to the ice-cold solution was added sodium azide (2·5 g.) in water (6 ml.) in one portion, with ice-cooling. After 10 min. the mixture was diluted with water, and the oil which precipitated was taken up in ether. The ethereal extract was washed with aqueous sodium hydrogen carbonate solution and dried (Na_2SO_4). The ether was evaporated off at the water pump at <25°. The brown azide was warmed with acetic acid (15 ml.) (<80°) until nitrogen evolution ceased (about 30 min.), then heated at 100° for 1 hr. Concentrated hydrochloric acid (10 ml.) was added and the mixture refluxed for 12 hr. The mixture was concentrated *in vacuo*. The hydrochloride. m. p. 250° (75%), of the amine crystallised and was washed with ether but not purified further. The *picrate*, prepared from an aqueous solution of the hydrochloride, had m. p. 182—183° (decomp.) (from aqueous ethanol) (Found : C, 57·6; H, 5·4; N, 12·4. $C_{22}H_{26}O_7N_4$ requires C, 57·6; H, 5·7; N, 12·2%).

cis-12-2′-*Dimethylaminoethyl*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydrophenanthrene* (XIII*c*).—The crude hydrochloride of (XIII*b*) (1·4 g.) in water (3 ml.) was basified with sodium hydroxide and extracted with ether. The ether was evaporated and to the residue were added with cooling 90% formic acid (1·3 g.) and 30% formaldehyde solution (0·56 ml.). The mixture was placed in a bath at 90—100°. Evolution of carbon dioxide began within a few sec.; the flask was removed from the bath until the evolution subsided (10 min.), and then heated at 95—100° for 8 hr. Concentrated hydrochloric acid (2 ml.) was added and the mixture was concentrated at the water-pump for 2 hr. at 100°. The crystalline material which formed (1·5 g.) was converted into the *picrate* of the tertiary amine in ethanolic solution (Found : C, 59·0; H, 6·2; N, 11·4. Calc. for $C_{24}H_{30}O_7N_4$: C, 59·3; H, 6·2; N, 11·5%). This had m. p. 187—188·5° (from ethanol), alone or mixed with an authentic sample of (XIII*c*), kindly furnished by Prof. R. Grewe. Mixed with an authentic specimen of the *trans*-isomer of (XIII*c*), kindly supplied by Dr. Marshall Gates, it melted at 169—175°.

1 : 2 : 9 : 10 : 11 : 12-*Hexahydropyrrolidino*(2′ : 3′-4 : 12)*phenanthrene* (XV).—When the acid (XII*b*) was treated with thionyl chloride as described for (XIII*a*) a product melting at about 140° with the properties of a lactone was obtained. On attempted crystallisation from ethanol, no crystalline material could be recovered, apparently owing to ester formation.

To the keto-acid (XII*b*) (1 g.) in benzene (5 ml.) was added thionyl chloride (5 ml.) and the mixture kept for 48 hr. at −5° to −10°. The solvent and excess of chloride were removed in a high vacuum and the Curtius reaction carried out as described above for (XIII*a*). After 12 hr.' refluxing with concentrated hydrochloric acid, the mixture was concentrated *in vacuo* and to the residual brown oil was added water (2 ml.). The mixture was extracted with ether to remove non-basic material. The aqueous solution was strongly basified with sodium hydroxide and extracted with ether. The ethereal solution was extracted with 2N-hydrochloric acid. Upon concentration of the acid layer, the hydrochloride of (XV) was obtained as a hygroscopic brown oil in 40% overall yield.

1 : 2 : 9 : 10 : 11 : 12-*Hexahydro*-9-*ketopyrrolidino*(2′ : 3′-4 : 12)*phenanthrene* (XVI*a*).—*Method* (*a*). The acid chloride was prepared from (XI*b*) as described above for (XII*b*) at −5° to −10°. The azide was prepared and converted into the amine as above but in this case it was possible to isolate the *pyrrolidine* in 20% overall yield as crystals, m. p. 87—89° (from hexane) (Found : C, 80·4; H, 7·1; N, 5·9. $C_{16}H_{17}ON$ requires C, 80·3; H, 7·2; N, 5·9%).

N-*Methyl derivative* (XVI*b*). Methylation was carried out by Bachmann and Fornefeld's method (*J. Amer. Chem. Soc.*, 1951, **73**, 52). The pyrrolidine (XVI*a*) (1·5 g.) was treated in ethyl methyl ketone (3 ml.) with methyl sulphate (0·8 g.) at room temperature. After 10 min. the solution became slightly warm and after several hr. two layers were formed The mixture was left overnight, the lower layer then crystallising. After a total of 16 hr., the mixture was refluxed for 1 hr., water (5 ml.) was added, and refluxing was continued for 3 additional hr. Water was added, followed by aqueous sodium hydroxide. A solid amine was precipitated; it was taken up in ether. Removal of the ether yielded the yellow N-*methylpyrrolidine* (XVI*b*),

m. p. 132—133° (from ethanol) (overall yield, 20%) (Found : N, 5·5. $C_{17}H_{19}ON$ requires N, 5·5%). This autoxidised rapidly in solution, to give brown material.

Method (*b*). The acid (XI*b*) (6·45 g.) was treated with an excess of diazomethane in ether. Immediately after the nitrogen evolution ceased, acetic acid was added. The ethereal solution was washed with sodium hydrogen carbonate solution, then water, and dried (Na_2SO_4). Evaporation yielded an oil which was treated in ethanol (25 ml.) with 100% hydrazine (10·5 ml.). After 3 hr.' refluxing, the volatile material was removed *in vacuo* and the glassy residue was dissolved in 3N-hydrochloric acid (180 ml.). Ether (100 ml.) was added to form an upper layer, the mixture chilled in an ice-bath, and sodium nitrite (10 g.) in water (90 ml.) was added with cooling. The ethereal layer was separated and the aqueous layer extracted once with ether. The combined ethereal solutions were washed with water, and sodium hydrogen carbonate solution, and dried (Na_2SO_4). The ether was removed *in vacuo* (below 25°) and the residual brown oil was treated as in method (*a*) with acetic acid. The subsequent working up was as in method (*a*) and the pyrrolidine (XVI*a*) was obtained in 20% overall yield. The product thus obtained was purer than that formed by method (*a*). Admixture gave no m. p. depression.

Ketal of (XI*a*).—Compound (XI*a*) (2 g.), ethylene glycol (6 ml.), toluene-*p*-sulphonic acid (0·1 g.), and toluene (20 ml.) were refluxed for 7·5 hr., during which 4·5 ml. were collected as a lower layer in an azeotropic separator. The mixture was cooled and poured into dilute potassium carbonate solution. After ether-extraction and removal of the solvents, the 4 : 9-*bisethylene glycol ketal* of 12-2′-cyanoethyl-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4 : 9-diketophenanthrene crystallised on trituration with a fresh portion of ether [yield, 1·7 g.; m. p. 136—137° (from ethanol)]. There was no carbonyl absorption in the infra-red (Found : C, 70·9; H, 7·1. $C_{21}H_{25}O_4N$ requires C, 71·0; H, 7·1%).

When the ketal was heated for 30 min. with 20% aqueous ethanol containing a trace of hydrochloric acid, the starting material (XI*a*) was recovered.

Cyanoethylation of 3-*Keto*-2-*phenyl*cyclo*hexylacetonitrile*.—The nitrile (10·4 g.) and Triton B (1 ml.) in dioxan (80 ml.) were treated with acrylonitrile (4 ml.) in dioxan (20 ml.), the temperature rising to 37°. After 2 hr.' stirring, the mixture was acidified with dilute hydrochloric acid and the dioxan removed *in vacuo*. The residue was dissolved in ethanol (100 ml.) and crystalline material was obtained in the hot solution. After filtration at 40°, 2 : 6 : 6-*tris*-2′-*cyanoethyl*-3-*keto*-2-*phenyl*cyclo*hexylacetonitrile* (3 g.) was obtained, having m. p. 161—162° (from ethanol) (Found : N, 12·6. $C_{21}H_{23}ON_3$ requires N, 12·6%).

cis-12-*Carbamylmethyl*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4 : 9-*diketophenanthrene* (XI*c*).—*Method a*. To the oily acid chloride prepared from 1 g. of (XI*b*) was added benzene (50 ml.), and dry ammonia was passed through the solution at 5—10° for 2 hr. The amide, precipitated as tan-coloured crystals (70%), had m. p. 205° (from aqueous acetic acid).

Method b. To the acid (XI*b*) (1 g.) was added an excess of diazomethane in ether. After 5 min., the solution was evaporated and the residue was dissolved in dry ethanol (10 ml.). Dry ammonia was passed through the solution at 0° for 3 hr. The mixture was kept at room temperature for 48 hr., giving the *amide*, m. p. 205—206° (from dilute acetic acid) (90%) (Found : C, 71·5; H, 6·6. $C_{17}H_{19}O_3N$ requires C, 71·6; H, 6·7%).

Halogeno-amides from (VI*a*).—Compound (VI*a*) (1 g.) was added to a solution of sodium acetate (2·5 g.) in acetic acid (5 ml.). To this ice-cold solution was added slowly with efficient stirring chloroacetyl chloride (3 ml.). The 4-*ethylene glycol ketal* of *trans*-10-chloroacetamido-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4 : 9-diketophenanthrene was deposited as crystals, m. p. 199—200° (from ethanol) (Found : Cl, 9·8. $C_{18}H_{20}O_4NCl$ requires Cl, 10·1%).

The *bromoacetoamido-ketal*, obtained analogously from bromoacetyl chloride, had m. p. 210—211° (from ethanol) (Found : Br, 20·5. $C_{18}H_{20}O_4NBr$ requires Br, 20·3%).

The *iodoacetamido-ketal* had m. p. 200—201° (from ethanol) (Found : I, 30·0. $C_{18}H_{20}O_4NI$ requires I, 28·8%).

Hydrolysis of the ketals in aqueous ethanol containing a catalytic amount of hydrochloric acid afforded the corresponding free halogenoamides (VII*b*) : *chloro-amide*, m. p. 186° (from methanol) (Found : Cl, 11·5. $C_{16}H_{16}O_3NCl$ requires Cl, 11·6%); *bromo-amide*, m. p. 200—201° (from ethanol) (Found : Br, 22·7. $C_{16}H_{16}O_3NBr$ requires Br, 22·9%); *iodo-amide*, m. p. 178—179° (from ethanol) (Found : I, 31·7. $C_{16}H_{16}O_3NI$ requires I, 32·0%).

Attempted intramolecular cyclisation of each of the three free halogeno-amides in the presence of alkaline catalysts, such as sodamide, potassium *tert.*-butoxide, lithium amide, under a variety of conditions, failed. Bromination of the bromo-amide, m. p. 200—201°, in acetic acid solution with one mol. of bromine followed by treatment with activated zinc led to no definable product.

trans-10-*Acetoxyacetamido*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4 : 9-*diketophenanthrene* (VII*c*). —The amine hydrochloride (cf. VII*a*) (3 g.) was suspended in cold chloroform (50 ml.) and pyridine (2 g.) was added and the mixture was stirred with cooling until all of the solid had dissolved. Acetylglycolloyl chloride (1·8 g.) in chloroform (10 ml.) was added with stirring and cooling during 1 hr., and the mixture finally refluxed for 30 min. The solution was cooled and washed several times with water. The solvent was evaporated. The *amide* (3·4 g.), crystallised from ethanol or toluene, had m. p. 205° (Found : C, 65·5; H, 5·8. $C_{18}H_{19}O_5N$ requires C, 65·6; H, 5·8%). We are indebted to Dr. Orrie M. Friedman for suggesting the use of acetylglycolloyl chloride.

Diketo-lactam (XVII).—(*a*) The acetoxy-amide (VII*c*) (4 g.), ethylene glycol (10 g.), toluene (25 ml.), benzene (14 ml.), and toluene-*p*-sulphonic acid (0·1 g.) were heated together under reflux for 9 hr., during which 6·5 ml. of liquid were collected as lower layer in an azeotropic separator. The mixture was cooled and solid sodium methoxide was added to neutralise the acid present. After being washed with water, the organic layer was evaporated to dryness; the residue was triturated with light petroleum. The solid *ketal* obtained (2·3 g.) recrystallised from toluene and had m. p. 240—241° (Found : C, 69·1; H, 6·0. $C_{18}H_{19}O_4N$ requires C, 69·0: H, 6·1%). The infra-red absorption spectrum showed bands at 2·95, 5·93, and 6·02 μ.

(*b*) The ketal (2 g.) on treatment with aqueous ethanol containing hydrochloric acid at 60° for 2 hr. gave the free *diketo-lactam* (XVII), m. p. 257—258° (from ethanol or benzene–light petroleum) (Found: C 71·2; H, 5·5. $C_{16}H_{15}O_3N$ requires C, 71·4; H, 5·6%). The infra-red absorption spectrum showed bands at 2·95, 5·85, 5·92, and 6·02 μ. A mixture with its ketal melted at 213—248°.

N-*Methylmorphinan* (XIX).—(*a*) The diketo-lactam (XVII) (250 mg.) was refluxed with diethylene glycol (6 ml.), potassium hydroxide (0·42 g.), and 100% hydrazine (1 g.) for 8 hr. The condenser was removed and the internal temperature was raised to 195—200° and kept thereat for 2 hr., and finally the mixture was refluxed for 4 hr. The resulting dark brown solution was cooled and poured into an excess of dilute hydrochloric acid. The resulting lactam was obtained as a gum (140 mg.); it was triturated alternately with dilute acid, dilute alkali, and water and then dried *in vacuo*. The infra-red absorption spectrum showed a band at 6·01 μ (corresponding to the lactam) but the bands at 5·85 and 5·92 μ were absent.

(*b*) The gummy lactam was dissolved in dry ether (25 ml.) and refluxed with lithium aluminium hydride (1 g.) in dry ether (25 ml.) for 145 hr. The excess of reducing agent was decomposed by an equivalent amount of water, and the ethereal solution was washed with alkali and with water and dried (KOH). Evaporation *in vacuo* afforded a yellow oil (68 mg.).

(*c*) Formic acid (90%; 0·5 ml.) was carefully added to the above amine (68 mg.) with ice-cooling, and then 30% formaldehyde solution (0·2 ml.). The mixture was heated at 95—100° for 8 hr. After cooling, hydrochloric acid was added and the mixture concentrated *in vacuo*. The semi-solid residue was treated with acetone and ether. *N*-Methylmorphinan hydrochloride (47 mg.), m. p. 229—231°, was obtained (Found : Cl, 12·7. Calc. for $C_{17}H_{23}NCl$: Cl, 12·8%). Grewe and Mondon (*loc. cit.*) report m. p. 231—233°.

The hydrochloride was converted into the free base, m. p. 59—60°. Grewe and Mondon report m. p. 61°. The sulphate, m. p. 205° (from alcohol–ether), on admixture with an authentic sample (m. p. 205°), kindly supplied by Prof. R. Grewe, gave no m. p. depression. The micro-infra-red absorption spectrum, carried out with single crystals of the specimens of *N*-methylmorphinan sulphate, conclusively demonstrated the identity of the specimens over the whole absorption range.

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