342. *Synthesis of 3-Substituted Phenanthrenes. The Course of Intramolecular Cyclisation of 2-(m-Substituted Phenyl)cyclohexylacetic Acids.*

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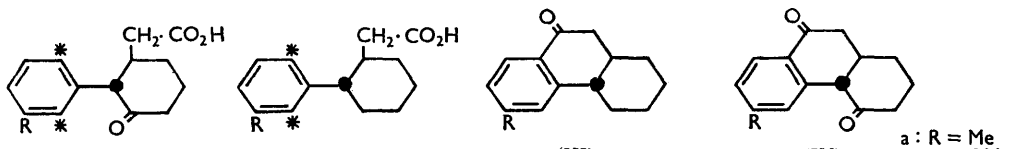
2-*m*-Tolyl- and 2-*m*-methoxyphenyl-cyclohexylacetic acid and their 3-oxo-derivatives cyclise intramolecularly to afford octahydrophenanthrene derivatives, shown by conversion into 3-substituted phenanthrenes to bear a methyl or a methoxyl group exclusively in one position. The compounds submitted to cyclisation are accessible through Michael condensation of 2-arylcyclohex-2-enones with malonic esters followed by standard transformations.

2-ARYLCYCLOHEXYLACETIC ACIDS and their 3-oxo-derivatives have been used as precursors of hydrophenanthrenes.[1,2] In all of these cases only one position was open to attack in the intramolecular Friedel–Crafts reaction.

Since in *meta*-substituted analogues (I, II) there are two positions (marked *) open to such attack, it seemed of interest to determine experimentally the course of their reaction.

2-*m*-Tolyl- and 2-*m*-methoxyphenyl-cyclohex-2-enone were submitted to Michael condensation with t-butyl malonate. The products were hydrolysed and decarboxylated, giving compounds of type (I) which were reduced by the Huang-Minlon procedure [3] to compounds of type (II). Cyclisation of the product (I) or (II) with anhydrous hydrogen



fluoride gave octahydropenanthrenes (IV, III) in high yields. Further treatment in each case gave solely 3-methylphenanthrene or 3-methoxyphenanthrene.

It is thus clear that intramolecular cyclisation occurred at one position, *viz.*, *para* to the substituent in the phenyl nucleus. No isomeric phenanthrenes were isolated despite careful chromatography.

In the practically quantitative intramolecular cyclisations of 3-oxo-2-*o*-tolylcyclohexylacetic acid [2] and 3-oxo-2-(2,3-dimethoxyphenyl)cyclohexylacetic acid [4] the position attacked is *meta* with reference to an *ortho-para*-directing group. It therefore appears that the reason for the apparently exclusive attack of the position *para* to the methyl or the methoxyl group in the compounds described in this paper is preponderantly a steric one.

EXPERIMENTAL

1-m-*Tolylcyclohexene.*—To *m*-tolylmagnesium bromide, prepared from *m*-bromotoluene (20 g., 0·11 mole) and magnesium (2·7 g., 0·11 g.-atom) in dry ether (120 ml.), cyclohexanone (11·4 g., 0·11 mole) in dry ether (11 ml.) was added with stirring at room temperature. The complex began to be precipitated before addition was complete. The mixture was then refluxed for 1 hr., kept overnight, and decomposed with saturated ammonium chloride solution. The ether layer was dried and the solvent removed. The residual oil was boiled with anhydrous oxalic acid (3·8 g.) in toluene (95 ml.) until no more water was obtained in an azeotropic collector.[5] The usual isolation gave the cyclo-olefin, b. p. 76—78°/0·07 mm. (16 g., 80%).

2-m-*Tolylcyclohex-2-enone Oxime.*—To a solution of 1-*m*-tolylcyclohexene (6·05 g., 0·03 mole)

[1] Bachmann and Fornefeld, *J. Amer. Chem. Soc.*, 1950, **72**, 5529.
[2] Klibansky and Ginsburg, *J.*, 1957, 1293.
[3] Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487.
[4] Elad and Ginsburg, unpublished results.
[5] Bergmann, Pappo, and Ginsburg, *J.*, 1950, 1369.

in acetic acid (6·5 ml.) cold n-pentyl nitrite (4·7 g., 0·04 mole) was added. The mixture was cooled to −15°, and concentrated hydrochloric acid (4·0 ml.) was then added dropwise with stirring at this temperature. The addition was complete in about 30 min., but stirring was continued for a further 2 hr. at −10°. The nitrosochloride was filtered off with suction, washed with ice-cold ethanol, and dried [5·7 g.; m. p. 118—121° (decomp.)]. The nitrosochloride was immediately converted into the oxime by slowly warming its suspension in pyridine (20 ml.) to 75°. After 10 min. all of the solid had dissolved. The solution was cooled and excess of hydrochloric acid was added. The precipitated oxime was filtered off, washed with water, and dried (5·5 g., 77%). The pure *oxime* had m. p. 107° (from ethanol) (Found: C, 76·9; H, 7·2; N, 6·9. $C_{13}H_{15}ON$ requires C, 77·6; H, 7·5; N, 6·9%).

2-m-*Tolylcyclohex-2-enone*.—The crude oxime (20 g., 0·1 mole), concentrated hydrochloric acid (20 ml.), and water (150 ml.) were refluxed for 3 hr. After cooling, the free ketone was taken up in ether, and the extract washed with 5% sodium carbonate solution, then water, and dried (Na_2SO_4). After removal of solvent, the residue was distilled in a vacuum. The unsaturated *ketone* had b. p. 123—125°/0·5 mm. (10 g., 55%), $\nu_{max.}$ (in $CHCl_3$), 1680 cm.$^{-1}$ (C:C·C:O).

The red 2 : 4-*dinitrophenylhydrazone* had m. p. 163° (from ethanol–ethyl acetate) (Found: C, 61·8; H, 4·95; N, 15·3. $C_{19}H_{18}O_4N_4$ requires C, 62·3; H, 4·95; N, 15·3%). The colourless *semicarbazone* had m. p. 203·5—204° (from ethanol) (Found: C, 69·3; H, 6·7; N, 17·1. $C_{14}H_{17}ON_3$ requires C, 69·1; H, 7·0; N, 17·3%).

3-*Oxo*-2-m-*tolylcyclohexylacetic Acid* (Ia).—A mixture of 2-*m*-tolylcyclohex-2-enone (10 g., 0·05 mole), freshly distilled t-butyl malonate (21 g., 0·1 mole) and potassium t-butoxide (from 0·42 g. of potassium and 6·6 ml. of t-butyl alcohol) was kept at 60° for 3 hr., then overnight at room temperature. After acidification with glacial acetic acid, the mixture was taken up in benzene, washed with water until neutral in reaction, and dried (Na_2SO_4). Then naphthalene-β-sulphonic acid (0·15 g.) was added, and the whole refluxed until gas evolution was complete. The cooled solution was extracted with saturated potassium carbonate solution, leaving neutral ester-products in the benzene layer. The benzene was removed and the residue was again saponified as above. The alkaline extracts were combined, acidified with dilute hydrochloric acid, and extracted with ether. The ether was evaporated, and the thick residual oil decarboxylated at 180° until gas evolution was complete. The residue was taken up in saturated sodium carbonate solution and filtered, and the clear solution acidified with dilute hydrochloric acid. Extraction with ether and removal of the solvent gave the viscous monobasic *acid*, which crystallised slowly (7 g., 53%; m. p. 114·5—115·5°, from methylcyclohexane), $\nu_{max.}$ (in $CHCl_3$) 1710 cm.$^{-1}$ (strong broad peak; includes carbonyl C:O and carboxyl C:O) (Found: C, 73·05; H, 7·2; O, 19·4. $C_{15}H_{18}O_3$ requires C, 73·1; H, 7·4; O, 19·5%).

2-m-*Tolylcyclohexylacetic Acid* (IIa).—The keto-acid (Ia) (6·8 g., 0·028 mole) was refluxed with diethylene glycol (75 ml.), potassium hydroxide (6 g.), and 95% hydrazine hydrate (9 ml.) for 2 hr. The condenser was then removed, the temperature was raised to 200°, and the mixture refluxed overnight. The cooled solution was acidified with dilute hydrochloric acid and extracted with chloroform. After the usual working-up the *acid* (4·4 g., 71%) was obtained, having m. p. 122—122·5° (from methanol) (Found: C, 77·0; H, 8·9; O, 14·0. $C_{15}H_{20}O_2$ requires C, 77·55; H, 8·7; O, 13·8%).

1 : 2 : 3 : 4 : 4*a* : 9 : 10 : 10*a*-*Octahydro*-6-*methyl*-9-*oxophenanthrene* (IIIa).—2-*m*-Tolylcyclohexylacetic acid (5·5 g., 0·024 mole) was treated with anhydrous hydrogen fluoride (*ca.* 200 g.) and after 4 hr. the mixture was worked up in the usual way.[6] From the acidified alkaline extract, starting material was regenerated (0·4 g.). The neutral ketonic material, obtained from the chloroform extract as an oil, crystallised slowly. It recrystallised from ethanol (carbon). The pure ketone (2·6 g.) had m. p. 102—103°. The ethanolic mother-liquor was evaporated to dryness and the residue was taken up in a minimal volume of hexane–benzene (1 : 1) and chromatographed on neutral alumina (50 g.). Elution with benzene gave more (1·45 g.) pure *ketone*, m. p. 103° (from ethanol) (total yield 85%), $\nu_{max.}$ (in $CHCl_3$) 1680 cm.$^{-1}$ (acetophenone-type C:O) (Found: C, 84·1; H, 8·7; O, 7·3. $C_{15}H_{18}O$ requires C, 84·1; H, 8·5; O, 7·5%).

The ketone gave a deep red 2 : 4-*dinitrophenylhydrazone*, m. p. 239—240° (from ethyl acetate) (Found: C, 63·7; H, 5·8; N, 13·7. $C_{21}H_{22}O_4N_4$ requires C, 63·9; H, 5·6; N, 14·2%).

1 : 2 : 3 : 4 : 4*a* : 9 : 10 : 10*a*-*Octahydro*-9-*hydroxy*-6-*methylphenanthrene* (Va).—To a solution

[6] For leading references cf. " Organic Reactions," Vol. II, pp. 158—162, Wiley, New York, 1949.

of the ketone (IIIa) (1·5 g., 0·007 mole) in methanol (25 ml.) was added sodium borohydride (0·65 g.) at room temperature with stirring. The mixture was set aside overnight and the solvent was evaporated under reduced pressure. Water and dilute hydrochloric acid were added and the mixture was extracted with chloroform. Drying (Na_2SO_4) and evaporation of the solvent gave a quantitative yield of the *alcohol*, m. p. 129—130° (from methylcyclohexane) (Found: C, 82·9; H, 9·7; O, 7·1. $C_{15}H_{20}O$ requires C, 83·3; H, 9·3; O, 7·4%).

3-Methylphenanthrene.—The alcohol (Va) (1·43 g.) was dissolved in benzene (75 ml.), naphthalene-β-sulphonic acid (0·02 g.) was added, and the mixture was refluxed for 1 hr. (azeotropic receiver). The cooled solution was washed with water and dried (Na_2SO_4), and the benzene was removed under reduced pressure. The residue (1·3 g.) was dehydrogenated with 30% palladised charcoal (0·15 g.) at 300° for 45 min., then taken up in chloroform and filtered. Removal of the solvent gave colourless prisms, m. p. 65° (from methanol–acetone) (lit.,[7] m. p. 65°).

3-Methylphenanthraquinone.—This compound, prepared by Haworth's method,[8] had m. p. 206° (from ethanol). The quinoxaline derivative was obtained as yellow needles, m. p. 210° (from acetic acid) (lit.,[8] m. p. 205—206° and 208°, respectively).

1 : 2 : 3 : 4a : 4 : 9 : 10 : 10a-Octahydro-6-methyl-4 : 9-dioxophenanthrene (IVa).—Crude 3-oxo-2-*m*-tolylcyclohexylacetic acid (Ia) (2·0 g.) was treated with anhydrous hydrogen fluoride (*ca.* 100 g.). After 4 hr. the mixture was worked up in the usual way. From the acidified potassium carbonate solution starting material was regenerated (0·1 g.), and the ether solution gave an oily residue, which was chromatographed in hexane–benzene (3 : 2) on neutral alumina (75 g.). Elution with the same solvent mixture gave diketone (1·6 g., 89%). No other substance was eluted from the column. The pure *diketone* had m. p. 109° (from methylcyclohexane), $\nu_{max.}$ (in $CHCl_3$) 1710 (alicyclic C:O), 1680 cm.$^{-1}$ (acetophenone-type C:O) (Found: C, 78·8; H, 7·0; O, 14·0. $C_{15}H_{16}O_2$ requires C, 78·9; H, 7·1; O, 14·0%).

The ketone formed a red *bis-2 : 4-dinitrophenylhydrazone*, m. p. 209° (from pyridine) (Found: C, 55·8; H, 4·2; O, 21·5; N, 18·7. $C_{27}H_{24}O_8N_8$ requires C, 55·1; H, 4·1; O, 21·75; N, 19·0%).

1 : 2 : 3 : 4 : 4a : 9 : 10 : 10a-Octahydro-6-methyl-4-oxophenanthrene (VIa).—The diketone (IVa) (2·1 g.) was hydrogenated in acetic acid (45 ml.) in the presence of 10% palladised carbon (0·3 g.) at an initial hydrogen pressure of 60 lb./sq. in. After hydrogen uptake ceased, the catalyst and the solvent were removed. The oily monoketone was used in the following step without purification. It had $\nu_{max.}$ (in $CHCl_3$) 1710 cm.$^{-1}$ (alicyclic C:O). It formed a yellow *2 : 4-dinitrophenylhydrazone*, m. p. 193—194° (from ethanol–ethyl acetate) (Found: C, 63·5; H, 5·7; N, 13·4. $C_{21}H_{22}O_4N_4$ requires C, 63·9; H, 5·6; N, 14·2%).

1 : 2 : 3 : 4 : 4a : 9 : 10 : 10a-Octahydro-6-methylphenanthrene (VIIa).—The crude ketone (VIa) (2 g.) was reduced by the Huang-Minlon procedure [3] with potassium hydroxide (2·1 g.), 95% hydrazine hydrate (3·9 ml.), and diethylene glycol (29 ml.). The oily product obtained after the usual working up was chromatographed in light petroleum–benzene (4 : 1) on neutral alumina (100 g.). Elution with the same solvent mixture gave the oily hydrocarbon (1·2 g., 64%), whose infrared absorption shows only C–H bands. The crude compound was used in the next step.

3-Methylphenanthrene.—The crude hydrocarbon (VIIa) was dehydrogenated as described above, with 30% palladised carbon, giving 3-methylphenanthrene identical in m. p. and mixed m. p. with the product from the first reaction sequence.

1-m-Methoxyphenylcyclohexene.—The olefin was prepared analogously to the *m*-tolyl compound, from *m*-bromoanisole [9] (36·1 g., 0·2 mole), magnesium turnings (4·7 g., 0·2 g.-atom) and cyclohexanone (19 g., 0·2 mole). The crude alcohol was dehydrated as above, giving the *olefin* (40·5 g., 70%), b. p. 106—108°/0·02 mm. (Found: C, 82·7; H, 8·6; O, 8·4. $C_{13}H_{16}O$ requires C, 82·9; H, 8·6; O, 8·5%).

2-m-Methoxyphenylcyclohex-2-enone Oxime.—The olefin (47·4 g., 0·25 mole) was converted into the oxime as described for the *m*-tolyl compound (90% yield). The pure *oxime* had m. p. 158·5—159·5° (from propan-2-ol) (Found: C, 71·7; H, 6·7; N, 6·4. $C_{13}H_{15}O_2N$ requires C, 71·9; H, 7·0; N, 6·45%).

2-m-Methoxyphenylcyclohex-2-enone.—The crude oxime (53·5 g., 0·24 mole) was refluxed with dilute hydrochloric acid (48·5 ml. of concentrated acid and 378 ml. of water) for 3 hr. The

[7] Pschorr, *Ber.*, 1906, **39**, 3106.
[8] Haworth, *J.*, 1932, 1125.
[9] Natelson and Gottfried, *J. Amer. Chem. Soc.*, 1939, **61**, 1001.

usual working up gave the yellow unsaturated *ketone* (21·7 g., 50%), b. p. 140—142°/0·1 mm., $\nu_{max.}$ (in $CHCl_3$) 1675 cm.$^{-1}$ (C:C·C:O). The ketone was characterised as its red 2 : 4-*dinitrophenylhydrazone*, m. p. 170·5—171° (from ethyl acetate) (Found: C, 59·7; H, 4·65; N, 14·7. $C_{19}H_{18}O_5N_4$ requires C, 59·7; H, 4·75; N, 14·65%).

3-*Oxo*-2-m-*methoxyphenylcyclohexylacetic acid* (Ib).—The Michael condensation between the above unsaturated ketone (21·7 g.; 0·1 mole) and t-butyl malonate (47·5 g., 0·22 mole) in the presence of potassium t-butoxide (prepared from 0·84 g. of potassium and 13·2 ml. of t-butyl alcohol) gave a gum (22·2 g., 85%). Trituration with light petroleum induced crystallisation. The crude *acid*, recrystallised twice from 2,2,4-trimethylpentane–benzene, had m. p. 107—108° (Found: C, 68·4; H, 7·0; O, 24·75. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9; O, 24·4%). The orange 2 : 4-*dinitrophenylhydrazone* had m. p. 201° (from propan-2-ol) (Found: C, 57·0; H, 5·2; N, 12·7. $C_{21}H_{22}O_7N_4$ requires C, 57·0; H, 5·0; N, 12·7%).

2-m-*Methoxyphenylcyclohexylacetic Acid* (IIb).—The keto-acid (Ib) (15 g., 0·06 mole) was reduced by the Huang-Minlon method [3] with 95% hydrazine hydrate (19·4 ml.), potassium hydroxide (12·9 g.), and diethylene glycol (161 ml.). A thick oil (13·5 g.) was obtained. Infrared absorption showed that partial demethylation occurred during the reduction.[10] For this reason the crude product (5 g.) was methylated in acetone (50 ml.) by alternate addition of methyl sulphate (12 ml.) and potassium hydroxide solution (22·2 g. in 14·8 ml. of water) at 50° with vigorous stirring. Then a distillation head was attached to the flask, the temperature slowly raised to 60°, and the acetone removed by distillation. The mixture was stirred at 60° for 1 hr. and at 95° for another hour. Dilution with water and extraction with ether removed neutral material (0·5 g.). The aqueous solution was acidified with dilute hydrochloric acid and extracted with ether. Evaporation of the solvent gave the acid as a thick syrup (3·9 g.). It was characterised as its S-*benzylthiuronium salt*, m. p. 169° (from aqueous ethanol) (Found: C, 66·75; H, 7·4; N, 6·7. $C_{23}H_{30}O_3N_2S$ requires C, 66·6; H, 7·3; N, 6·75%).

1 : 2 : 3 : 4 : 4*a* : 9 : 10 : 10*a*-*Octahydro*-6-*methoxy*-9-*oxophenanthrene* (IIIb).—The crude acid (IIb) (2·5 g.) was treated with anhydrous hydrogen fluoride (*ca.* 100 g.) and set aside for 4 hr. A small amount of starting material and only a single neutral ketonic *product* (2 g., 87%) were obtained. This had m. p. 82·5—83° (from 2,2,4-trimethylpentane), $\nu_{max.}$ (in $CHCl_3$) 1675 cm.$^{-1}$ (acetophenone-type C:O) (Found: C, 78·2; H, 8·1; O, 13·7. $C_{15}H_{18}O_2$ requires C, 78·2; H, 7·9; O, 13·9%). The deep red 2 : 4-*dinitrophenylhydrazone* had m. p. 244—245° (from ethyl acetate) (Found: C, 61·85; H, 5·25; N, 13·6; O, 19·2. $C_{21}H_{22}O_5N_4$ requires C, 61·45; H, 5·4; N, 13·65; O, 19·5%).

1 : 2 : 3 : 4 : 4*a* : 9 : 10 : 10*a*-*Octahydro*-6-*hydroxy*-9-*oxophenanthrene*.—This compound was prepared from the crude product (5 g.), obtained in the Huang-Minlon reduction of (Ib) without remethylation. The usual cyclisation by hydrogen fluoride gave a crude gum (3·7 g.) which on treatment with charcoal in acetic acid gave a pure phenolic ketone (2·3 g.), m. p. 254° (from acetic acid). The acetic acid mother-liquor was evaporated to dryness, and the residue chromatographed in a minimal volume of benzene–hexane (1 : 1) on alumina (65 g.; Fisher). Elution with hexane–benzene (2 : 3) gave the methoxy-ketone (0·7 g.), m. p. 82—83° (from 2,2,4-trimethylpentane), identical in m. p. and mixed m. p. with compound (IIIb). Further elution with chloroform–methanol (19 : 1) gave the phenolic *ketone* (0·6 g.), m. p. 254° (from acetic acid) (Found: C, 77·0; H, 7·4; O, 15·6. $C_{14}H_{16}O_2$ requires C, 77·75; H, 7·5; O, 14·8%).

Methylation of this ketone with methyl sulphate and sodium hydroxide in the usual way gave the methoxy-ketone (IIIb), identical with that described above.

1 : 2 : 3 : 4 : 4*a* : 9 : 10 : 10*a*-*Octahydro*-6-*methoxyphenanthrene* (VIIb).—The ketone (IIIb) (2 g.) was hydrogenated in acetic acid (40 ml.) in the presence of 10% palladised carbon (0·2 g.) at an initial hydrogen pressure of 60 lb./sq. in. The *product* (1·5 g., 80%) had b. p. 128—130°/0·1 mm. (Found: C, 82·8; H, 9·5; O, 7·6. $C_{15}H_{20}O$ requires C, 83·2; H, 9·3; O, 7·4%).

3-*Methoxyphenanthrene*.—The above material (VIIb) (0·75 g.) was dehydrogenated with 30% palladised carbon (0·08 g.) at 300° for 45 min. Chloroform-extraction, filtration, and evaporation gave 3-methoxyphenanthrene, m. p. 61° (picrate, m. p. 124°) (lit.,[11] m. p. 61° and 123—124°, respectively).

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[10] Cf. Gates and Tschudi, *J. Amer. Chem. Soc.*, 1956, **78**, 1380.
[11] Pschorr, Wolfes, and Buckow, *Ber.*, 1900, **33**, 162.