263. *Steric Aspects of the Intramolecular Cyclisation of 2-Arylcyclohexylacetic Acids. Part II.*†

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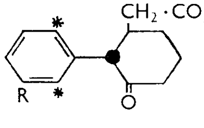
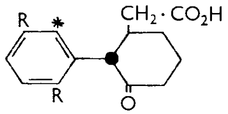
Cyclisation of 2-*p*-xylyl-3-oxocyclohexylacetic acid gave rise, unexpectedly, to two isomeric diketones; one appeared to be stable in alkaline equilibration. Both 2-dimethoxyphenyl-3-oxocyclohexylacetic acid and 2-*p*-xylylcyclohexylacetic acid yielded only one ketone on cyclisation. From the course of these reactions suggestions for the stereochemistry of the compounds are made.

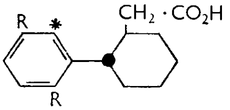
Friedel–Crafts-type cyclisation of 2-(*m*-substituted phenyl)cyclohexylacetic acids (I) occurs at only one position, *viz.*, *para* to the substituent in the phenyl nucleus.[1] The reason for this apparently exclusive attack of one of the two available (marked *) positions was surmised to be steric. Therefore 2-*p*-xylylcyclohex-2-enone was submitted to Michael condensation with t-butyl malonate. The keto-acid (II*a*) obtained was reduced by the Huang-Minlon method [2] to the acid (III*a*). It was supposed that the availability of only one position (*) in the cyclisation of (II*a*) and (III*a*) might considerably lower the yield in standard cyclisation conditions; however, the corresponding octahydro-compounds (IV*a*, V*a*) were obtained in relatively high yields. The structures of (IV*a*) and (V*a*) were proved by transformation into the corresponding phenanthrene derivatives.



(I)

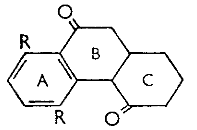


(II)

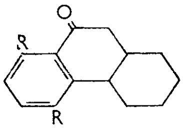


(III)

(*a*); R = Me
(*b*); R = OMe



(IV)



(V)

Cyclisation of (II*a*) gave rise, unexpectedly, to a mixture of two isomeric diketones. The main product (diketone *A*, m. p. 125°) crystallised directly from the crude reaction mixture. From the mother-liquor a second diketone (*B*, m. p. 79—80°) could be separated by chromatography. Since diketone *A* also could be converted into *B*, in high yield, by treatment with sodium methoxide, *B* is the thermodynamically stable isomer.

Two stereochemically different diketones can be formulated representing *cis*- or *trans*-fused B/C ring systems in (IV*a*). Earlier it was shown [3,4] that *trans*-adducts resulted in Michael condensation of 2-phenyl- and 2-(2,3-dimethoxyphenyl)-3-oxo-cyclohex-2-enone and the stereochemistry is apparently retained in the course of following hydrogen fluoride cyclisation. In agreement, we obtained only one diketone when *trans*-2-(*p*-dimethoxyphenyl)-3-oxocyclohexylacetic acid (II*b*) was cyclised to the corresponding diketone (IV*b*). This difference in the steric course of cyclisation of 2-*p*-xylyl- and 2-*p*-dimethoxyphenyl-substituted 3-oxocyclohexylacetic acids (II*a* and II*b*) can be explained by the aid of molecular models. Dreiding models [5] show that in B/C *trans*-fused diketone (IV*a*) considerable

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† The Paper entitled " Synthesis of 3-Substituted Phenanthrenes. The Course of Intramolecular Cyclisation of 2-(*m*-Substituted Phenyl)cyclohexylacetic Acids " (*J.*, 1959, 1727) is regarded as Part I.

[1] Bien and Boazi, *J.*, 1959, 1727.

[2] Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487.

[3] Ginsburg and Pappo, *J.*, 1951, 938; *J. Amer. Chem. Soc.*, 1953, **75**, 1094.

[4] Amiel, Loffler, and Ginsburg, *J. Amer. Chem. Soc.*, 1954, **76**, 3625.

[5] Dreiding, *Helv. Chim. Acta*, 1959, **42**, 1339.

steric compression would arise from the proximity of the C-ring carbonyl and a 5-methyl group, but this steric hindrance would not exist between a 5-methoxyl group and the same carbonyl. The models also show that a B/C *cis*-fused compound (IV) would be free from this type of interaction if R is methyl or methoxyl.

A negative proof for the existence of a steric effect caused by proximity of a 5-methyl group and the C-ring carbonyl in the octahydrophenanthrene system was achieved in the cyclisation of 2-*p*-xylylcyclohexylacetic acid giving rise, as expected, only to a single product. Sodium methoxide epimerisation of it returned the unchanged material.

Both the experimental observations and the stereochemical considerations suggest a higher thermodynamic stability for the B/C *cis*-fused diketone (IV*a*) and therefore this stereochemistry is suggested for diketone *B*, the single product obtained after alkaline or acidic equilibration of the crude reaction mixture. Recently, in steroid- and sapogenin-type compounds, having an aromatic ring A and C_{11}-ketone, the B/C *cis*-fused isomer has been found to be of higher or at least similar stability compared with the corresponding B/C *trans*-fused one.[6]

Work is now in progress for unequivocal proof of the stereochemistry of the dioxo-octahydrophenanthrenes and their transformation products.

EXPERIMENTAL

1-p-*Xylylcyclohexene*.—To *p*-xylylmagnesium bromide, prepared from 2-bromo-*p*-xylene (179·7 g.) and magnesium (23·3 g.) in dry ether (1150 ml.), cyclohexanone (94·24 g.) in dry ether (115 ml.) was slowly added with stirring at room temperature. The mixture was then refluxed for 1 hr., kept overnight, and decomposed by adding saturated ammonium chloride solution until the precipitate coagulated. The ether layer was dried and the solvent removed. The residual tertiary alcohol was dehydrated by boiling it with anhydrous oxalic acid (30 g.) in toluene (1000 ml.) until no more water was obtained in an azeotropic collector.[7] The usual isolation gave the cyclo-olefin, b. p. 112°/0·6 mm. (111 g.) n_D^{20} 1·534.

2-p-*Xylylcyclohex-2-enone Oxime*.—To a solution of 1-*p*-xylylcyclohexene (100 g.) in acetic acid (112 ml.) n-pentyl nitrite (83 g.) was added. The solution was cooled to −15°, and concentrated hydrochloric acid (70 ml.) then added dropwise with stirring. The stirring was continued for a further 2 hr. at −10°. The oily nitrosochloride solidified after addition of cold ethanol (*ca*. 150 ml.) and was filtered off with suction, washed with ice-cold ethanol, and dried (60 g.). It was immediately converted into the oxime by slowly warming its suspension in pyridine (340 ml.) to 75°. After 15 min. all of the solid had dissolved. The solution was cooled and excess of hydrochloric acid was added. The precipitated *oxime*, filtered off, washed with water, and dried (40·5 g.), had m. p. 163° (from methanol) (Found: C, 78·2; H, 8·05; N, 6·3. $C_{14}H_{17}NO$ requires C, 78·1; H, 8·0; N, 6·5%).

2-p-*Xylycyclohex-2-enone*.—The crude oxime (40·5 g.), concentrated sulphuric acid (44 ml.), and water (800 ml.) were refluxed for 3 hr. in nitrogen. 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 the solvent, the residue was distilled in a vacuum. The unsaturated *ketone* had b. p. 130°/0·25 mm. (16·1 g.). The red 2,4-*dinitrophenylhydrazone* had m. p. 154° (from ethanol) (Found: C, 62·8; H, 5·2; N, 14·9. $C_{20}H_{20}N_4O_4$ requires C, 63·15; H, 5·3; N, 14·7%). The colourless *semicarbazone* had m. p. 163° (from methanol) (Found: C, 70·2; H, 7·1; N, 16·5. $C_{15}H_{19}N_3O$ requires C, 70·0; H, 7·4; N, 16·3%).

2-p-*Xylyl-3-oxocyclohexylacetic Acid* (II*a*).—A mixture of 2-*p*-xylylcyclohex-2-enone (33·5 g.), freshly distilled t-butyl malonate (69 g.), and potassium t-butoxide (from 1·41 g. of potassium and 24 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, and dried (Na_2SO_4). The solvent was evaporated, glacial acetic acid (200 ml.), water (88 ml.), and concentrated hydrochloric acid (10·5 ml.) were added and the mixture refluxed until gas evolution was complete (about 2 hr.). The acetic acid was distilled off under vacuum, benzene was added, and extracted several times with saturated potassium

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[6] Elks, Oughton, and Stephenson, *Proc. Chem. Soc.*, 1959, 6; Buchi, Kaltenbronn, Crombie, Godin, and Whiting, *ibid.*, 1960, 274.

[7] Bergmann, Pappo, and Ginsburg, *J.*, 1950, 1369.

carbonate solution. The combined alkaline extracts were 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 on standing (35 g.), m. p. 136° (from methylcyclohexane)(Found: C, 73·6; H, 7·6; O, 18·5. $C_{16}H_{20}O_3$ requires C, 73·8; H, 7·7; O, 18·4%).

1,2,3,4,4a,9,10,10a-*Octahydro*-5,8-*dimethyl*-4,9-*dioxophenanthrene* (IV*a*).—2-*p*-Xylyl-3-oxocyclohexylacetic acid (II*a*) (3·6 g.) was treated with anhydrous hydrogen fluoride (*ca.* 150 g.) and after 4 hr. air was blown over the mixture to evaporate the hydrogen fluoride. To the residue saturated potassium carbonate solution was added in small portions (carefully) until neutral and the precipitate taken up in ether. Evaporation of the solvent gave a crystalline *ketone*, which on recrystallisation from methylcyclohexane (containing a few drops of isopropyl alcohol) gave diketone *A* (1·9 g.), m. p. 125—126° (Found: C, 79·1; H, 7·4, O, 13·3. $C_{16}H_{18}O_2$ requires C, 79·3; H, 7·5; O, 13·2%). The *monosemicarbazone* had m. p. 202·5—203·5° (from aqueous methanol) (Found: C, 68·5; H, 6·9; N, 13·8. $C_{17}H_{21}N_3O_2$ requires C, 68·2; H, 7·1; N, 14·0%). The methylcyclohexane mother-liquor was evaporated to dryness and the residue was taken up in a minimum of hexane–benzene (2 : 1) and chromatographed on neutral alumina (65 g.). Elution with hexane–benzene (1 : 1) gave more diketone *A* (0·84 g.). Continued elution with benzene–chloroform (1 : 1) eluted an isomeric diketone *B*. The same isomer could be prepared directly by isomerisation of pure diketone *A* or of the crude cyclisation product.

Preparation of Diketone B.—Diketone *A* (2 g.) was dissolved in dry methanol (20 ml.), sodium methoxide (0·05 g.) was added and the mixture refluxed for 2 hr. The new equilibrium mixture (1·4 g.) was isolated as an oil by adding saturated sodium chloride solution (15 ml.) after most of the methanol had been removed and subsequent ether extraction. The oil was solidified after a short-path distillation at 120° (bath)/0·08 mm. and melted at 68—70°. By repeated distillation the analytically pure *diketone B* was obtained, m. p. 79—80° (Found: C, 79·1; H, 7·45; O, 13·1. $C_{16}H_{18}O_2$ requires C, 79·3; H, 7·5; O, 13·2%).

2-p-*Xylylcyclohexylacetic Acid* (III*a*).—The keto-acid (II*a*) (5 g.) was refluxed with diethylene glycol (50 ml.), potassium hydroxide (4 g.), and 95% hydrazine hydrate (6 ml.) for 2 hr. (oil-bath temp. *ca.* 140°). The condenser was then removed, the temperature 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 residue was crystallised from 2,2,4-trimethylpentane yielding the *acid* (3·3 g.), m. p. 140—141° (Found: C, 77·8; H, 8·9; O, 13·1. $C_{16}H_{22}O_2$ requires C, 78·0; H, 9·0; O, 13·0%). From the mother-liquor the solvent was removed and the residue, taken up in benzene, was percolated through a silicic acid column (40 g.) giving more of the pure acid (0·6 g.).

1,2,3,4,4a,9,10,10a-*Octahydro*-5,8-*dimethyl*-9-*oxophenanthrene* (V*a*).—2-*p*-Xylylcyclohexylacetic acid (III*a*) (3·18 g.) was treated with anhydrous hydrogen fluoride and after 4 hr. the mixture was worked up as described for compound (IV*a*). The neutral ketone obtained from the ether extract, was recrystallised from methanol (containing a few drops of water) giving monoketone (2·25 g.). The mother-liquor was evaporated to dryness, the residue taken up in a small amount of hexane–benzene (9 : 1) and chromatographed on neutral alumina (28 g.). Elution with hexane–benzene (9 : 1) gave more of the *monoketone* (0·4 g.), m. p. 82° (from methanol) (Found: C, 84·0; H, 8·7; O, 7·0. $C_{16}H_{20}O$ requires C, 84·2; H, 8·8; O, 7·0%). The 2,4-*dinitrophenylhydrazone* had m. p. 137° (chloroform–methanol) (Found: C, 64·15; H, 5·6; O, 16·35; N, 13·4. $C_{22}H_{24}N_4O_4$ requires C, 64·7; H, 5·9; O, 16·7; N, 13·7%).

1,4-*Dimethylphenanthrene*.—The crude ketone (V*a*) (1·6 g.) was reduced by the Huang-Minlon procedure with potassium hydroxide (1·6 g.), 95% hydrazine hydrate (2·3 ml.), and diethylene glycol (20 ml.). The oil obtained after the usual working up was chromatographed in hexane on neutral alumina (45 g.). Elution with the same solvent gave oily hydrocarbon (1 g.) which was dehydrogenated without further purification with 30% palladised charcoal (0·12 g.) at 300° for 45 min., then taken up in chloroform and filtered. Removal of the solvent gave viscous oil (*ca.* 1 g.), which was chromatographed in pentane on neutral alumina (30 g.). Elution with pentane gave crystalline hydrocarbon, m. p. 52·5° (from methanol) (lit.,[8] m. p. 50—51°). The yellow picrate melted at 143° (from methanol) (lit.,[8] m. p. 142·5—143·5°). The same hydrocarbon was obtained when diketone (IV*a*) was reduced by the same method.

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[8] Johnson, Goldman, and Schneider, *J. Amer. Chem. Soc.*, 1945, **67**, 1360.

1-p-*Dimethoxyphenylcyclohexan*-1-*ol*.—*p*-Dimethoxybenzene (96·7 g.) was treated with phenyl-lithium in anhydrous ether.[9] To the solution cyclohexanone (33 g.) in anhydrous ether (157 ml.) was added dropwise with continuous stirring. The reaction was slightly exothermic and a gentle reflux was held during the addition. Reflux was continued for 1 hr., then the mixture was cooled and kept at room temperature for an additional hour and finally decomposed with water. The separated ether layer was washed with water until neutral, dried (Na_2SO_4), and the solvent removed. The residue could be purified either by evaporative distillation or by crystallisation from light petroleum. The *alcohol* (54 g.) had m. p. 61·5—62·5° (Found: C, 71·2; H, 8·5; OMe, 25·9. $C_{14}H_{20}O_3$ requires C, 71·2; H, 8·5; OMe, 26·2%).

1-p-*Dimethoxyphenylcyclohexene*.—Dehydration of the above alcohol with oxalic acid in toluene, as described above for 1-*p*-xylylcyclohexene, gave the *olefin* (82% yield), b. p. 177—178°/18 mm., m. p. 47—48° (from propan-2-ol) (Found: C, 77·1; H, 8·2; OMe, 28·0. $C_{14}H_{18}O_2$ requires C, 77·0; H, 8·3; OMe, 28·4%).

2-p-*Dimethoxyphenylcyclohex*-2-*enone Oxime*.—The olefin (10 g.) could be converted into the oxime in low yield as described for the *p*-xylyl compound. In some runs no direct precipitation of the oxime occurred and ether extraction of the acidified solution was necessary. The pure *oxime* (1·0 g.) had m. p. 154—155° (from methanol) (Found: C, 68·0; H, 6·8; N, 5·7. $C_{14}H_{17}NO_3$ requires C, 68·0; H, 6·9; N, 5·7%).

2-p-*Dimethoxyphenylcyclohex*-2-*enone*.—The oxime (4 g.) was refluxed with dilute sulphuric acid (3 ml. of concentrated acid in 60 ml. of water) for 17 hr. under nitrogen. The usual working up gave yellow-brown oil which solidified when distilled at 90° (bath temp.)/0·04 mm. The pure unsaturated *ketone* (3 g.) had m. p. 64·5—65·5° (from methylcyclohexane) (Found: C, 72·3; H, 7·0; O, 20·6. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9; O, 20·7%).

2-p-*Dimethoxyphenyl*-3-*oxocyclohexylacetic Acid* (IIb).—The Michael condensation between the above unsaturated ketone (6·48 g.) and t-butyl malonate (11·72 g.) in the presence of potassium t-butoxide (prepared from 0·23 g. of potassium and 3·7 ml. of t-butyl alcohol) gave the crude *acid* (5·0 g.) which after repeated recrystallisation from benzene had m. p. 120—121° (Found: C, 65·6; H, 6·8; O, 27·5. $C_{16}H_{20}O_5$ requires C, 65·75; H, 6·9; O, 27·35%).

1,2,3,4,4a,9,10,10a-*Octahydro*-5,8-*dimethoxy*-4,9-*dioxophenanthrene* (IVb).—The crude acid (II*b*) (3·1 g.) was treated with anhydrous hydrogen fluoride and set aside for 5 hr. After most of the hydrogen fluoride was removed by a stream of dry air, the mixture was made alkaline with dilute sodium hydrogen carbonate solution and extracted with ether. The ether solution was washed with water and dried (Na_2SO_4). Removal of the solvent yielded a crystalline residue (2·5 g.) from which only one single *diketone* could be obtained, m. p. 148—150° (from methylcyclohexane) (Found: C, 70·1; H, 6·5; O, 23·1. $C_{16}H_{18}O_4$ requires C, 70·05; H, 6·6; O, 23·3%).

Homogeneity of the acid was shown by thin-layer chromatography on alumina plates in two different solvent systems. The single spot had R_F 0·74 in chloroform and 0·46 in benzene–chloroform (1 : 1) (detection with iodine vapour).

Attempt to Epimerise (IVb).—Diketone (IVb) (107 mg.) was dissolved in dry methanol (1·5 ml.), 2N-sodium methoxide in methanol (0·05 ml.) was added, and the mixture was refluxed for 2 hr. The usual working up gave only unchanged starting material identified by m. p., mixed m. p., and infrared spectrum.

1,2,3,4,4a,9,10,10a-*Octahydro*-5,8-*dimethoxyphenanthrene*.—Diketone (IV*b*) (0·5 g.) was reduced by the Huang-Minlon procedure with potassium hydroxide (0·85 g.), 64% hydrazine hydrate (1·3 ml.), and diethylene glycol (11 ml.). The product after the usual working up was chromatographed in hexane on neutral alumina (10 g.). Elution with the same solvent gave crystalline *hydrocarbon* (0·2 g.), which was purified by sublimation at 60° (bath temp.)/0·6 mm., m. p. 105—106° (Found: C, 78·15; H, 9·1; O, 13·1. $C_{16}H_{22}O_2$ requires C, 78·0; H, 9·0; O, 13·0%).

1,4-*Dimethoxyphenanthrene*.—The above hydrocarbon was dehydrogenated with 30% palladised carbon as described for the *p*-xylyl compound giving 1,4-dimethoxyphenanthrene, m. p. 121—123° (lit.,[10] m. p. 121—122°).

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[9] Wittig, Pockels, and Droge, *Ber.*, 1938, **71**, 1910.
[10] Grob, Jundt, and Wicki, *Helv. Chim. Acta*, 1949, **32**, 2427.