544. *Syntheses in the Morphine Series. Part V.* Model Experiments for the Introduction of Oxygen at* $C_{(6)}$.

By Dov Elad and David Ginsburg.

In the substituted *cyclo*hexanones and octahydro-oxophenanthrenes investigated, the most efficient method for introduction of a carbonyl group α to an existing one is an indirect one, through preparation of the α-hydroxyimino-ketones.

Attempted conversion of the stable methyl *trans*-3-oxo-2-phenyl*cyclo*hexylacetate and *trans*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4-oxophenanthrene into the corresponding *cis*-isomers, by halogenation, dehydrohalogenation, and hydrogenation, failed.

In Part IV * the synthesis of a tetracyclic compound (I*a*) was described. This substance bears an oxygen function at $C_{(5)}$ which can be used as a key to ring C of morphine (II). It is necessary first to introduce an oxygen atom at $C_{(6)}$ as this position bears a hydroxyl group in morphine itself. Subsequently, the 5-oxygen atom in a substance such as (I*b*) can be removed with a view to obtaining dihydrothebainone as the final product in the reaction sequence. Alternatively, the 5-oxygen atom can be utilised together with the 4-methoxy group with a view to obtaining dihydrocodeinone as the ultimate product. The best means for accomplishing the oxygenation of $C_{(6)}$, therefore, assumes paramount importance in our route of morphine synthesis. In this communication, experiments with model compounds to this end are described.

The substance chosen as the simplest model for the system under investigation was 2-phenyl*cyclo*hexanone. Oxidation of this ketone with selenium dioxide, as in the similar oxidation of 2-methyl*cyclo*hexanone (Godchot and Cauquil, *Compt. rend.*, 1936, **202**, 326), yielded, as the major product, 2-phenyl*cyclo*hex-2-enone identical with the compound described by Ginsburg and Pappo (*J.*, 1951, 516). Although a small amount of the desired

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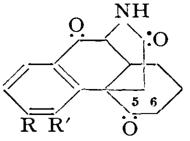
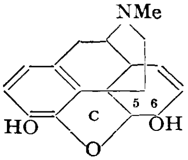
* Part IV, *J.*, 1953, 1524.

diketone was present in the reaction mixture, as shown by the strongly positive ferric chloride test, this route was clearly inefficient.

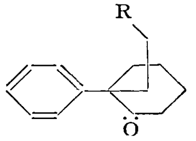
In order to avoid the difficulties inherent in substances containing a tertiary hydrogen atom adjacent to a carbonyl group, models were chosen in which this hydrogen atom was replaced by a substituted alkyl group, *e.g.*, (III*a*, *b*, c), obtained by cyanoethylation, etc., of 2-phenyl*cyclo*hexanone (Bachmann and Wick, *J. Amer. Chem. Soc.*, 1950, **72**, 3388). Bromination of these substances with bromine or with *N*-bromosuccinimide gave the 6-bromo-derivatives. Attempted conversion of these α-bromo-ketones into the corresponding ketols under a large variety of reaction conditions failed (see Experimental section). In most cases the starting material was recovered unchanged. The difficulty in removing the $C_{(6)}$ bromine atom under S_N1 displacement conditions may be explained by the simple electromeric effect operating in the attempted removal as bromide ion of a bromine atom α to a carbonyl group. A study of models shows that irrespective of whether one places the phenyl group or the β-substituted ethyl group at $C_{(2)}$ in the polar or in the equatorial conformation, either in the chair or in the boat form of the *cyclo*hexane ring, an equatorial bromine atom at $C_{(6)}$ is sterically hindered with respect to approach from the rear (S_N2). Since one would expect the bulky bromine atom to assume the equatorial conformation in preference to the polar, this subtle steric effect may be responsible for the sluggishness of the bromine atom under S_N2 conditions also.



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

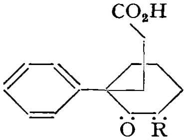


(II)

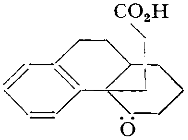


(III*a*; R = CO_2H)
(III*b*; R = CN)
(III*c*; R = CO_2Me)

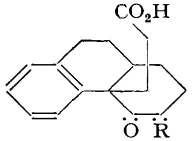
The next method employed involved indirect oxygenation at the α-carbon atom through preparation of the α-hydroxyimino-ketone, with subsequent hydrolysis to the β-diketone. Indeed, this proved to be the method of choice and appeared to solve the problem also insofar as yield was concerned. When (III*a*) is treated with *n*-amyl nitrite in the presence of sodium ethoxide, the α-hydroxyimino-ketone (IV*a*) is obtained in 93% yield. When acid catalysis was employed, a very low yield of this substance was obtained. It was hydrolysed by two methods described by Barltrop, Johnson, and Meakins (*J.*, 1951, 181) to the desired β-diketone (IV*b*). Treatment of (IV*a*) with zinc and acetic acid did not give the expected ketol; reversal of the hydroximination reaction took place and (III*a*) was isolated in low yield (cf. Caunt, Crow, Haworth, and Vodoz, *J.*, 1950, 1631).



(IV*a*; R = :N·OH)
(IV*b*; R = :O)



(V)



(VI*a*; R = :N·OH)
(VI*b*; R = :O)

In order to approach more closely the system of primary interest in this work, 12-2'-carboxyethyl-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-4-oxophenanthrene (V) (Part IV) was used as a model substance. The α-hydroxyimino-ketone (VI*a*) was obtained in 90% yield under alkali-catalysed conditions. Transoximation with formaldehyde–hydrochloric acid yielded the desired αβ-diketone (VI*b*).

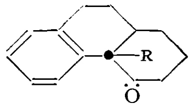
Clearly, the introduction of the oxime group α to the carbonyl group in these compounds is possible only because $C_{(2)}$ in 2-phenyl*cyclo*hexanone and $C_{(12)}$ in the octahydrophenanthrene derivative are quaternary. It is well known that cleavage of the molecule takes place by attack of a nitroso-ion on a tertiary carbon atom, with the formation of the oximes of the keto-acids or keto-esters which result from such cleavage.

This cleavage reaction has been used extensively (cf. Lapworth and Wechsler, *J.*, 1907, **91**, 977, 1919; Woodward and Doering, *J. Amer. Chem. Soc.*, 1945, **67**, 860).

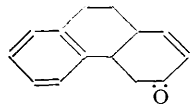
Thus, treatment of 2-phenyl*cyclo*hexanone with *n*-amyl nitrite in the presence of sodium ethoxide gave in high yield the oxime of δ-benzoylvaleric acid. Similarly, the octahydro-oxophenanthrene (VII*a*) yielded γ-(1-hydroxyimino-2-tetralyl)butyric acid. The derivatives of the keto-acids, and not those of the keto-esters, were isolated because Claisen solution was used in the isolation procedure.

The mechanism of the formation of *hetero*cholestenone by the high-temperature treatment of 2-bromocholestan-3-one with potassium acetate in acetic acid is still obscure (Butenandt and Ruhenstroth, *Ber.*, 1944, **77**, 397). This rearrangement involves the conversion of the system $\cdot CHBr\cdot CO\cdot CH_2\cdot \overset{|}{C}H\cdot CH_2\cdot$ into $\cdot CH_2\cdot CH_2\cdot CO\cdot \overset{|}{C}:CH\cdot$ with the loss of one mol. of hydrogen bromide. It seemed of interest, purely on grounds of analogy, to investigate whether in one of the systems of interest in morphine synthesis, it would be possible to carry out a similar rearrangement (VII*b* ⟶ VIII). If this rearrangement could be carried out, one would have a novel method for oxygenation at $C_{(6)}$. Further, a substance such as (VIII) could be reduced and used as a model for solving other points, the knowledge of which is required in the problem of morphine synthesis. Thus, for example, it might be expected that bromination of the dihydro-derivative of (VIII) would take place at $C_{(4)}$, by analogy with the bromination of 3-phenyl*cyclo*hexanone at $C_{(2)}$. The latter point was proved by dehydrobromination to 3-phenyl*cyclo*hex-2-enone identical with the product described by Abdullah (*J. Ind. Chem. Soc.*, 1935, **12**, 62).

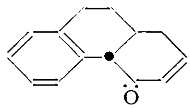
Bromination of (VII*a*) in carbon tetrachloride (cf. Bachmann and Wick, *loc. cit.*, for the similar bromination of 2-phenyl*cyclo*hexanone) yields the 12-bromo-derivative (VII*b*). Heating the latter with potassium acetate–acetic acid at 200° yields an αβ-ethylenic ketone (IX). Since reduction of (IX) yields (VII*a*), the desired rearrangement did not take place. Dehydrobromination of (VII*b*) by lutidine or 2 : 4-dinitrophenylhydrazone yields a different αβ-ethylenic ketone (X), which on catalytic hydrogenation also leads to the starting material (VII*a*). Isolation of two 2 : 4-dinitrophenylhydrazones in the latter reaction pointed to the possibility that a mixture of (VII*a*) and the *cis*-ketone (XI) had been obtained, but in view of experience in a similar reaction sequence employing methyl 3-oxo-2-phenyl*cyclo*hexylacetate, this possibility seemed remote (see below). Indeed, it was shown that the formation of a mixture of two 2 : 4-dinitrophenylhydrazones could be controlled by means of the amount of acid in the 2 : 4-dinitrophenylhydrazine solution employed and that the low-melting form could be converted into the high-melting form by means of acid; they may be the *syn*- and the *anti*-form, respectively, of the 2 : 4-dinitrophenylhydrazone. However, both forms are derivatives of the *trans*-octahydro-oxophenanthrene (VII*a*), as mixtures of them could be obtained directly from pure (VII*a*) which was not put through the bromination–dehydrobromination–hydrogenation sequence.



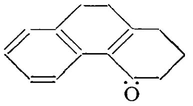
(VII*a*; R = H)
(VII*b*; R = Br)



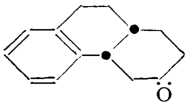
(VIII)



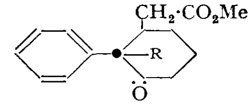
(IX)



(X)



(XI)



(XII*a*; R = H)
(XII*b*; R = Br)
(XII*c*; R = Cl)

The greater stability of the *trans*-ketone (VII*a*), compared with that of the still unknown *cis*-isomer (XI), is paralleled also in the substituted *cyclo*hexanone series. Bromination or chlorination of methyl 3-oxo-2-phenyl*cyclo*hexylacetate (XII*a*) yields (XII*b* and *c*, respectively). Dehydrohalogenation of the halides, followed by catalytic hydrogenation, affords only the *trans*-product (XII*a*).

EXPERIMENTAL

Selenium Dioxide Oxidation of 2-*Phenyl*cyclo*hexanone*.—To a boiling solution of 2-phenyl*cyclo*hexanone (8·7 g.) in absolute ethanol (25 ml.) a solution of sublimed selenium dioxide (5·5 g.) in absolute ethanol (30 ml.) was added dropwise during 1 hr. The mixture was heated under reflux for 6 hr., the precipitated selenium was removed by filtration, and the solvent removed under reduced pressure. The residue was extracted with ether, filtered, and fractionated. The first fraction, b. p. 135—140°/3 mm. (2·2 g.), m. p. 97° (from heptane), showed no m. p. depression upon admixture with authentic 2-phenyl*cyclo*hex-2-enone. A further crop of this ketone could be obtained from the higher-boiling fraction. The mother-liquor gave an intense colour with alcoholic ferric chloride.

Reaction of 2-*Phenyl*cyclo*hexanone with* n-*Amyl Nitrite*.—To a solution of sodium ethoxide (1·27 g. of sodium in 25 ml. of absolute ethanol) were added 2-phenyl*cyclo*hexanone (8·7 g.) and, with ice-cooling, *n*-amyl nitrite (8·8 ml.). The mixture became homogeneous after several hours and was kept in the refrigerator for 48 hr. Acetic acid (10 ml.) and a large volume of water were added, the mixture was extracted twice with ether, and the combined ethereal extracts were shaken twice with Claisen solution. The alkaline solution was acidified with acetic acid and diluted with water. After refrigeration, the solution deposited colourless crystals, m. p. 119—120° (from aqueous ethanol), of the *oxime* of δ-benzoylvaleric acid (5·6 g.). The filtrate was extracted with ether, the solvent was removed, and the residue furnished an additional crop of product (1·4 g.; total yield 67%) (Found: C, 65·8; H, 6·8; N, 6·4. $C_{12}H_{15}O_3N$ requires C, 65·1; H, 6·8; N, 6·3%).

Hydrolysis of the oxime with dilute hydrochloric acid, containing a small amount of ethanol to give a homogeneous solution, yielded δ-benzoylvaleric acid, m. p. 78—79° (from aqueous ethanol). The semicarbazone, prepared in pyridine, had m. p. 186—187° (from aqueous ethanol). Von Auwers and Treppmann (*Ber.*, 1915, **48**, 1217) reported m. p.s 77—78° and 187°, respectively, for these substances.

2-2′-*Carboxyethyl*-6-*hydroxyimino*-2-*phenyl*cyclo*hexanone*.—To an ice-cold solution of sodium ethoxide (from 0·5 g. of sodium and 10 ml. of ethanol) were added 2-2′-carboxyethyl-2-phenyl*cyclo*hexanone (2·5 g.) and *n*-amyl nitrite (1·8 ml.). The orange mixture was kept in the refrigerator for 48 hr. and then treated as above, except that sodium hydrogen carbonate was used instead of Claisen solution. The *hydroxyimino-acid* was obtained as cream-coloured crystals, m. p. 168—169° (decomp.). Recrystallisation from aqueous ethanol raised the m. p. to 174° (decomp.). The substance gives a green colour with alcoholic ferric chloride (Found: C, 65·7; H, 6·2; N, 5·3. $C_{15}H_{17}O_4N$ requires C, 65·4; H, 6·2; N, 5·1%).

2-2′-*Carboxyethyl*-6-*oxo*-2-*phenyl*cyclo*hexanone*.—(*a*) The hydroxyimino-compound (0·2 g.), formaldehyde solution (40%; 1 ml.), and hydrochloric acid (2N; 0·2 ml.) were heated on the steam-bath for 10 min. Water (10 ml.) was added to the resulting yellow solution and the precipitated oil was taken up in ether. The ethereal extract was washed with water, the ether removed, and the remaining oil gave an intense brown colour with alcoholic ferric chloride. The product was not as pure as that obtained by method (*b*).

(*b*) To a solution of the hydroxyimino-ketone (1 g.) and sodium nitrite (2·4 g.) in 50% aqueous ethanol (400 ml.), concentrated sulphuric acid (2·4 ml.) was added dropwise with cooling. The mixture was kept at 35—40° for 36 hr. Sodium hydrogen carbonate solution was used to adjust the pH to 6 and the mixture was concentrated under reduced pressure to about half of its original volume. The oil which separated was extracted with ether, the ethereal extract washed with water, and the solvent removed. After several weeks, the αβ-*diketone* became semi-solid (Found: C, 69·4; H, 6·1. $C_{15}H_{16}O_4$ requires C, 69·2; H, 6·2%). It gave a deep brown colour with alcoholic ferric chloride.

6-*Bromo*-2-2′-*carboxyethyl*-2-*phenyl*cyclo*hexanone*.—To a boiling solution of (III*a*) (1·2 g.) in carbon tetrachloride (20 ml.) was added dropwise a solution of bromine (0·3 ml.) in carbon tetrachloride (10 ml.). The colour of the bromine disappeared immediately. After removal of the solvent under reduced pressure the remaining oil was crystallised from aqueous methanol or heptane. The colourless *bromo-acid* had m. p. 149—150°. Further recrystallisation raised the m. p. to 151—152° (Found: C, 55·4; H, 5·3; Br, 24·7. $C_{15}H_{17}O_3Br$ requires C, 55·4; H, 5·2; Br, 24·6%).

6-*Bromo*-2-2′-*cyanoethyl*-2-*phenyl*cyclo*hexanone*.—To a solution of (III*b*) (1·1 g.) in carbon tetrachloride (20 ml.) was added dropwise with cooling a solution of bromine (0·3 ml.) in carbon tetrachloride (10 ml.). A heavy brown oil separated. The solvent was removed under reduced pressure and the oily residue was extracted twice with boiling heptane. Colourless crystals, m. p. 116—117°, of the *bromo-nitrile* were obtained from the heptane solution (Found: C, 56·7; H, 5·5; Br, 26·3. $C_{15}H_{16}ONBr$ requires C, 56·0; H, 5·2; Br, 26·2%).

The bromo-nitrile (1 g.), acetic acid (10 ml.), and hydrochloric acid (1 : 1; 10 ml.) were heated under reflux for 15 hr. under carbon dioxide, then poured into water and cooled. The precipitated bromo-acid was recrystallised from heptane and proved to be identical with the bromo-acid obtained by bromination of (III*a*).

*6-Bromo-2-2'-carbomethoxyethyl-2-phenyl*cyclo*hexanone.*—The ester (III*c*) (2·6 g.), *N*-bromosuccinimide (1·9 g.), and a trace of benzoyl peroxide were added to carbon tetrachloride (20 ml.), and the mixture was heated under reflux for 12 hr. The succinimide was removed by filtration and the solvent removed under reduced pressure. The resulting *bromo*-ester was an oil which did not crystallise. Hydrolysis of the bromo-ester as described above for the bromo-nitrile yielded the bromo-acid, m. p. 151—152°, identical with the bromination product of (III*a*).

Attempted displacement of the 6-bromine atom in the above substances failed under the following reaction conditions: silver nitrate–pyridine, silver acetate–benzene, potassium formate–methanol, aqueous potassium carbonate, potassium acetate–acetic acid. Further, neither lutidine nor 2 : 4-dinitrophenylhydrazine in acetic acid had any effect on the substances which were recovered unchanged even after long reflux periods.

*Methyl 2-Chloro-3-oxo-2-phenyl*cyclo*hexylacetate.*—To a solution of methyl 3-oxo-2-phenyl-*cyclo*hexylacetate (2·6 g.) in carbon tetrachloride (50 ml.) was added dropwise a solution of sulphuryl chloride (1·5 g.) in carbon tetrachloride (10 ml.). The mixture was refluxed for 2 hr. There was then no further evolution of sulphur dioxide and hydrogen chloride. The solvent was removed under reduced pressure and the residue was triturated with light petroleum. After recrystallisation of the colourless solid (2·5 g.), the *chloro*-derivative had m. p. 111—112° (from light petroleum) (Found: C, 64·1; H, 6·1; Cl, 12·6. $C_{15}H_{17}O_3Cl$ requires C, 64·2; H, 6·1; Cl, 12·7%).

Dehydrochlorination with 2 : 6-lutidine gave an oil whose 2 : 4-dinitrophenylhydrazone had m. p. 112—113° (from ethanol). Hydrogenation of the oil in ethanol with 10% palladised charcoal at an initial pressure of 60 lb./sq. in. gave methyl *trans*-3-oxo-2-phenyl*cyclo*hexylacetate, m. p. and mixed m. p. 81° (from methyl*cyclo*hexane).

*Methyl 2-Bromo-3-oxo-2-phenyl*cyclo*hexylacetate.*—(*a*) To a solution of methyl 3-oxo-2-phenyl*cyclo*hexylacetate (5·7 g.) in carbon tetrachloride (60 ml.) was added at 0—5° a solution of bromine (1·2 ml.) in carbon tetrachloride (20 ml.). A brown oil separated at the end of the rapid addition. The solvent was removed under reduced pressure and the residue triturated with methanol. The *bromo*-ester (6·2 g.) had m. p. 131—132° (from hexane) (Found: C, 55·8; H, 5·4; Br, 24·4. $C_{15}H_{17}O_3Br$ requires C, 55·4; H, 5·2; Br, 24·6%).

(*b*) A mixture of methyl ester (5·15 g.), *N*-bromosuccinimide (3·72 g.), and carbon tetrachloride (50 ml.) was heated on the steam-bath for 30 min. Since no apparent reaction had taken place, a trace of benzoyl peroxide was added. After 45 min.' additional boiling, all the *N*-bromosuccinimide had been replaced by succinimide which was removed by filtration. The solvent was removed under reduced pressure and the residue treated as above, m. p. 131—132° (5·2 g.). On admixture with the product obtained by method (*a*) there was no m. p. depression.

Dehydrobromination was accomplished by 1 hr.' heating with 2 : 6-lutidine. After the usual working up an oily unsaturated ester was obtained which gave the same 2 : 4-dinitrophenylhydrazone, m. p. 112—113°, as was obtained from the above chloro-ester. Hydrogenation of the unsaturated ester in ethanol in the presence of 10% palladised charcoal at an initial pressure of 60 lb./sq. in. yielded authentic methyl *trans*-3-oxo-2-phenyl*cyclo*hexylacetate, m. p. and mixed m. p. 81°. No isomeric ester could be isolated.

*Bromination of 3-Phenyl*cyclo*hexanone.*—A mixture of 3-phenyl*cyclo*hexanone (2·2 g.), *N*-bromosuccinimide (1·9 g.), and carbon tetrachloride (20 ml.) was heated under reflux for 2 hr. Hydrogen bromide was evolved during this time. The succinimide was removed, the solvent evaporated under reduced pressure, and the residue heated with 2 : 6-lutidine (20 ml.) for 2 hr. The lutidine was removed under reduced pressure, the residual oil dissolved in ether, and the extract washed with dilute hydrochloric acid and water. After removal of the ether, the residue was treated with ethanolic 2 : 4-dinitrophenylhydrazine. A deep red 2 : 4-dinitrophenylhydrazone (0·8 g.) was obtained, having m. p. 224—226° (from ethanol), identical with the 2 : 4-dinitrophenylhydrazone of 3-phenyl*cyclo*hex-2-enone (cf. Ginsburg and Pappo, *J.*, 1951, 516).

Bromination of 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*Octahydro*-4-*oxophenanthrene*.—To the octahydro-oxophenanthrene (VII*a*) (2 g.) in carbon tetrachloride (20 ml.) was added with ice-cooling a solution of bromine (1·6 g.) in carbon tetrachloride (10 ml.). The colour of the bromine disappeared immediately. The solvent was removed under reduced pressure and the residual oil was essentially pure 12-*bromo*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4-*oxophenanthrene* (VII*b*) (Found : Br, 28·9. $C_{14}H_{15}OBr$ requires Br, 28·7%). In one experiment, on treatment of the oil with hot butanol, a very small amount of solid, m. p. 118—120°, remained undissolved. This is probably the 3 : 12-*dibromo*-derivative (Found : Br, 44·4. $C_{14}H_{14}OBr_2$ requires Br, 44·7%).

Dehydrobromination.—(a) *With lutidine*. To the 12-bromo-compound (2·8 g.) was added 2 : 6-lutidine (20 ml.), and the solution refluxed for 2 hr. After the usual working up, the residual oily αβ-ethylenic ketone (X) was treated with 2 : 4-dinitrophenylhydrazine in ethanol. The 2 : 4-*dinitrophenylhydrazone* of 1 : 2 : 3 : 4 : 9 : 10-hexahydro-4-oxophenanthrene had m. p. 230—232° (from ethanol–chloroform) (Found : C, 63·4; H, 4·6; N, 14·8. $C_{20}H_{18}O_4N_4$ requires C, 63·5; H, 4·8; N, 14·8%); $\lambda_{max.} = 3930$ Å; $\varepsilon = 24,000$ (in $CHCl_3$). It was unaccompanied by any isomeric hydrazone, as shown by attempted chromatographic separation on alumina.

When the 12-bromo-compound was treated directly with 2 : 4-dinitrophenylhydrazine in ethanol, the same 2 : 4-dinitrophenylhydrazone, m. p. 230—232°, was obtained, unaccompanied by any isomer.

(b) *With potassium acetate–acetic acid*. The 12-bromo-compound (VII*b*) (2·8 g.) and a solution of potassium acetate in acetic acid (21%; 85 ml.) were heated in a sealed tube at 200—210° for 5 hr. The mixture was poured into a large volume of water and extracted with ether, and the extract washed with 2N-potassium hydroxide until the aqueous layer remained alkaline. After evaporation of the ether, the residual oil was treated with ethanolic 2 : 4-dinitrophenylhydrazine. A mixture of 2 : 4-dinitrophenylhydrazones was obtained, separable by fractional crystallisation. The 2 : 4-*dinitrophenylhydrazone* of 1 : 4 : 9 : 10 : 11 : 12-hexahydro-4-oxo-phenanthrene (IX) was much less soluble and had m. p. 269—270° (from 1 : 1 ethanol–chloroform) (Found : C, 63·6; H, 4·7; N, 14·7. $C_{20}H_{18}O_4N_4$ requires C, 63·5; H, 4·8; N, 14·8%); $\lambda_{max.}$ 3970 Å; $\varepsilon = 28,000$ (in $CHCl_3$). The isomeric 2 : 4-dinitrophenylhydrazone, m. p. 230—232°, identical with the one described above could be obtained from the mother-liquor. Mixtures were always obtained by this dehydrobromination procedure, consisting of 50—80% of the higher-melting isomer.

Hydrogenation of αβ-*Ethylenic Ketones*.—Ketone (IX) or (X) (1 g.) was hydrogenated in ethanol (20 ml.) in the presence of 10% palladised charcoal (0·3 g.) at 60°, at an initial pressure of 60 lb./sq. in. After 2 hr., the catalyst was removed and the ethanol distilled under reduced pressure. The solution afforded a mixture of two 2 : 4-dinitrophenylhydrazones. The mixture was extracted with boiling methanol, and the methanolic solution was allowed to cool. A high-melting β-*form* was obtained as light orange rosettes, m. p. 217—218° (Found: C, 63·0; H, 5·0; N, 14·5. $C_{20}H_{20}O_4N_4$ requires C, 63·2; H, 5·3; N, 14·7%). The methanol-insoluble α-form was recrystallised from ethanol–chloroform and was obtained as yellow prismatic needles, m. p. 196°, identical with the compound described by Ginsburg and Pappo (*J*., 1951, 938). When the low-melting form was dissolved in 1 : 1 ethanol–sulphuric acid, kept overnight, and then diluted with aqueous ethanol, a mixture was obtained containing an appreciable amount of the high-melting form. The α-form (196°) showed $\lambda_{max.}$ 3690 Å ($\varepsilon = 24,000$ in $CHCl_3$). The β-form (m. p. 217—218°) showed $\lambda_{max.}$ 3700 Å ($\varepsilon = 23,000$ in $CHCl_3$).

Reaction of (VII*a*) *with* n-*Amyl Nitrite*.—To a solution of sodium ethoxide (from 0·07 g. of sodium and 5 ml. of ethanol), were added (VII*a*) (0·6 g.) in ethanol (3 ml.) and *n*-amyl nitrite (0·5 g.), with ice-cooling. After being kept in the refrigerator for 48 hr., the mixture was treated as described for the similar reaction of 2-phenyl*cyclo*hexanone (see above). The *oxime*, m. p. 128—129°, of γ-(1 : 2 : 3 : 4-tetrahydro-1-oxo-2-naphthyl)butyric acid was obtained from aqueous ethanol (Found : C, 68·2; H, 6·9; N, 5·6. $C_{14}H_{17}O_3N$ requires C, 68·0; H, 6·9; N, 5·7%).

The same product can be obtained by use of *n*-butyl nitrite.

The free keto-acid, obtained by acid hydrolysis, had m. p. 64—65° (from heptane). Bachmann and Wendler (*J. Amer. Chem. Soc.*, 1946, **68**, 2580) reported m. p. 64—65°.

γ-2-*Naphthylbutyric Acid*.—The methyl ester of the above keto-acid was obtained by treating the keto-acid (600 mg.) with ethereal diazomethane. The ester was an oil whose 2 : 4-dinitro-phenylhydrazone had m. p. 158—160° (from ethanol).

The crude methyl ester was treated in methanol (10 ml.) with sodium borohydride (100 mg.). After dilution with water and ether-extraction, the ether was removed and the crude reduction product heated in *p*-cymene with 10% palladised charcoal (0·5 g.) under reflux for

4 hr. (nitrogen). After cooling of the mixture, ether was added, the catalyst removed, and the ether evaporated. The residue was heated in methanolic potassium hydroxide (30%; 10 ml.) under reflux for 90 min. After dilution with water, acidification, and ether-extraction, the ether was washed with aqueous sodium hydrogen carbonate and the alkaline extract was acidified. The precipitate had m. p. 103—104° (from heptane). Newman and Zahm (*ibid.*, 1943, **65**, 1097) report m. p. 98—99° for γ-2-naphthylbutyric acid.

cis-12-2′-*Carboxyethyl*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-3-*hydroxyimino*-4-*oxophenanthrene* (VI*a*).—To an ice-cold solution of sodium ethoxide (from 0·25 g. of sodium and 5 ml. of ethanol) were added, with cooling, (V) (1·35 g.) and *n*-amyl nitrite (0·9 ml.). After several hours in the refrigerator all of the solid had dissolved and the orange solution was refrigerated for a total of 48 hr. After the usual working up the *hydroxyimino-oxo-acid* (VI*a*) (1·35 g., 90%) was obtained, having m. p. 204° (decomp.; sinters at 196°). An analytical sample was obtained by washing the precipitated product with ether (Found: C, 67·6; H, 6·3; N, 4·2. $C_{17}H_{19}O_4N$ requires C, 67·8; H, 6·4; N, 4·7%).

cis-12-2′-*Carboxyethyl*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*Octahydro*-3 : 4-*dioxophenanthrene*.—The hydroxyimino-compound (VI*a*) (0·6 g.), formaldehyde solution (40%; 3 ml.), and hydrochloric acid (2N; 0·6 ml.) were heated on the steam-bath. After 6 min. all of the solid had dissolved and the light orange solution became turbid. After being heated for 4 additional min. the mixture was cooled and water (10 ml.) was added. After a further few minutes, the supernatant liquid was decanted from the precipitated oil, and the residue was extracted twice with boiling heptane containing a few drops of benzene. A solid, m. p. 124—127°, was precipitated from the organic extract. After four recrystallisations (charcoal) the *diketone* had m. p. 140—143° (from heptane) (yield, 35%) (Found: C, 71·5; H, 6·3. $C_{17}H_{18}O_4$ requires C, 71·3; H, 6·3%). The product gave a dark brown colour with alcoholic ferric chloride.

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