Cyclohexenone Derivatives. Part VII.[1] Novel Aromatisation Reaction of Some Aryloxocyclohexenylacetic Acid Derivatives

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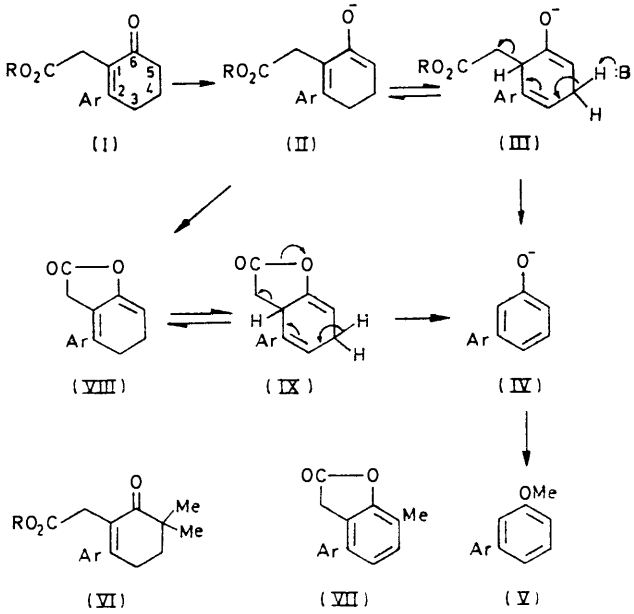
Methyl 2-aryl-6-oxocyclohex-1-enylacetates (I; R = Me) and some related compounds, when heated with a number of base–solvent systems, undergo aromatisation, the cyclohexenone system becoming phenolic with concomitant loss of the acetate side-chain. Sodium hydride in dimethylformamide at 100° is most effective for this transformation, and few alkoxides in aprotic solvents also catalyse the reaction. The mechanism is discussed. The results of dehydrogenation using pyridine hydrochloride are also reported.

DURING the last few years, we have developed [2] an efficient synthesis of 2-aryl-6-oxocyclohex-1-enylacetates (I) from the Mannich base of an aryl methyl ketone and ethyl β-oxoadipate.[3] Introduction of an angular methyl group in these compounds [*e.g.* (I; Ar = 6-methoxy-2-naphthyl)] was expected to lead to products which were easily converted into hydroaromatic steroids. This has been achieved with related cyclopentenone derivatives by reductive methylation,[4] which unfortunately yields a preponderance of *cis*-isomers.[5] We hoped to achieve more stereospecific angular methylation by treating the esters (I) with a suitable base and methyl iodide,[6] followed by catalytic hydrogenation of the resulting βγ-unsaturated cyclohexenones. Sodium hydride in dimethylformamide (DMF) is an excellent reagent for generating carbanions from active methylene compounds prior to their alkylation,[7] and possesses advantages over other metal–solvent combinations [8] and no abnormal side reaction has yet been reported. However, when methyl 2-(2-naphthyl)-6-oxocyclohex-1-enylacetate (I; Ar = β-$C_{10}H_7$, R = Me) was treated with NaH–DMF–MeI, no angular methylation took place. Instead, a phenolic ether (V; Ar = β-$C_{10}H_7$) was isolated in high yield (~70%), and identified by comparison with an authentic specimen from 3-(2-naphthyl)cyclohex-2-enone. Subsequently, the esters (I; Ar = Ph, *p*-MeO·C_6H_4, or α- or β-$C_{10}H_7$, R = Me) and an acid (I; Ar = β-$C_{10}H_7$, R = H) were treated with sodium hydride (3 mol) in DMF, first at room temperature and then at 100°, without adding methyl iodide; in each case, 3-arylphenols



SCHEME 1

(IV) were obtained in varying yields along with some intractable gum.

The first step of the reaction is apparently the abstraction of a proton from C(5) instead of C(3), the resultant

[1] Part VI, D. Nasipuri, K. Mitra, and S. Venkataraman, *J.C.S. Perkin I*, 1972, 1836.

[2] (*a*) D. Nasipuri, A. C. Chaudhuri, and J. Roy, *J. Chem. Soc.*, 1958, 2734; (*b*) D. Nasipuri and J. Roy, *ibid.*, 1960, 1571.

[3] J. C. Bardhan, *J. Chem. Soc.*, 1936, 1848; J. Korman, *J. Org. Chem.*, 1957, **22**, 849; E. C. Taylor and A. McKillop, *Tetrahedron*, 1967, **23**, 897.

[4] G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Amer. Chem. Soc.*, 1965, **87**, 275.

[5] A. J. Birch and G. S. R. Subba Rao, *Austral. J. Chem.*, 1970, **23**, 547; E. G. Brain, F. Cassidy, M. F. Constantine, J. C. Hanson, and J. D. Tidy, *J. Chem. Soc.* (*C*), 1971, 3846.

[6] H. O. House, 'Modern Synthetic Reactions,' Benjamin, New York, 1965, p. 191, and references cited therein.

[7] L. F. Fieser and M. Fieser, 'Reagents for Organic Synthesis,' Wiley, New York, 1967, p. 278.

[8] H. E. Zaugg, D. A. Dunnigan, R. J. Michaels, L. R. Swett, T. S. Wang, A. H. Sommers, and R. W. DeNet, *J. Org. Chem.*, 1961, **26**, 644; F. D. Popp and M. J. Wafer, *Chem. Comm.*, 1966, 207; J. R. Kershaw and B. C. Uff, *ibid.*, p. 331; F. D. Popp and J. M. Wafer, *J. Heterocyclic Chem.*, 1967, **4**, 183.

enolate ion (II) being stabilised by an extended conjugation with the aromatic ring (Scheme 1). This was supported by the isolation of two crystalline compounds (VI and VII; Ar = β-$C_{10}H_7$) in low yield along with 3-(2-naphthyl)anisole as the major product, when the ester (I; Ar = β-$C_{10}H_7$, R = Me) was treated with either NaH–DMF–MeI or $KOC_5H_{11}^t$–C_6H_6–MeI. The structure of compound (VI) was proved by its i.r. and n.m.r. spectra; that of compound (VII) was confirmed by synthesis [condensation of the methiodide of 2-dimethylaminoethyl 2-naphthyl ketone and ethyl α-methyl-β-oxoadipate [9] followed by hydrolysis and dehydrogenation of the resultant 5-methyl acid with palladium–charcoal]. A recent observation of methylation of 3-(2-naphthyl)-2-methylcyclohex-2-enone [10] is also in accord.

In the next step, the conjugated enolate anion (II) possibly aromatises *via* its isomeric cyclohexa-1,4-diene structure (III) by a base-catalysed elimination reaction as shown in Scheme 1. The aromatisation of the diene, coupled with the ability of the acetate group to depart with an electron pair, seems to provide the necessary driving force for the reaction. The latter point was illustrated by the failure of the homologous ester (I; Ar = β-$C_{10}H_7$, $CH_2{\cdot}CH_2{\cdot}CO_2Me$ for $CH_2{\cdot}CO_2Me$) to undergo aromatisation. This compound was prepared from 2-dimethylaminoethyl 2-naphthyl ketone and ethyl β-oxopimelate [11] by an analogous series of reactions.[2] 3-(2-Naphthyl)cyclohex-2-enone likewise did not react.

We have modified our earlier interpretation [12] of the course of the reaction. Thus while we do not eliminate the possibility of the lactonic intermediates [(VIII) and (IX)], we have not found evidence of their presence. For instance, the enolate ion (II; Ar = β-$C_{10}H_7$) formed by heating the ester (I) with sodium hydride in benzene did not produce any lactonic or acidic materials but gave the original ester on acidification. Again, model experiments having shown that 2-naphthyl benzoate is cleaved into 2-naphthol and benzoic acid quantitatively with no trace of *NN*-dimethylbenzamide by sodium hydride and dimethylformamide at 100°, we now consider that the effective base is sodium dimethylaminomethoxide itself rather than sodiodimethylamine derived from it [12] [equation (1)]. The generation and reaction of this

$$Me_2N{\cdot}CHO + NaH \longrightarrow Me_2N{\cdot}CH_2O^-Na^+ \rightleftharpoons Me_2N^-Na^+ + CH_2O \quad (1)$$

species has been evidenced also from other work [13] with sodium hydride and dimethylformamide.

Subsequently, other base–solvent systems were used for aromatisation of methyl 2-(2-naphthyl)-6-oxocyclohex-1-enylacetate (I; Ar = β-$C_{10}H_7$, R = Me). The results are shown in the Table. Approximately 3 equiv. of base were used for one mole of ester. No aromatisation was observed using one mole of base in any case. As expected, the alkoxides in appropriate solvents were also effective for bringing about the transformation, though to a lesser extent. Incidentally, the cleavage of

Aromatisation of methyl 2-(2-naphthyl)-6-oxocyclohex-1-enylacetate

Experiment no.	Base–Solvent	Temp. (°C)	Time (h)	Yield phenol (%) [a]
1	NaH–DMF	100	0·75	70
2	NaOEt–DMF	100	1	45
3	$KOC_5H_{11}^t$–C_6H_6	80	1·5	26
4	NaOEt–Dioxan	105	1	10
5	NaH–Dioxan	105	1	0 [b]
6	NaH–C_6H_6	80	1	0 [b]
7	NaOMe–MeOH	70	3	0 [b]

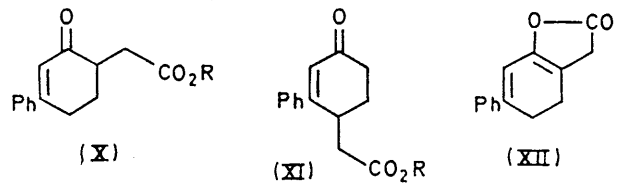
[a] Yield based on isolation of 3-(2-naphthyl)phenol by column chromatography. [b] Unchanged ester was recovered.

2-naphthyl acetate and 2-naphthyl benzoate to 2-naphthol took place quantitatively with a molar amount of sodium hydride in DMF at 100° (1 h), and in good yield (70—95%) with sodium ethoxide in DMF. Sodium hydride in dioxan failed to bring about appreciable cleavage of 2-naphthyl benzoate though it partially cleaved 2-naphthyl acetate, probably through the abstraction of a proton from the acetate group. No hydrogen, however, was liberated in the latter reaction and cleavage by hydride transfer from sodium hydride could not be wholly excluded.

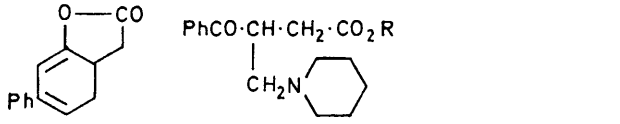
With the esters of the type (I; R = Me), the highest yield of phenol (IV) (70%) was obtained for (I; Ar = β-$C_{10}H_7$, R = Me) using NaH in DMF. Even the corresponding acid afforded a considerable yield of 3-(2-naphthyl)phenol (25—30%) under these conditions. When the naphthyl group was replaced by phenyl or *p*-methoxyphenyl, the yields dropped to 25—30% and the derived acids gave no detectable amounts of phenol. The higher yield with the 2-naphthyl derivatives might be due to a smaller fractional loss in the total resonance energy during deconjugation [(II) ⟶ (III)] of the enolate ion than in the phenyl derivatives. The 1-naphthyl derivative gave the corresponding phenol only in 8% yield but a steric factor might be involved in this case.[14] Two isomeric esters [(X) and (XI; R = Me)] were also treated with NaH–DMF under similar conditions. The former gave an appreciable yield of phenol (IV; Ar = Ph) (25%) but the latter failed to react, as expected. A specimen of lactone, possibly a mixture of isomers (XII) and (XIII) as evidenced by n.m.r. spectra, was prepared by heating the acid (X; R = H) with acetic anhydride and sodium acetate,[15] but failed to give a detectable amount of phenol with NaH–DMF at 100°. The ester (XI; R = Me) was prepared in good yield from 3-benzoylpropionic acid *via* its Mannich base (XIV; R = Me), the methiodide of which was condensed with ethyl acetoacetate; the product was

[9] M. Guha, U. Rakshit, and D. Nasipuri, *J. Indian Chem. Soc.*, 1960, **37**, 267.
[10] H. Carpio, W. H. Rooks, and P. Crabbe, *J. Medicin. Chem.*, 1970, **13**, 634.
[11] M. Guha and D. Nasipuri, *Org. Synth.*, 1962, **42**, 41.
[12] D. Nasipuri, A. Bhattacharya, and B. G. Hazra, *Chem. Comm.*, 1971, 660.
[13] J. M. Z. Gladych and R. Hornby, *Chem. and Ind.*, 1970, 652; J. S. Brimacombe, B. D. Jones, M. Stacey, and J. J. Willard, *Carbohydrate Res.*, 1966, **2**, 167.
[14] D. Nasipuri and A. Bhattacharya, *Indian J. Chem.*, 1972, **10**, 799.
[15] R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Amer. Chem. Soc.*, 1952, **74**, 4223.

hydrolysed and re-esterified. The structure was confirmed by spectral data.

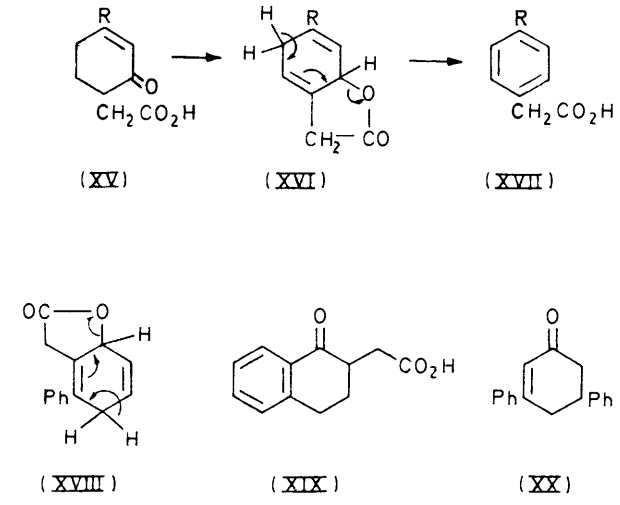


(X) (XI) (XII)



(XIII) (XIV)

Recently, aromatisation of 4-substituted 2-oxocyclohex-3-enylacetic acids (XV) to 4-substituted arylacetic acids (XVII) under acid catalysis has been reported.[16] This transformation is believed to involve the lactone (XVI) which is in equilibrium with carbonium ions and



(XV) (XVI) (XVII) (XVIII) (XIX) (XX)

SCHEME 2

isomeric lactones (Scheme 2). Some of the cyclohexenone derivatives described here were treated similarly (heating with pyridine hydrochloride for 1 h). 2-Phenyl-6-oxocyclohex-1-enyl acetic acid (I; Ar = Ph, R = H) gave 58% of biphenyl-2-ylacetic acid, conceivably through the lactone (XVIII), under conditions where the 4-phenyl acid (XV; R = Ph) was quantitatively aromatised. The lower yield in the former case may be due to conformational restraint in the γ-lactone (VIII) having two double bonds exocyclic to a five-membered ring, so that its formation is not favoured. 2-Phenyl-4-oxocyclohex-2-enylacetic acid (XI; H instead of Me) and 4-phenyl-2-oxocyclohex-3-enylpropionic acid (XV; R = Ph, $CH_2{\cdot}CH_2{\cdot}CO_2H$ for $CH_2{\cdot}CO_2H$) remained unchanged under these conditions, as expected from the mechanism. 2-Methyl-6-oxocyclohex-1-enylacetic acid (I; Ar = Me, R = H) and 1,2,3,4-tetrahydro-1-oxo-2-naphthylacetic acid (XIX) [17] also did not aromatise. The reason for failure in the last two cases is not apparent. The diphenylcyclohexenone (XX), prepared from chalcone [18] by Michael condensation with ethyl acetoacetate, also failed to aromatise, proving that the derived enol does not tautomerise to the allylic alcohol, although by so doing one of the double bonds would become conjugated with an aromatic ring.

[16] G. Palazzo and L. Baiocchi, *Tetrahedron Letters*, 1968, 4739.
[17] W. E. Bachman and G. D. Johnson, *J. Amer. Chem. Soc.*, 1949, **71**, 3463; W. H. Putarbaugh and R. L. Readshaw, *ibid.*, 1960, **82**, 3635.

EXPERIMENTAL

T.l.c. was carried out on 20 × 20 cm plates, with 0·1 mm layers of silica gel G. Petroleum refers to the fraction of b.p. 40—60°. Sodium hydride was used as a 50% suspension in mineral oil (Fluka AG); dimethylformamide (DMF), b.p. 150—152°, was dried by distilling over phosphorus pentoxide. Analytical g.l.c. was carried out on a column (6 ft × ¼ in) of 10% poly(diethylene glycol adipate) on Gaschrom-Z(60—80 mesh) with nitrogen as carrier gas. N.m.r. spectra were recorded with HA100, A60, or T60 spectrometers with [^{2}H]chloroform as solvent and tetramethylsilane as internal reference. All organic extracts were dried over anhydrous sodium sulphate.

Methyl 2-Aryl-6-oxocyclohex-1-enylacetates (I; R = Me).—The methyl esters (I; R = Me) were prepared [2] by condensation of the Mannich base methiodide of a methyl aryl ketone with ethyl β-oxoadipate (1 mol. equiv.) in the presence of potassium ethoxide (1·5 mol. equiv.) in benzene and ethanol. The crude product was directly hydrolysed with aqueous 6% potassium hydroxide solution and the acid esterified with methanolic 3% hydrogen chloride. The yields of the ester (I) varied within 45—60%. Methyl 2-(2-naphthyl)-6-oxocyclohex-1-enylacetate (I; Ar = β-$C_{10}H_7$; R = Me) (45%) crystallised from methanol in needles, m.p. 135—136° (lit.,[2a] 131°), $\nu_{max.}$ (Nujol) 1730 and 1665 cm^{-1}; τ (100 MHz) 2·10 and 2·55 (7H, m, ArH), 6·38 (3H, s, CO_2Me), 6·78 (2H, s, $CH_2{\cdot}CO_2Me$), 7·24 (2H, t, *J* 7 Hz, allylic CH_2), 7·42 (2H, t, *J* 7 Hz, $CH_2{\cdot}CO$), and 7·82 (2H, m, CH_2). The *2,4-dinitrophenylhydrazone* had m.p. 183° (from benzene–methanol) (Found: C, 63·4; H, 4·5; N, 11·7. $C_{25}H_{22}N_4O_6$ requires C, 63·3; H, 4·6; N, 11·8%). The derived acid crystallised from aqueous ethanol in needles, m.p. 161° (lit.,[2a] 156°). Methyl 2-(1-naphthyl)-6-oxocyclohex-1-enylacetate (I; Ar = α-$C_{10}H_7$, R = Me) [14] had m.p. 77°. Methyl 2-phenyl-6-oxocyclohex-1-enylacetate (I; Ar = Ph, R = Me) crystallised from benzene–petroleum in prisms, m.p. 85—86° (lit.,[2b] m.p. 82·5°), $\nu_{max.}$ ($CHCl_3$) 1735, 1660, and 1620 cm^{-1}, τ (60 MHz) 2·63 (5H, m, ArH), 6·35 (3H, s, CO_2Me), 6·93 (2H, s, CH_2CO_2Me), 7·40 (4H, m, =C–CH_2 and OC–CH_2), and 7·80 (2H, m). Methyl 2-*p*-methoxyphenyl-6-oxocyclohex-1-enylacetate (I; Ar = *p*-$MeOC_6H_4$, R = Me) [9] had m.p. 137°. *Methyl 2-(2-naphthyl)-6-oxocyclohex-1-enylpropionate* was prepared by replacing ethyl β-oxoadipate with ethyl β-oxopimelate in the above sequence of reactions and was obtained as a gum (50%), b.p. 190—200° at 0·2 mmHg (Found: C, 77·6; H, 6·7. $C_{20}H_{20}O_3$ requires C, 77·9; H, 6·5%), $\nu_{max.}$ ($CHCl_3$) 1735, 1665, and 1616 cm^{-1}.

3-Arylcyclohex-2-enones.—3-(2-Naphthyl)-, 3-(1-naphthyl)-, and 3-phenylcyclohex-2-enones were prepared by

[18] R. Connor and D. B. Andrews, *J. Amer. Chem. Soc.*, 1934, **56**, 2713.

modification of a known procedure.[19] In a typical experiment, ethyl acetoacetate (21 g, 0·16 mol) was added to a solution of sodium (3·6 g, 0·16 mol) in ethanol (90 ml) followed by the hydrochloride of 2-dimethylaminoethyl 2-naphthyl ketone (21 g, 0·08 mol). The mixture was cooled and dimethyl sulphate (20·2 g, 0·16 mol) was added dropwise with stirring during 0·5 h. Ethanol was distilled off and the oil obtained after acidification was hydrolysed with aqueous 10% potassium hydroxide (180 ml) under nitrogen for 4 h. Usual work-up and distillation of the organic matter afforded 3-(2-naphthyl)cyclohex-2-enone as an oil (11 g), b.p. 170—180° at 0·2 mmHg, which crystallised from benzene–petroleum in pale yellow plates, m.p. 100° (lit.,[20] 98—99°). 3-(1-Naphthyl)cyclohex-2-enone was similarly prepared from 2-dimethylaminoethyl 1-naphthyl ketone [14] and had b.p. 160—170° at 0·2 mmHg, and m.p. 54—56° (from benzene–petroleum) (Found: C, 86·1; H, 6·3. $C_{16}H_{14}O$ requires C, 86·5; H, 6·3%) (Woods *et al.*[20] reported it as a glass, b.p. 165—175° at 0·5 mmHg). The dinitrophenylhydrazone had m.p. 225° (lit.,[20] 223—224°). 3-Phenylcyclohex-2-en-1-one,[21] similarly prepared, had m.p. 64°. A by-product obtained in *ca.* 10% yield from the high boiling fraction of the last-named reaction crystallised from ether–petroleum in prisms, m.p. 110°, of 2-(2-*oxo*-4-*phenylcyclohex*-3-*enyl*)*ethyl phenyl ketone* (Found: C, 82·7; H, 6·7. $C_{21}H_{20}O_2$ requires C, 82·9; H, 6·6%), $\nu_{max.}$ (KBr) 1675, 1645, and 1610 cm^{-1}, τ (60 MHz) 1·90 (2H, 2d), 2·50 (8H, m), 3·60 (1H, t, *J* 1—2 Hz, vinyl H), 6·84 (2H, t, *J* 7 Hz), 7·20 (2H, t, *J* 7 Hz), and 7·80 (4H, m).

3-*Arylphenols*.—The foregoing 3-arylcyclohex-2-enones (1 g) in *p*-cymene (5 ml) were boiled with 10% palladium–charcoal for 5 h with intermittent flushing by nitrogen. The phenols were extracted with aqueous 5% potassium hydroxide, precipitated with acid, and finally purified by crystallisation and sublimation. 3-(2-*Naphthyl*)*phenol* had m.p. 114—115° (benzene–petroleum) (Found: C, 87·4; H, 5·5. $C_{16}H_{12}O$ requires C, 87·3; H, 5·5%), the *methyl ether* (V; Ar = β-$C_{10}H_7$) crystallised from petroleum in prisms, m.p. 90° (Found: C, 87·3; H, 6·0. $C_{17}H_{14}O$ requires C, 87·2; H, 6·0%), τ (60 MHz) 1·85—3·10 (11H, m, ArH) and 6·12 (3H, s, OMe). 3-(2-*Naphthyl*)*phenyl acetate*, prepared from the phenol by acetylation had m.p. 73° (ether–petroleum) (Found: C, 82·2; H, 5·2. $C_{18}H_{14}O_2$ requires C, 82·4; H, 5·3%). 3-(1-*Naphthyl*)*phenol* was obtained as a gum (Found: C, 87·5; H, 5·6%), its methyl ether was also a liquid, τ (60 MHz) 1·90—3·10 (11H, m, ArH) and 6·13 (3H, s, OMe). 3-Phenylphenol crystallised from ether–petroleum in fine needles, m.p. 80—81° (lit.,[22] 78°) (Found: C, 84·4; H, 5·8. Calc. for $C_{12}H_{10}O$: C, 84·7; H, 5·9%).

2-*Oxo*-4-*phenylcyclohex*-3-*enylacetic Acid* (XV; R = Ph).—The methiodide of β-dimethylaminopropiophenone (35·4 g, 0·2 mol) was condensed with ethyl α-acetosuccinate as described in the general procedure. Work-up afforded a thick orange liquid (39 g), b.p. 190—200° at 0·6 mmHg. This was hydrolysed to yield the *acid* (XV; R = Ph) (30 g) as a crystalline solid, m.p. 146° (from aqueous methanol) (Found: C, 73·3; H, 6·2. $C_{14}H_{14}O_3$ requires C, 73·1; H, 6·1%); 2,4-*dinitrophenylhydrazone*, m.p. 228° (from ethyl acetate) (Found: C, 58·3; H, 4·3; N, 13·9. $C_{20}H_{18}N_4O_6$ requires C, 58·5; H, 4·4; N, 13·7%); *semicarbazone*, m.p. 213° (from ethanol) (Found: N, 14·5. $C_{15}H_{17}O_3N_3$ requires N, 14·6%). The *methyl ester* had m.p. 82° (from ether–petroleum) (Found: C, 73·7; H, 6·7. $C_{15}H_{16}O_3$ requires C, 73·8; H, 6·6%), $\nu_{max.}$ ($CHCl_3$) 1725, 1655, and 1610 cm^{-1}, τ (60 MHz) 2·50 (5H, m), 3·52 (1H, t, *J* 1—2 Hz), 6·25 (3H, s), 7·20 (5H, m), and 7·80 (2H, m); 2,4-*dinitrophenylhydrazone*, m.p. 203° (from benzene–methanol) (Found: N, 13·3. $C_{21}H_{20}N_4O_6$ requires N, 13·2%).

Enol-lactones [(XII) *and* (XIII)].—The acid (XV; R = Ph) (2·3 g, 0·01 mol), fused sodium acetate (20 mg, 0·00025 mol), and acetic anhydride (27 ml) were refluxed under nitrogen for 4 h. Acetic anhydride was removed under reduced pressure, the residue was taken up in ether, and the ethereal extract was thoroughly washed with aqueous 7% sodium carbonate solution and evaporated. The residue was adsorbed on silica gel (50 g). Elution with 5% ether–petroleum afforded an oil (0·95 g) which was sublimed at 200—210° (0·4 mmHg). The sublimate appeared homogeneous to t.l.c. (Found: C, 78·7; H, 6·1. $C_{14}H_{12}O$ requires C, 79·3; H, 5·7%), $\nu_{max.}$ (film) 1780br, 1660w, and 1605 cm^{-1}, the n.m.r. spectrum (60 MHz) showed a vinyl proton signal centred at τ 4·15 (*ca.* 1·5H, m).

3-(2-*Oxo*-4-*phenylcyclohex*-3-*enyl*)*propionic Acid*.—This acid was prepared as its lower homologue (XV; R = Ph), using ethyl α-acetoglutarate in place of ethyl α-acetosuccinate, and was obtained as a crystalline *solid*, m.p. 143—144° (from aqueous ethanol) (Found: C, 73·5; H, 6·8. $C_{15}H_{16}O_3$ requires C, 73·8; H, 6·6%), $\nu_{max.}$ ($CHCl_3$) 1715, 1650, and 1600 cm^{-1}, τ (60 MHz) 0·15 (1H, s, CO_2H), 2·60 (5H, m, ArH), 3·60 (1H, t, *J* 1—2 Hz, vinyl H), and 7·00—8·40 (9H, complex m).

5-*Methyl*-2-(2-*naphthyl*)-6-*oxocyclohex*-1-*enylacetic Acid*.—The methiodide of 2-dimethylaminoethyl 2-naphthyl ketone was condensed by the usual method with ethyl α-methyl-β-oxoadipate. The product on hydrolysis afforded the *acid* in 60% yield, m.p. 153—155° (from ether–petroleum) (Found: C, 77·3; H, 6·2. $C_{19}H_{18}O_3$ requires C, 77·6; H, 6·1%), $\nu_{max.}$ ($CHCl_3$) 1715, 1665, and 1605 cm^{-1}.

Lactone (VIII).—The foregoing acid (2 g) in *p*-cymene (20 ml) was heated with 10% palladium–charcoal (500 mg) for 5 h. The product was taken up in ether and the ethereal solution was extracted with aqueous 5% potassium hydroxide. The alkaline extract was acidified and warmed on a water-bath, and the resulting gum was extracted with ether. The extract was washed with aqueous sodium hydrogen carbonate solution, dried, and evaporated. The residue on sublimative distillation afforded the *lactone* (VIII) (0·95 g), b.p. 170—180° at 0·2 mmHg, m.p. 141° (from benzene–petroleum) (Found: C, 83·0; H, 5·0. $C_{19}H_{14}O_2$ requires C, 83·2; H, 5·1%), $\nu_{max.}$ (KBr) 1785 and 1620 cm^{-1}, τ (60 MHz) 2·00—2·80 (9H, m, ArH), 6·16 (2H, s, CH_2), and 7·62 (3H, s, ArMe).

Methyl 3-*Benzoyl*-4-*piperidinobutyrate* (XIV; R = Me).—A mixture of 3-benzoylpropionic acid (30·4 g) and piperidine hydrochloride (20·7 g) was heated at 120° for 5—10 min. To the resulting slurry, paraformaldehyde (5·1 g) was added all at once and the heating was continued for an additional 40 min. The viscous homogeneous oil was kept at 100° under reduced pressure for 45 min to remove water. The warm glassy mass was dissolved in dry ethanol (15 ml) and the solution was diluted with acetone (100 ml). On cooling,

[19] F. C. Novello and M. E. Christy, *J. Amer. Chem. Soc.*, 1953, **75**, 5431.

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the *hydrochloride* of 3-*benzoyl*-4-*piperidinobutyric acid* (XIV; R = H) crystallised out (35 g), m.p. 152—154° (Found: C, 61·1; H, 7·6. $C_{16}H_{22}ClNO_3$ requires C, 61·6; H, 7·1%). Freshly distilled thionyl chloride (6 ml) was dropped into ice-cold methanol (80 ml). After 5 min, the above hydrochloride (20 g) was added and the mixture was shaken vigorously until a clear solution resulted. It was kept at 0° for 24 h, methanol was removed at reduced pressure, and the residue was dissolved in the minimum quantity of water. The cooled aqueous solution was basified with aqueous 40% potassium hydroxide. The organic matter was extracted with ether; the extract was washed once with water, dried, and evaporated. The residual *amino-ester* (17 g) formed a viscous pale yellow oil, $\nu_{max.}$ (film) 1738, 1682, and 1602 cm^{-1}, τ (60 MHz) 2·10 (2H, m), 2·52 (3H, m), 6·38 (3H, s), 6·60 (1H, m), 7·25 (2H, d), 7·70 (6H, m), and 8·60 (6H, m). It was not further purified.

Methyl 4-*Oxo*-2-*phenylcyclohex*-2-*enylacetate* (XI; R = Me).—The foregoing amino-ester (15·5 g) was converted into its methiodide by adding methyl iodide (7·7 g) in the cold. To the semi-solid methiodide was added ethyl acetoacetate (7·1 g) followed by a solution of potassium (2·12 g) in ethanol (25 ml) with vigorous shaking. Stirring was continued at room temperature for 4 h more and the mixture was refluxed for 1·5 h after addition of a fresh solution of potassium (1·1 g) in ethanol (15 ml). Decomposition with 2N-sulphuric acid and usual work-up furnished a brown gum (13·5 g). This was hydrolysed with aqueous 6% potassium hydroxide (150 ml) for 5 h under nitrogen to furnish a gummy acid which crystallised from aqueous acetone in *plates* (7·5 g), m.p. 136—137° (Found: C, 72·9; H, 6·2. $C_{14}H_{14}O_3$ requires C, 73·0; H, 6·1%), $\nu_{max.}$ ($CHCl_3$) 1715, 1660, and 1610 cm^{-1}; τ (60 MHz) −0·31 (1H, s), 2·50 (5H, m), 4·62 (1H, s), 6·40 (1H, m), and 7·40—8·00 (6H, m); 2,4-*dinitrophenylhydrazone*, m.p. 232° (from benzene–methanol) (Found: C, 58·3; H, 4·4; N, 13·3. $C_{20}H_{18}N_4O_6$ requires C, 58·5; H, 4·4; N, 13·7%). The *methyl ester* was an oil, b.p. 175—178° at 0·6 mmHg (Found: C, 73·7; H, 6·8. $C_{15}H_{16}O_3$ requires C, 73·8; H, 6·6%); 2,4-*dinitrophenylhydrazone*, m.p. 192° (from benzene–methanol) (Found: C, 58·8; H, 4·9; N, 12·9. $C_{21}H_{20}N_4O_6$ requires C, 59·4; H, 4·7; N, 13·2%).

1,2,3,4-*Tetrahydro*-1-*oxonaphthalene*-2-*acetic Acid* (XIX).—This acid was prepared by the method of Hazra and De Dalal:[23] diethyl malonate was alkylated successively with phenethyl bromide and ethyl chloroacetate, and the product was hydrolysed to the substituted succinic acid; formation of the anhydride and finally a Friedel–Crafts ring-closure of the resultant α-phenethylsuccinic anhydride gave the required acid, m.p. 110° (lit.,[17] 106—108, 109—110°).

3,5-*Diphenylcyclohex*-2-*enone* (XX).—Ethyl 2-oxo-4,6-diphenylcyclohex-3-ene-1-carboxylate [18] was prepared by Michael condensation of chalcone and ethyl acetoacetate in the presence of piperidine; m.p. 112—113° (lit.,[18] 111—112·5°), $\nu_{max.}$ ($CHCl_3$) 1730, 1662, and 1602 cm^{-1}, τ (60 MHz) 2·60 (10H, m, ArH), 3·42 (1H, t, *J* 1 Hz, vinyl H), 5·87 (2H, q, *J* 7 Hz, OCH_2Me), 6·20 (2H, m, methine H), 6·95 (2H, m, CH_2), and 8·90 (3H, t, *J* 7 Hz, Me). The keto-ester (4 g) was hydrolysed by aqueous 10% sodium hydroxide (15 ml) to afford the *ketone* (XX) (2·5 g), b.p. 180—185° at 0·2 mmHg, m.p. 89—90° (from ether–petroleum) (Found: C, 86·8; H, 6·6. $C_{18}H_{16}O$ requires C, 87·1; H, 6·5%), $\nu_{max.}$ ($CHCl_3$) 1665 and 1600 cm^{-1}.

Alkylation Experiments.—Attempted angular methylation of methyl 2-(2-*naphthyl*)-6-*oxocyclohex*-1-*enylacetate* (I; Ar = β-$C_{10}H_7$, R = Me). (*a*) NaH–DMF–MeI method. The ester (I; Ar = β-$C_{10}H_7$, R = Me) (0·5 g, 1·7 mmol) in DMF (10 ml) was heated with sodium hydride (0·25 g, 5 mmol) under nitrogen at 100° for 45 min; *ca.* 40 ml of hydrogen was evolved and a deep red solution resulted. It was cooled, methyl iodide (5 ml) was added, and the mixture was stirred at room temperature for 4 h. The product was decomposed with 2N-sulphuric acid and worked up in the usual manner to afford a yellow oil (0·55 g). This was hydrolysed by heating with potassium hydroxide (0·2 g, 3·4 mmol) in methanol (5 ml) under nitrogen for 2 h. The resulting brown gum was absorbed on silica gel (25 g) and eluted with petroleum (25 ml fractions). The first few fractions gave the mineral oil (from sodium hydride). Subsequent fractions (ether–petroleum, 5 : 95) afforded an oil (280 mg) which solidified and crystallised from petroleum in prisms, m.p. 90°, identical with 3-(2-naphthyl)anisole (V; Ar = β-$C_{10}H_7$) (i.r. and mixed m.p.) (total yield *ca.* 70%). Ether–petroleum (10 : 90) eluted some yellow gum, and then a solid (25—30 mg), which crystallised from benzene–petroleum in needles, m.p. 140°, identical with the lactone (VIII) (i.r., n.m.r., and mixed m.p.) (Found: C, 83·4; H, 5·4. Calc. for $C_{19}H_{14}O_2$: C, 83·2; H, 5·1%). Further elution with the same solvent afforded another crystalline solid (40 mg, 8%), m.p. 212° (from methanol), identified as the *keto-acid* (VI; Ar = β-$C_{10}H_7$, R = H) (Found: C, 78·4; H, 6·7. $C_{19}H_{18}O_3$ requires C, 77·9; H, 6·5%), $\nu_{max.}$ (Nujol) 1710, 1670, 1608 (carbonyl), 1380, and 1352 cm^{-1} (*gem*-dimethyl), τ (60 MHz) −0·52 (1H, s, CO_2H), 2·05—2·75 (7H, m, ArH), 6·75 (2H, s, $CH_2{\cdot}CO_2H$), 7·24 (2H, t, *J* 6 Hz, allylic CH_2), 8·00 (2H, t, *J* 6 Hz, CH_2), and 8·78 (6H, s, CMe_2). Elution with ether–petroleum (40 : 60) afforded an unidentified gum (60 mg). When 2-(2-naphthyl)-6-oxocyclohex-1-enylacetic acid was similarly treated with 4 mol. equiv. of sodium hydride and an excess of methyl iodide, the lactone (VIII) was obtained in slightly higher yield (~10%).

(*b*) $KOC_5H_{11}{}^t$–C_6H_6–MeI method. Alcohol-free potassium t-pentyloxide prepared from potassium (0·073 g, 1·87 mmol) was dissolved in dry benzene (10 ml), and to it was added the ester (I; Ar = β-$C_{10}H_7$, R = Me) (0·5 g, 1·70 mmol) in benzene (2 ml) under nitrogen. The mixture was stirred for 2 h at room temperature, then cooled, and methyl iodide (2·5 g) was added. The whole was refluxed for 8 h and then worked up in the usual way to yield a gum (0·45 g). This was hydrolysed and the acids were chromatographed over silica gel as before. Elution with ether–petroleum (10 : 90) afforded the dimethylated keto-acid (VI; Ar = β-$C_{10}H_7$, R = H) (70 mg), m.p. 212°, and further elution with ether–petroleum (20 : 80) gave 2-(2-naphthyl)-6-oxocyclohex-1-enylacetic acid (300 mg; 60%), m.p. 155—160°, identified by comparison of i.r. spectra.

Aromatisation Reaction.—General methods. (*a*) With sodium hydride and DMF. The ester (I; R = Me) (1·70 mmol) in dimethylformamide (10 ml), was heated with sodium hydride (5 mmol) under nitrogen at 100° for 30—45 min; 1 mol. equiv. of hydrogen was evolved. The resulting deep red solution was decomposed with cold 2N-sulphuric acid and worked up in the usual way. The crude product was chromatographed over silica gel. The phenolic components were eluted by ether–petroleum (10 : 90). The rest of the organic material was eluted by 20—30% ether in petroleum and remained unidentified. Methyl 2-(2-naphthyl)-6-oxocyclohex-1-enylacetate (0·5 g) afforded 3-(2-naphthyl)-phenol (260 mg; 70%), m.p. 110—113° identified by its

[23] B. G. Hazra and Ila De Dalal, unpublished work.

i.r. spectrum, and mixed m.p. with a synthetic specimen, m.p. 115°. It was further converted into 3-(2-naphthyl)-phenyl acetate, m.p. 73°, $\nu_{max.}$ (Nujol) 1755, 1378, 1220, 1015, 785, and 740 cm^{-1}. The phenol was preceded in the chromatogram by a trace (25 mg) of a *lactone* [possibly (VIII; Ar = β-$C_{10}H_7$)] (Found: C, 82·9; H, 5·6. $C_{18}H_{14}O_2$ requires C, 82·5; H, 5·3%), $\nu_{max.}$ 1815 cm^{-1}. 2-(2-Naphthyl)-6-oxocyclohex-1-enylacetic acid (0·5 g) on similar treatment yielded the same phenol (120 mg, 30%), m.p. 106—111°. Methyl 2-(1-naphthyl)-6-oxocyclohex-1-enylacetate (I; Ar = α-$C_{10}H_7$, R = Me), and other esters [(I; Ar = Ph, $MeOC_6H_4$; R = Me) and (X; R = Me)] under the same conditions yielded products which showed the presence of original ester in t.l.c. These were hydrolysed with alkali and the sodium hydrogen carbonate-insoluble part was chromatographed for the phenol. In case of the 1-naphthyl derivative (0·5 g), lactonic material (20 mg), $\nu_{max.}$ (film) 1805 cm^{-1}, and a phenol (40 mg) were obtained, the latter having an identical i.r. spectrum with that of synthetic 3-(1-naphthyl)phenol. Methyl 6-oxo-2-phenylcyclohex-1-enylacetate (I; Ar = Ph, R = Me) (0·5 g) afforded 3-phenylphenol (100—180 mg, 28—37%), m.p. 80°. The results of the other two esters (I; Ar = *p*-MeO·C_6H_4, R = Me) and (X; R = Me) were similar. In the case of the phenyl derivatives, the total reaction products (unhydrolysed) were also analysed by g.l.c. In addition to the peak due to 3-phenylphenol, three major peaks appeared in the chromatogram with much longer retention time; one was due to the original ester but the other two were not identified.

(*b*) With sodium ethoxide and DMF and other base–solvent systems. Methyl 2-(2-naphthyl)-6-oxocyclohex-1-enylacetate (I; Ar = β-$C_{10}H_7$, R = Me) (1·70 mmol) was heated with 5 mmol of the following bases: alcohol-free sodium ethoxide in DMF (10 ml), and in dioxan (10 ml); sodium hydride in dioxan (10 ml), and in benzene (10 ml); potassium t-pentyloxide (alcohol-free) in benzene (20 ml); and sodium methoxide in methanol (12 ml). The results are summarised in the Table. Cleaner products were obtained with these bases and usually three components were isolated, *viz.* the phenol, the unchanged ester, and its corresponding acid.

(*c*) With pyridine hydrochloride. The substituted oxocyclohexyl acetic acid (0·5 g) was intimately mixed with freshly distilled pyridine hydrochloride (0·5 g) and heated at 200—210° for 1 h.[16] The product was digested with water and the solid acid was filtered off and crystallised. 6-Oxo-2-phenylcyclohex-1-enylacetic acid (0·5 g) afforded biphenyl-2-ylacetic acid (0·26 g, 58%), m.p. 117—118° (lit.,[24] 114—115°) (Found: C, 79·4; H, 6·0. Calc. for $C_{14}H_{12}O_2$: C, 79·2; H, 5·7%), τ (60 MHz) 0·33 (1H, s, CO_2H), 2·61br (9H, s, ArH), and 6·37 (2H, s, CH_2·CO_2H).

Cleavage of 2-Naphthyl Acetate and 2-Naphthyl Benzoate.—2-Naphthyl acetate and 2-naphthyl benzoate (0·1 mol) were separately treated with the following bases: (*a*) sodium hydride (0·12 mol) in DMF at 100° (1 h); (*b*) sodium ethoxide (alcohol-free) (0·2 mol) in DMF at 100° (2 h); (*c*) sodium ethoxide (0·2 mol) in dioxan at 105° (1 h); and (*d*) sodium hydride (0·12 mol) in dioxan (1 h). The volume of solvent used was 10—15 ml for 0·5 g of the ester. With reagents (*a*), (*b*), and (*c*), both the esters were cleaved to the extent of 70—100%, determined by the amount of 2-naphthol isolated. With reagent (*d*), 2-naphthyl acetate was 50% cleaved but 2-naphthyl benzoate remained unaffected.

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