407. *Synthesis of Piperidine Derivatives. Part II. Aryldecahydroquinolines.*

By G. M. Badger, J. W. Cook, and Thomas Walker.

As part of a scheme to prepare new pharmacologically active bases, 4-*phenyl*- and 4-p-*methoxyphenyl*-1-*ethyldecahydroquinolines* have been synthesised by hydrogenation in ethanolic solution over copper chromite of the *oximes* of ethyl β-2-keto*cyclo*hexyl-β-phenyl- and -β-*p*-methoxyphenyl-propionate. Condensation of 2-benzylidene*cyclo*hexanone with ethyl sodiomalonate gave, not the expected malonic ester (III; Ar = Ph, R = Et) but a *lactone* (V; Ar = Ph) derived from it by loss of ethanol. Some transformations of this lactone are described. 2-*p*-Methoxybenzylidene*cyclo*hexanone reacted similarly with ethyl sodiomalonate.

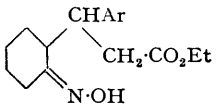
In recent years a number of new synthetic analgesics have been described. Two outstanding examples are pethidine (a piperidine derivative) and amidone (a basic derivative of diphenylmethane). Thorp, Walton, and Ofner (*Nature*, 1947, **160**, 605) have reported that (—)-amidone has about twice the analgesic activity of morphine (compare Scott and Chen, *J. Pharm. Exp. Ther.*, 1946, **87**, 63). Like morphine, both pethidine and amidone appear to produce drug-addiction, and a satisfactory analgesic free from this undesirable side-effect has not yet been found. Possibly the two effects are inseparable, but this can only be determined by

examining a sufficient number of new products. Other analgesics structurally related to pethidine have been examined pharmacologically by, for example, Jensen and Lundquist (*Dansk Tidsskr. Farm.*, 1943, **17**, 173) and MacDonald *et al.* (*Brit. J. Pharmacol.*, 1946, **1**, 4).

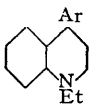
Among the more efficient of the newer antispasmodics are the diethylaminoethyl esters of diphenylacetic acid (trasentin), *cyclo*hexylphenylacetic acid (trasentin 6H), fluorene-9-carboxylic acid (pavatrine), and 9 : 10-dihydroanthracene-9-carboxylic acid (see Blicke, *Ann. Rev. Biochem.*, 1944, **13**, 549). Relatively simple piperidine derivatives are also known to have antispasmodic activity (Cerkovnikov and Prelog, *Ber.*, 1941, **74**, 1648; Fellows and Cunningham, *Federation Proc.*, 1942, **1**, 151; Lee and Freudenberg, *J. Org. Chem.*, 1944, **9**, 537; Foster, Moench, and Clark, *J. Pharm. Exp. Ther.*, 1946, **87**, 73; Kwartler and Lucas, *J. Amer. Chem. Soc.*, 1947, 69, 2582), and Dr. J. D. P. Graham has found (unpublished experiments) that some of the piperidine bases synthesised by Barr and Cook (*J.*, 1945, 438) have marked antispasmodic properties: the hydrochloride of 3 : 4-diphenyl-1-methylpiperidine, for example, has high musculotropic activity. It seems that all the efficient antispasmodics, although varying widely in molecular structure, are salts of strong tertiary bases, and this may be an important requirement for this type of pharmacological action.

In Part I of this series, Barr and Cook (*loc. cit.*) described the synthesis of 3 : 4-diaryl-1-alkylpiperidines by copper chromite hydrogenation of appropriate γ-cyano-esters in alcoholic solvents, which supplied the *N*-alkyl substituents. The present communication describes the synthesis, by a somewhat analogous method, of decahydroquinoline derivatives which are being examined for analgesic and antispasmodic action by Dr. J. D. P. Graham, who will publish his results elsewhere.

The *oxime* (I; Ar = Ph) of ethyl β-2-keto*cyclo*hexyl-β-phenylpropionate (Vorländer and Kunze, *Ber.*, 1926, **59**, 2078) was hydrogenated in ethanolic solution over copper chromite to give 4-*phenyl*-1-*ethyldecahydroquinoline* (II; Ar = Ph). For this structure four optically inactive stereoisomeric forms are possible, but the liquid base, obtained in satisfactory yield, gave a well-crystallised *picrate* and appeared to be stereochemically homogeneous. In view of the high temperature used for hydrogenation it probably belongs to the *trans*-decahydroquinoline series. 4-p-*Methoxyphenyl*-1-*ethyldecahydroquinoline* (II; Ar = *p*-C_6H_4·OMe), similarly prepared from the *oxime* (I; Ar = *p*-C_6H_4·OMe), was a crystalline solid, and it also was formed free, or almost free, from stereoisomerides. By being heated with hydrobromic acid in acetic acid the latter base was demethylated to the *hydrobromide* of 4-*p*-hydroxyphenyl-1-ethyldecahydroquinoline. 4-Phenyl-1-ethyldecahydroquinoline was completely dehydrogenated by being heated with palladium black, the *N*-ethyl group being eliminated, with formation of the known 4-phenylquinoline (Königs and Nef, *Ber.*, 1886, **19**, 2430; Koenigs and Meimberg, *Ber.*, 1895, **28**, 1039).



(I.)



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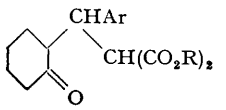
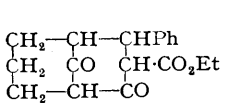


(III.)

An obvious route to the keto-acid required for the preparation of the oxime (I; Ar = Ph) was the condensation of 2-benzylidene*cyclo*hexanone with ethyl sodiomalonate followed by hydrolysis of the product and then thermal decarboxylation. This Michael reaction was described by Vorländer and Kunze (*loc. cit.*) who allowed a suspension of ethyl sodiomalonate in benzene or ether to react with the unsaturated ketone at room temperature during two days. They obtained a liquid product which was assumed to be ethyl β-2-keto*cyclo*hexylbenzylmalonate (III; Ar = Ph, R = Et), as it was hydrolysed to the malonic acid and converted by concentrated ammonia into the corresponding diamide. By carrying out the Michael reaction in boiling benzene (2 hours) we obtained, not the liquid ester of Vorländer and Kunze, but a crystalline compound which was shown by elementary analysis and ethoxyl determination to have been formed from the diester (III) by loss of a molecule of ethanol. Our product was insoluble in cold aqueous sodium hydroxide, but was readily hydrolysed by boiling alkali to the malonic acid (III; Ar = Ph, R = H). Elimination of ethanol from the diester (III; Ar = Ph, R = Et) by means of sodium ethoxide could give the strainless *bicyclo*nonane derivative (IV) (cf. Rabe, *Ber.*, 1903, **36**, 225, 227; 1904, **37**, 1671), but the product gave no colour with ferric chloride, rapidly decolourised bromine water, and reduced ammoniacal silver solution. These and other reactions indicate that it is an unsaturated lactone, namely, *ethyl* 4-*phenyl*-3 : 4 : 5 : 6 : 7 : 8-

hexahydrocoumarin-3-carboxylate (V; Ar = Ph). The position of the ethylenic bond has not been established, but on general grounds the position shown is probable.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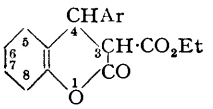
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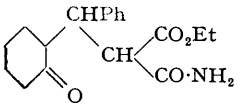
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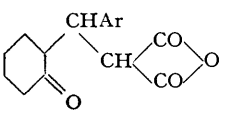
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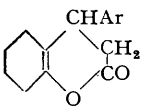
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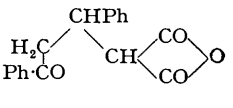
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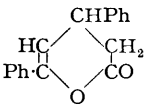

(X.)

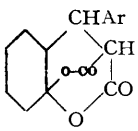
When an ethanolic solution of the carbethoxy-lactone (V; Ar = Ph) was treated with concentrated aqueous ammonia the lactone ring was opened with formation of *α-carbethoxy-β-2-ketocyclohexyl-β-phenylpropionamide* (VI). Similar production of an amide of a keto-acid by the action of ammonia on an unsaturated δ-lactone (X) was recorded by Mannich and Butz (*Ber.*, 1929, **62**, 456). We also obtained the monoamide (VI) by treatment of the diester (III; Ar = Ph, R = Et) with ethanolic ammonia. This result is at variance with the work of Vorländer and Kunze (*loc. cit.*) who obtained the diamide from their crude diester (III; Ar = Ph, R = Et). Possibly the explanation of the discrepancy is that in the concentration which we used the monoamide crystallised as soon as it was formed.

By the action of concentrated sulphuric acid the carbethoxy-lactone (V; Ar = Ph) was converted into *β-2-ketocyclohexylbenzylmalonic anhydride* (VII; Ar = Ph). This well-crystallised anhydride was remarkably stable and could be distilled under reduced pressure without decomposition. It was hydrolysed by hot dilute alkali to the malonic acid (III; Ar = Ph, R = H), which was reconverted into the anhydride by treatment with thionyl chloride in benzene. Concentrated sulphuric acid did not dehydrate either the malonic acid or its diethyl ester. Possibly the action of sulphuric acid on the carbethoxy-lactone involves addition of sulphuric acid followed by elimination of ethyl hydrogen sulphate.*

Anhydrides of simple dialkylmalonic acids were prepared by Einhorn (*Annalen*, 1908, **359**, 145) who found them to be polymeric and amorphous; Staudinger and Ott (*Ber.*, 1908, **41**, 2208) showed that they lost carbon dioxide when heated and gave ketens. The malonic anhydride (VII; Ar = Ph) contrasted strikingly with the anhydrides of Einhorn and Staudinger, not only in being crystalline and monomeric and capable of crystallisation from ethanol, but also in its behaviour on thermal treatment. This led to loss of carbon dioxide and formation of *4-phenyl-3 : 4 : 5 : 6 : 7 : 8-hexahydrocoumarin* (VIII; Ar = Ph). Some analogous examples have been described by Mannich and Butz (*loc. cit.*) who found, for example, that the anhydride (IX) lost carbon dioxide when heated and was converted into the unsaturated lactone (X). Probably a determining factor in these transformations is the presence of a carbonyl group so situated as to permit lactone formation.

The literature contains little reference to the action of ketonic reagents on unsaturated

* *Added, June* 29th, 1948.—When this paper was read at a meeting of the Chemical Society on February 5th, 1948, it was suggested by Dr. A. J. Birch (see *Chem. and Ind.*, 1948, 156; similar suggestions were subsequently sent to us by Dr. S. H. Harper and Dr. C. W. Shoppee) that the compounds described as malonic anhydrides are in reality dilactones, and that structure (VII) should be replaced by the formula inset.

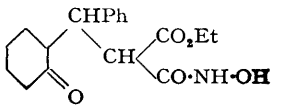


We accept this suggestion, for the properties of the compounds in question are in better accord with a dilactone structure than a malonic anhydride structure, although it is by no means easy to distinguish between them experimentally. We have attempted this in a number of ways. The only experiment which has given decisive results was the hydrogenation of the phenyl dilactone (m. p. 169°) over Adams's platinum catalyst in acetic acid solution. This led to the uptake of 2·8 mols. of hydrogen and the formation of the corresponding *cyclo*hexyl dilactone (in which Ar in the inset formula becomes C_6H_{11}). This *hexahydride* formed colourless needles (from ethanol), m. p. 137° (Found: C, 68·9; H, 7·75. $C_{16}H_{22}O_4$ requires C, 69·1; H, 7·9%). Hydrolysis with sodium hydroxide solution gave a sparingly soluble sodium salt; the acid regenerated from this could not be obtained pure, as on repeated recrystallisation it reverted to the dilactone, m. p. 137°.

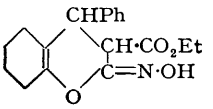
We regard this as evidence in favour of the dilactone structure given above in preference to (VII), for the reason that it is inconceivable that a carbonyl group (as in VII) could have resisted hydrogenation under conditions which led to reduction of phenyl to *cyclo*hexyl. A corollary of this conclusion is that the malonic anhydrides of Mannich and Butz (*loc. cit.*) (*e.g.*, IX) have similar dilactone structures. Analogous dilactones have been described by Qudrat-i-Khuda (*J.*, 1929, 201, 713).

lactones, although it is well known that saturated lactones react with phenylhydrazine to give phenylhydrazides of the corresponding hydroxy-acids. However, Minunni, Ottaviano, and Spina (*Gazzetta*, 1929, **59**, 116), in attempting to remove the arylidene group from α-arylidene-aminocinnamo-β-lactones with phenylhydrazine, found that the lactone ring was opened with formation of the phenylhydrazide of α-amino-β-hydroxycinnamic acid. The lactone ring was not affected by hydroxylamine. When the hexahydrocoumarin (V; Ar = Ph) was treated with 2 : 4-dinitrophenylhydrazine in ethanol there was obtained a heavy red oil, from which was isolated a small amount of the crystalline 2 : 4-*dinitrophenylhydrazone* of ethyl β-2-keto*cyclo*hexylbenzylmalonate (III; Ar = Ph, R = Et). The same dinitrophenylhydrazone was obtained directly from this ester. Its formation from the lactonic-ester was evidently due to opening of the lactone ring by addition of ethanol. A similar reaction was observed by Mannich and Butz (*loc. cit.*), who found that boiling methanol converted the unsaturated lactone (X) into the methyl ester of the corresponding keto-acid.

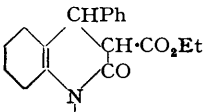
The lactonic ester (V; Ar = Ph) reacted with hydroxylamine as it did with ammonia, for the product was a *hydroxamic acid* (XI). It was insoluble in sodium carbonate solution but soluble in aqueous sodium hydroxide and it gave a deep red colouration with ferric chloride. Unlike many hydroxamic acids, our compound (XI) did not reduce Fehling's solution (compare Yale, *Chem. Reviews*, 1943, **33**, 209), but it reduced hot ammoniacal silver nitrate solution. The hydroxamic acid (XI) lost the elements of water above its m. p. to form a compound for which we suggest the structure (XII) or, more probably, (XIII). Hydroxamic acids usually undergo the Lossen rearrangement when heated, but it was clear that our product of thermal dehydration was neither a primary nor a secondary product of such a rearrangement. It still contained the carbon skeleton of the hydroxamic acid, for treatment with 2 : 4-dinitrophenylhydrazine gave a small amount of the 2 : 4-dinitrophenylhydrazone of (III; Ar = Ph, R = Et). The dehydration product (XII or XIII) was insoluble in sodium carbonate solution but soluble in sodium hydroxide solution, and gave a purple colour with ferric chloride. Treatment with hot aqueous alkali hydrolysed the carbethoxy-group and gave an *acid* which likewise gave a colour with ferric chloride. This acid was decarboxylated at its m. p. to an oil which did not crystallise.



(XI.)



(XII.)



(XIII.)

A parallel series of experiments to that described above was carried out using as the starting point 2-*p*-methoxybenzylidene*cyclo*hexanone. This reacted with ethyl sodiomalonate in boiling benzene to give a product which was not obtained crystalline, but it evidently consisted essentially of the anticipated hexahydrocoumarin (V; Ar = *p*-C_6H_4·OMe). This reacted with concentrated sulphuric acid to give, in excellent yield, β-2-*keto*cyclo*hexyl*-p-*methoxybenzyl-malonic anhydride* (VII; Ar = *p*-C_6H_4·OMe). The latter, on heating, lost carbon dioxide and gave 4-p-*methoxyphenyl*-3 : 4 : 5 : 6 : 7 : 8-*hexahydrocoumarin* (VIII; Ar = *p*-C_6H_4·OMe). The same compound was obtained from the crude carbethoxy-lactone (V; Ar = *p*-C_6H_4·OMe) when purification was attempted by vacuum distillation. Hydrolysis of the anhydride (VII; Ar = *p*-C_6H_4·OMe) gave β-2-*keto*cyclo*hexyl*-p-*methoxybenzylmalonic acid* (III; Ar = *p*-C_6H_4·OMe, R = H), which was also formed by hydrolysis of the crude carbethoxy-lactone (V; Ar = *p*-C_6H_4·OMe). Decarboxylation of the malonic acid gave β-2-*keto*cyclo*hexyl*-β-p-*methoxy-phenylpropionic acid* which was esterified and the crude ester oximated to give (I; Ar = *p*-C_6H_4·OMe). The crude ester could not be purified by distillation as it decomposed to the lactone (VIII; Ar = *p*-C_6H_4·OMe).

Experimental.

Ethyl 4-*Phenyl*-3 : 4 : 5 : 6 : 7 : 8-*hexahydrocoumarin*-3-*carboxylate* (V; Ar = Ph).—2-Benzylidene*cyclo*hexanone (Poggi and Guastalla, *Gazzetta*, 1931, **61**, 405; cf. Vorländer and Kunze, *loc. cit.*) (35·7 g. in benzene (100 c.c.) was added all at once to a suspension of ethyl sodiomalonate [from sodium (4·33 g.) and ethyl malonate (30·1 g.)] in benzene (150 c.c.), and the mixture was refluxed for 2 hours. The cooled solution was shaken with ice-cold dilute sulphuric acid, washed with water, sodium carbonate solution, and then water, and dried. After removal of the benzene and a little unchanged ethyl malonate, the resulting oil was dissolved in warm ethanol. On cooling, *ethyl* 4-*phenyl*-3 : 4 : 5 : 6 : 7 : 8-*hexahydro-coumarin*-3-*carboxylate* (42 g.) separated. It formed colourless needles (from *cyclo*hexane), m. p. 69° (Found : C, 72·1; H, 6·6; OEt, 15·4. $C_{18}H_{20}O_4$ requires C, 72·0; H, 6·7; OEt, 15·0%). A further quantity (8 g.) was obtained by distilling (b. p. 185°/1 mm.) the residue from the alcoholic mother liquor.

β-2-*Keto*cyclo*hexylbenzylmalonic Acid* (III; Ar = Ph, R = H).—The above hexahydrocoumarin

(22 g.) was hydrolysed by 1½ hours' refluxing with excess of 40% aqueous alcoholic potassium hydroxide. The crude oily malonic acid solidified on standing in the refrigerator, and, after recrystallisation from 50% aqueous ethanol, formed colourless needles, m. p. 135° (Vorländer and Kunze, *loc. cit.*, give m. p. 135—136°).

*Ethyl β-2-Keto*cyclo*hexylbenzylmalonate* (III; Ar = Ph, R = Et).—The above keto*cyclo*hexylbenzylmalonic acid (3 g.) was esterified by passing dry hydrogen chloride into its solution in absolute ethanol. *Ethyl β-2-keto*cyclo*hexylbenzylmalonate* (3 g.) was obtained as a colourless viscous oil, b. p. 172° (air-bath)/1 mm. (Found: C, 70·1; H, 7·4. $C_{20}H_{26}O_5$ requires C, 69·4; H, 7·5%).

The 2 : 4-*dinitrophenylhydrazone*, prepared in ethanol, gave orange needles (from ethanol), m. p. 135—136° (Found: C, 59·2; H, 5·7; N, 10·7. $C_{26}H_{30}O_8N_4$ requires C, 59·3; H, 5·7; N, 10·6%).

*α-Carbethoxy-β-2-keto*cyclo*hexyl-β-phenylpropionamide* (VI).—(*a*) Concentrated ammonia was added to a hot solution of ethyl 4-phenyl-3 : 4 : 5 : 6 : 7 : 8-hexahydrocoumarin-3-carboxylate in ethanol until a faint turbidity appeared. Sufficient hot ethanol was then added to give a clear solution, and the mixture placed in the refrigerator. After 2 days, crystalline *α-carbethoxy-β-2-keto*cyclo*hexyl-β-phenylpropionamide* was obtained. It formed colourless needles (from ethanol), m. p. 183° (decomp.) (Found: C, 68·1; H, 7·2; N, 4·4. $C_{18}H_{23}O_4N$ requires C, 68·1; H, 7·25; N, 4·4%).

(*b*) A solution of ethyl β-2-keto*cyclo*hexylbenzylmalonate in ethanol, treated with concentrated ammonia as above, gave the same monoamide, m. p. and mixed m. p. 183° (decomp.).

*β-2-Keto*cyclo*hexylbenzylmalonic Anhydride* (VII; Ar = Ph).—Concentrated sulphuric acid (3 c.c.) was added to ethyl 4-phenyl-3 : 4 : 5 : 6 : 7 : 8-hexahydrocoumarin-3-carboxylate (2 g.) in a test tube. A deep red solution resulted with the evolution of considerable heat. The mixture was stirred with a glass rod, heated on the steam-bath for 1 minute, and then immediately cooled in ice. After being poured into ice-cold water, the product separated as an oil which was washed with water and treated with a little ethanol. The resulting crystalline *β-2-keto*cyclo*hexylbenzylmalonic anhydride* (1·6 g.) formed colourless needles (from ethanol), m. p. 169° (decomp.) (Found: C, 70·6; H, 6·0. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%). The best yields in this preparation were obtained only when small quantities, as above, were used, the reaction then being more easily controllable.

This anhydride was also formed when the malonic acid (III; Ar = Ph, R = H) was heated with thionyl chloride in benzene, a procedure used by Mannich and Butz (*loc. cit.*) for the preparation of malonic anhydrides of analogous structure. It boiled without decomposition at 160°/0·4 mm., the distillate being a colourless liquid which rapidly solidified. After recrystallisation from ethanol this had m. p. 169°, alone or mixed with an undistilled specimen.

By refluxing with excess of 10% aqueous sodium hydroxide until all went into solution, the anhydride (0·2 g.) was hydrolysed to *β-2-keto*cyclo*hexylbenzylmalonic acid* (0·2 g.), m. p. and mixed m. p. 135°.

4-Phenyl-3 : 4 : 5 : 6 : 7 : 8-hexahydrocoumarin (VIII; Ar = Ph).—This was obtained by heating the pure anhydride (VII; Ar = Ph) over a free flame until gas evolution ceased. The residual liquid was distilled at 160°/1 mm., a sample being redistilled for analysis. *4-Phenyl-3 : 4 : 5 : 6 : 7 : 8-hexahydrocoumarin* formed a colourless viscous liquid, b. p. 154°/0·3 mm. (Found: C, 78·6; H, 7·1. $C_{15}H_{16}O_2$ requires C, 78·8; H, 7·0%).

This hexahydrocoumarin (0·1 g.) was hydrolysed to *β-2-keto*cyclo*hexyl-β-phenylpropionic acid* (0·1 g.) by refluxing with 10% aqueous sodium hydroxide until all went into solution. The product had m. p. 125°, not depressed by an authentic specimen obtained by decarboxylation of *β-2-keto*cyclo*hexylbenzylmalonic acid* by the method of Vorländer and Kunze (*loc. cit.*).

Action of Dinitrophenylhydrazine on Ethyl 4-Phenyl-3 : 4 : 5 : 6 : 7 : 8-hexahydrocoumarin-3-carboxylate.—A solution of the carbethoxy-lactone in ethanol was treated with excess of 2 : 4-dinitrophenylhydrazine solution. After several hours, the supernatant liquid was decanted and the heavy red oil which had separated was dissolved in ethanol. On cooling in ice a few orange-yellow crystals of the dinitrophenylhydrazone of ethyl *β-2-keto*cyclo*hexylbenzylmalonate* separated. After recrystallisation, the product had m. p. 135°, not depressed by an authentic specimen (above).

Action of Hydroxylamine on Ethyl 4-Phenyl-3 : 4 : 5 : 6 : 7 : 8-hexahydrocoumarin-3-carboxylate.—A solution of the hexahydrocoumarin (3·3 g.) in ethanol (15 c.c.) was treated with a solution of hydroxylamine hydrochloride (1 g.) and anhydrous sodium acetate (2 g.) in a little water, and left overnight. Water (15 c.c.) was added, and the mixture cooled in the refrigerator. The solid (3 g.) was collected, dried on a porous plate and in a vacuum desiccator, and then recrystallised from benzene–light petroleum (b. p. 60—80°). The *hydroxamic acid* (XI) formed small colourless needles, m. p. 138° (decomp.) (Found: C, 65·1; H, 6·7; N, 4·4. $C_{18}H_{23}O_5N$ requires C, 64·9; H, 6·9; N, 4·2%).

This hydroxamic acid (1 g.) was heated at 145° (bath temp.) for 5 minutes. A solution of the residual oil, in a little ethanol, deposited colourless crystals of a *substance* (probably XIII) (0·75 g.) which after recrystallisation from ethanol formed colourless needles, m. p. 154° (Found: C, 68·7; H, 6·3; N, 4·4. $C_{18}H_{21}O_4N$ requires C, 68·6; H, 6·65; N, 4·4%). A solution of this product in ethanol was treated with excess of 2 : 4-dinitrophenylhydrazine solution. After a week, a few orange-yellow crystals were collected; these, after several recrystallisations from ethanol, were identified as the 2 : 4-dinitrophenylhydrazone of ethyl *β-2-keto*cyclo*hexylbenzylmalonate*, m. p. and mixed m. p. 135°.

The substance (m. p. 154°, 1·5 g.) was warmed with excess of 40% aqueous potassium hydroxide at 80° for ½ hour. The cooled solution, diluted with a little water, was acidified with dilute hydrochloric acid and extracted with ether. The oil obtained on distillation of the ether was dissolved in dry benzene, from which a crystalline *acid* (0·9 g.) separated; it formed very small needles, m. p. 146—147° (from benzene) (Found: C, 66·8; H, 5·8; N, 4·8. $C_{16}H_{17}O_4N$ requires C, 66·9; H, 5·9; N, 4·9%). This acid lost carbon dioxide at the m. p. to give a viscous oil which did not crystallise.

*Oxime of Ethyl β-2-Keto*cyclo*hexyl-β-phenylpropionate* (I; Ar = Ph).—A solution of hydroxylamine hydrochloride (3·4 g.) and anhydrous sodium acetate (7 g.) in a little water was added to a solution of ethyl *β-2-keto*cyclo*hexyl-β-phenylpropionate* (Vorländer and Kunze, *loc. cit.*, 7 g.) in ethanol, and the mixture refluxed for 5 minutes. After several hours at room temperature the solution deposited crystals (7 g.) of the *oxime*, which formed colourless needles (from ethanol), m. p. 126° (Found: C, 70·7; H, 7·9; N, 4·9. $C_{17}H_{23}O_3N$ requires C, 70·6; H, 7·95; N, 4·8%).

4-Phenyl-1-ethyldecahydroquinoline (II; Ar = Ph).—A solution of the above oxime (13 g.) in ethanol (300 c.c.) was reduced with hydrogen and copper chromite (6 g.) (*Org. Synth.*, Coll. Vol. II, p. 142) at 200° and 165 atmospheres for 3 hours. The catalyst was filtered off, the alcohol removed on the steam-bath, and the residual oil dissolved in ether. The ether solution was extracted three times with dilute hydrochloric acid, and washed with water. The hydrochloric acid extracts and washings were neutralised with sodium hydroxide, and the resulting oil was extracted with ether. Distillation gave *4-phenyl-1-ethyldecahydroquinoline* (8 g.) as a colourless liquid, b. p. 134°/1 mm. (Found: C, 84·0; H, 10·45; N, 5·8. $C_{17}H_{25}N$ requires C, 84·0; H, 10·3; N, 5·75%).

The *picrate*, prepared in ethanol, formed yellow needles (from glacial acetic acid), m. p. 204—207° (Found: C, 58·6; H, 6·0. $C_{23}H_{28}O_7N_4$ requires C, 58·4; H, 5·9%). The redistilled base regenerated from the pure picrate did not crystallise. The hydrochloride was very hygroscopic.

Dehydrogenation of 4-Phenyl-1-ethyldecahydroquinoline.—A mixture of the base (0·55 g.) and palladium black (0·07 g.) was heated at 300° for 6 hours in a slow stream of dry carbon dioxide. The resulting oil gave a picrate (0·65 g.) which m. p. and analysis showed to be the picrate of 4-phenylquinoline. It formed small yellow needles (from ethanol), m. p. 226° (Found: C, 58·3; H, 2·9; N, 12·6. Calc. for $C_{15}H_{11}N,C_6H_3O_7N_3$: C, 58·1; H, 3·2; N, 12·9%). For this picrate Koenigs and Meimberg (*loc. cit.*) give m. p. 224°, and Kenner and Statham (*J.*, 1935, 301) give m. p. 225°.

The base regenerated from the pure picrate was distilled at 135°/2 mm.; the distillate did not crystallise,* although Königs and Nef (*loc. cit.*) give m. p. 61—62° for 4-phenylquinoline. In order to complete the identification, therefore, the following salts were prepared. (*a*) The sulphate had m. p. 193—195° (lit., 195—196°); its aqueous solution fluoresced in ultra-violet light. (*b*) The methiodide formed long yellow needles (from ethanol), m. p. 222° (lit., 222°). (*c*) The chloroplatinate had m. p. 244° (Koenigs and Jaeglé, *Ber.*, 1895, **28**, 1050, give 244°).

Ethyl 4-p-Methoxyphenyl-3 : 4 : 5 : 6 : 7 : 8-hexahydrocoumarin-3-carboxylate (V; Ar = *p*-C_6H_4·OMe).—2-*p*-Methoxybenzylidene*cyclo*hexanone (21·6 g.) (Poggi and Guastalla, *loc. cit.*) in benzene (100 c.c.) was added all at once to a suspension of ethyl sodiomalonate [from sodium (2·3 g.) and ethyl malonate (16 g.)] in benzene (100 c.c.), and the mixture refluxed for 2 hours. After working up as for the benzylidene*cyclo*hexanone condensation, the product (34 g.) was obtained as a heavy viscous oil, which was sufficiently pure for the next stage of the synthesis. In an attempt to prepare a specimen for analysis, the oil (2 g.) was distilled in a vacuum. There was considerable decomposition, and the viscous brown distillate (b. p. 235°/7 mm.) was redistilled, giving a colourless oil (b. p. 190°/1 mm.). A solution of this oil in ethanol deposited crystals of *4-p-methoxyphenyl-3 : 4 : 5 : 6 : 7 : 8-hexahydrocoumarin* (0·4 g.), which after recrystallisation from ethanol formed long colourless needles, m. p. 113° (Found: C, 74·1; H, 6·9. $C_{16}H_{18}O_3$ requires C, 74·4; H, 7·0%).

*β-2-Keto*cyclo*hexyl-p-methoxybenzylmalonic Anhydride* (VII; Ar = *p*-C_6H_4·OMe).—Concentrated sulphuric acid (3 c.c.) was added to the crude ethyl *4-p*-methoxyphenyl-3 : 4 : 5 : 6 : 7 : 8-hexahydrocoumarin-3-carboxylate (2 g.). After being heated on the steam-bath for 1 minute, and then cooled in ice, the solution was poured into ice–water. The product, after being washed with water, was dissolved in ethanol (charcoal) from which colourless crystals of *β-2-keto*cyclo*hexyl-p-methoxybenzylmalonic anhydride* (1·3 g.) separated. After recrystallisation from ethanol this formed colourless needles, m. p. 154—155° (Found: C, 67·8; H, 6·0. $C_{17}H_{18}O_5$ requires C, 67·55; H, 5·95%). This anhydride (0·5 g.) was converted into *4-p*-methoxyphenyl-3 : 4 : 5 : 6 : 7 : 8-hexahydrocoumarin (0·3 g.) by being heated at 160° until evolution of gas had ceased. After recrystallisation this had m. p. and mixed m. p. 113°.

*β-2-Keto*cyclo*hexyl-p-methoxybenzylmalonic Acid* (III; Ar = *p*-C_6H_4·OMe; R = H).—(*a*) Ethyl *4-p*-methoxyphenyl-3 : 4 : 5 : 6 : 7 : 8-hexahydrocoumarin-3-carboxylate (24 g.) was hydrolysed by 1½ hours' boiling with 40% aqueous-alcoholic potassium hydroxide. *β-2-Keto*cyclo*hexyl-p-methoxybenzylmalonic acid* (15 g.) formed fine colourless needles (from acetic acid), m. p. 130°. Analysis of the specimen dried in a vacuum desiccator showed the presence of one molecule of acetic acid of crystallisation (Found: C, 60·0; H, 6·7. $C_{17}H_{20}O_6,C_2H_4O_2$ requires C, 60·0; H, 6·3%).

(*b*) Keto*cyclo*hexylmethoxybenzylmalonic anhydride (0·2 g.) was hydrolysed to the same keto*cyclo*hexylmethoxybenzylmalonic acid (m. p. and mixed m. p. 130°) by refluxing with excess of 10% aqueous sodium hydroxide.

*β-2-Keto*cyclohexyl-*β*-p-*methoxyphenylpropionic Acid.*—(*a*) *β*-2-Keto*cyclo*hexyl-*p*-methoxybenzylmalonic acid (35 g.) was heated at 150° (bath temp.) until evolution of carbon dioxide ceased. The oil obtained was dissolved in ethyl acetate, from which crystalline *β-2-keto*cyclo*hexyl-β-p-methoxyphenylpropionic acid* (25 g.) was obtained. It formed small colourless needles (from ethyl acetate), m. p. 125—126° (Found: C, 69·7; H, 7·2. $C_{16}H_{20}O_4$ requires C, 69·6; H, 7·2%).

(*b*) The same acid was obtained by refluxing *4-p*-methoxyphenyl-3 : 4 : 5 : 6 : 7 : 8-hexahydrocoumarin with excess of 10% aqueous sodium hydroxide.

*Ethyl β-2-Keto*cyclo*hexyl-β-p-methoxyphenylpropionate.*—Concentrated sulphuric acid (12 g.) was added to a solution of the above propionic acid (30 g.), in absolute ethanol (150 c.c.), and the mixture refluxed for 2½ hours. The product (27 g.) was obtained as a viscous oil suitable for the next stage of the synthesis. In an attempt to obtain a specimen for analysis, the crude ester (0·5 g.) was distilled. A colourless oil, b. p. 195°/1 mm., was obtained which solidified on treatment with ethanol. After recrystallisation from ethanol it was identified as *4-p*-methoxyphenyl-3 : 4 : 5 : 6 : 7 : 8-hexahydrocoumarin, m. p. and mixed m. p. 113°.

*Oxime of Ethyl β-2-Keto*cyclo*hexyl-β-p-methoxyphenylpropionate* (I; Ar = C_6H_4·OMe).—Hydroxylamine hydrochloride (9 g.) and anhydrous sodium acetate (18 g.) in a little water were added to a solution of the above crude ester (23 g.) in ethanol, and the mixture refluxed for 5 minutes. After several hours, the *oxime* (22 g.) was collected. It formed colourless needles (from ethanol), m. p. 146° (Found: C, 67·7; H, 7·8; N, 4·5. $C_{18}H_{25}O_4N$ requires C, 67·6; H, 7·8; N, 4·4%).

4-p-*Methoxyphenyl-1-ethyldecahydroquinoline.*—The above oxime (10 g.) in ethanol (300 c.c.) was

* *Added, June 29th*, 1948.—After several months this base crystallised spontaneously. It was recrystallised from light petroleum and then formed colourless needles, m. p. 61°.

reduced with hydrogen in the presence of copper chromite (5 g.) at 200° and 165 atmospheres for 3 hours. The acid-soluble fraction was distilled, giving 4-p-*methoxyphenyl*-1-*ethyldecahydroquinoline* (7 g.) as a colourless viscous oil, b. p. 175°/0·3 mm., which solidified on standing. It formed small colourless needles (from ethyl acetate), m. p. 89° (Found : C, 79·0; H, 9·8; N, 5·2. $C_{18}H_{27}ON$ requires C, 79·1; H, 9·9; N, 5·1%).

The *picrate*, prepared in ethanol and recrystallised from glacial acetic acid, formed stout yellow needles, m. p. 182—184° (Found : C, 57·4; H, 6·0. $C_{18}H_{27}ON,C_6H_3O_7N_3$ requires C, 57·3; H, 6·0%).

The *hydrochloride*, prepared by passing dry hydrogen chloride through a solution of the base in ether, formed colourless needles from ethanol–ether, m. p. 248—250° (Found : C, 69·9; H, 8·8. $C_{18}H_{28}ONCl$ requires C, 70·0; H, 9·0%).

4-p-*Hydroxyphenyl*-1-*ethyldecahydroquinoline Hydrobromide*.—Hydrobromic acid (3 c.c.; 48%) was added to a solution of the methoxy-base (1·3 g.) in glacial acetic acid (1·75 c.c.), and the mixture refluxed for 9 hours. On cooling in ice, 4-p-*hydroxyphenyl*-1-*ethyldecahydroquinoline hydrobromide* (1·27 g.) was obtained. It crystallised from glacial acetic acid in small colourless needles, m. p. 227—228° (Found : C, 59·95; H, 7·5; N, 4·3. $C_{17}H_{26}ONBr$ requires C, 60·0; H, 7·6; N, 4·1%). The free base, which was soluble in alkali, gave no colour with ferric chloride.

We thank the Department of Scientific and Industrial Research for a maintenance grant (to T. W.), and Mr. J. M. L. Cameron for the microanalyses. One of us (G. M. B.) has been working with an I.C.I. Research Fellowship.

UNIVERSITY OF GLASGOW. [*Received, January 19th*, 1948.]