Steric Aspects of the Intramolecular Cyclisation of 2-Arylcyclohexylacetic Acids. Part V [1]

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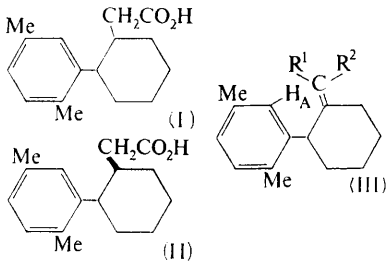
The conversion of different 2-(2,5-xylyl)cyclohexylidene compounds (III) into *cis*- and *trans*-2-(2,5-xylyl)cyclohexylacetic acids (I) and (II) is described and the steric factors governing the distribution of the *cis*- and *trans*-isomers formed in the reaction are discussed.

THE synthesis of *cis*-2-(2,5-xylyl)cyclohexylacetic acid (I)—a potential precursor of the *cis*-octahydrophenanthrene system—from the dinitrile (IIIa) has recently been reported.[2]

It was anticipated that by varying the substituents (R^1, R^2) in the cyclohexylidene derivative (III) hydrolysis of the dicyano-group might be eliminated, thus avoiding serious loss at this step, and that the *cis–trans* ratio (I)/(II) of isomers might also be influenced.



	R^1	R^2
a	CN	CN
b	H	CN
c	H	CO_2Et
d	CN	$CONH_2$
e	CN	CO_2Et

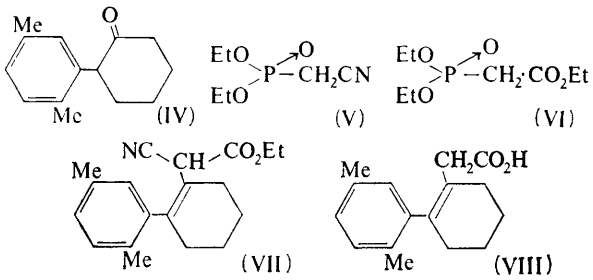
The phosphonate modification [3,4] of the Wittig reaction [5] was used for preparing the αβ-unsaturated nitrile (IIIb) and ester (IIIc) by the interaction of 2-(2,5-xylyl)cyclohexanone (IV) and the carbanions of the phosphonates (V) and (VI) which afforded (IIIb) and (IIIc) respectively in 61% and 32% yields. The difference in reactivity of the two phosphonates has been noted earlier [6] and may be explained by the bulkier nature of the ethoxycarbonyl group compared with the linear cyano-group.

The Cope modification [7] of the Knoevenagel condensation was used in attempts to prepare the compounds (IIId) and (IIIe). The reaction between 2-(2,5-xylyl)-cyclohexanone (IV) and cyanoacetamide afforded the expected α-cyanoacrylamide (IIId). On the other hand, the condensation between ethyl cyanoacetate and the ketone (IV) gave a mixture of the desired cyanoacetate (IIIe) and its double-bond isomer (VII). This view was supported by the following results. V.p.c. analysis of the reaction product showed the presence of two compounds and, in agreement with this, absorption peaks in the i.r. spectrum at 2200 and 2240 $cm.^{-1}$ correspond to the presence of a conjugated and nonconjugated nitrile group. Catalytic reduction, followed by acid hydrolysis gave a mixture of three acidic components which when treated with diazomethane and analysed by v.p.c. showed the presence of the methyl esters of *cis*- (I) and *trans*- (II) acid and that of the unsaturated acid (VIII).* The same unsaturated acid (VIII) was obtained as a single product when the crude reaction mixture was directly hydrolysed under acidic conditions without catalytic reduction. Acid (VIII) was prepared earlier from (IIIa) under similar conditions.[2] It has now been shown that the shift of the double bond from the αβ- to

* The experiment indicates certain selectivity in the reduction of the *exo*- and *endo*-cyclic double bond in compounds (IIIe) and (VII). Indeed, acid (VIII) withstands hydrogenation under normal conditions but undergoes slow reduction under forced conditions (see Experimental section).

[1] Part IV, S. Bien and U. Michael, *Chem. and Ind.*, 1967, 664.
[2] S. Bien, U. Michael, and L. Zamir, *J. Chem. Soc.* (*C*), 1967, 115.
[3] L. Horner, H. Hoffmann, and G. H. Wippel, *Ber.*, 1958, **91**, 61.
[4] W. S. Wadsworth jun. and W. D. Emmons, *J. Amer. Chem. Soc.*, 1961, **83**, 1733.
[5] For a recent review, see A. Maercker, 'Organic Reactions,' John Wiley, New York, 1965, vol. 14, p. 270.
[6] A. K. Bose and R. T. Dahill, jun., *J. Org. Chem.*, 1965, **30**, 505.
[7] A. C. Cope, C. M. Hoffman, C. Wyekoff, and E. Herdenbergh, *J. Amer. Chem. Soc.*, 1941, **63**, 3452.

βγ-position during acid hydrolysis is a general phenomenon for all compounds of type (III).



N.m.r. spectral data made it possible to establish the stereochemistry around the olefinic bond in compounds (IIIb) and (IIIc). The vinylic proton in these compounds resonated at 4·32 and 4·95 p.p.m. respectively. The signal of the corresponding proton in ethyl cyclohexylideneacetate [4] was found at 5·66 p.p.m. The large diamagnetic shielding of the vinylic proton is in exact agreement with that expected for (IIIb) and (IIIc), the vinylic proton being in the shielding area of the *p*-xylyl group, above or below the plane of the aromatic ring. One may expect that steric compression will be decreased and rotation less hindered when a phenyl group replaces the *p*-xylyl group. Indeed, the vinylic proton resonance in ethyl 2-phenylcyclohexylideneacetate was found at 5·10 p.p.m., *i.e.* less shielded than in compounds (IIIb) and (IIIc).

From model considerations it is also clear that either the cyanide group or the ester carbonyl in the structures (IIIa), (IIId), and (IIIe), but not in (IIIb) and (IIIc) would be across from the *ortho* proton (H_A) in a shielding position. Thus a one-proton shift in the aromatic region was observed only in the n.m.r. spectra of (IIIa), (IIId), and (IIIe) (Table 1).

TABLE 1

Chemical shifts for aromatic protons in compounds of type (III)

Compound	δ(CCl_4) (p.p.m.)
(IIIa)	6·98 (2H), 6·83 (1H)
(IIIb)	6·96 (3H)
(IIIc)	7·03 (3H)
(IIId)	7·13 (2H), 6·91 (1H)
(IIIe)	7·05 (2H), 6·86 (1H)

The various cyclohexylidene derivatives of type (III) were next compared as possible precursors of the *cis*-acid (I). For this investigation they were hydrogenated in ethanol in the presence of platinum and the functional groups hydrolysed (the substituted malonic acids underwent simultaneous decarboxylation). The crude acidic products were then treated with etheral diazomethane and the mixture of esters formed were analysed by v.p.c. For comparison the methyl esters of authentic *cis*- and *trans*-acids [(I) and (II)] were used. Results are summarized in Table 2.

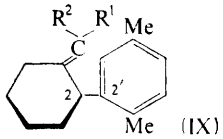
Molecular models show that insofar as rotation around the bond connecting the aromatic and alycyclic rings [the bond between 2 and 2′ in (IX)] is highly hindered, the double bond–catalyst interaction will be favoured from the remote side of the *p*-xylyl group thus leading to preferential formation of a *cis*-product. This appears to be the case in the hydrogenation of compounds

TABLE 2

Distribution of *cis*- and *trans*-isomers in the acid mixture obtained from compounds (III)

Starting material	*cis* (%)	*trans* (%)
(IIIa)	95	5
(IIIe)	89	11
(IIId)	87	13
(IIIb)	65	35
(IIIc)	50	50
(VIII)	82	18

(IIIa), (IIId), (IIIe) which have tetrasubstituted double bonds. In compounds (IIIb) and (IIIc), both with a trisubstituted double bond, the rotation around the bond connecting the two rings is less hindered and the *p*-xylyl



(IX)

group may rotate into a position which allows hydrogen approach from both sides of the double bond almost equally.

The *cis*-fusion in acid (I) was proved unambiguously by degradation of its methyl ester with ozone. The resulting ozonide on oxidation followed by hydrolysis gave *cis*-hexahydrohomophthalic acid, identical with an authentic sample (in m.p., i.r., and n.m.r. spectra) prepared from dimethyl homophthalate.[8]

EXPERIMENTAL

N.m.r. spectra were recorded on a Varian A-60 spectrophotometer employing tetramethylsilane as internal reference. V.p.c. analyses were performed on a Varian-Aerograph 600-D (Hy-Fi) instrument, using a 5 ft. × ⅛ in. glass column packed with XE-60 (1%) on 100—120 mesh Chromosorb Q.

2-(2,5-*Xylyl*)*cyclohexylideneacetonitrile* (IIIb).—Diethyl cyanomethylphosphonate (V) (9·2 g.) was added dropwise, with stirring under nitrogen, to a suspension of sodium hydride (1·28 g.) in dry dimethylformamide (35 ml.). Stirring was continued for an additional 14 hr. with constant nitrogen flushing. To the cooled mixture a solution of 2-(2,5-xylyl)cyclohexanone (10·5 g.) in dry dimethylformamide (20 ml.) was added dropwise. After the addition was completed the solution was stirred for 4 hr. at room temperature, poured into cold dilute sulfuric acid (*ca.* 0·5N) and the mixture was extracted with methylene chloride. After the solution had been dried (Na_2SO_4) the solvent was removed and the residue was fractionated. The oily product (7·1 g.), b.p. 115—120°/0·1 mm., solidified on standing and repeated recrystallisation from methanol afforded the pure *nitrile*, m.p. 90—91° (Found: C, 85·3; H, 8·4; N, 6·0. $C_{16}H_{19}N$ requires C, 85·3; H, 8·5; N,

[8] J. C. Sheehan and R. C. O'Neill, *J. Amer. Chem. Soc.*, 1950, **72**, 4614.

6·2%); in the n.m.r. spectrum (CCl_4) the vinylic proton resonated at δ 4·33 p.p.m.

Ethyl 2-(2,5-*Xylyl*)*cyclohexylideneacetate* (IIIc).—Diethyl ethoxycarbonylmethylphosphonate (VI) (24·25 g.) was added dropwise, with mechanical stirring under nitrogen, to a suspension of sodium hydride (2·62 g.) in dry 1,2-dimethoxyethane (100 ml.), and stirring was continued until evolution of hydrogen ceased. To the solution 2-(2,5-xylyl)cyclohexanone (23·0 g.) in 1,2-dimethoxyethane (75 ml.) was added at such a rate as to keep the temperature below 40°. After the addition was completed, the mixture was stirred for a further hour, then water and ether were added and the layers were separated. The aqueous phase was washed several times with ether, the combined ether fractions were dried (Na_2SO_4) and the solvent was removed. Fractional distillation of the residue afforded the *acetate* (10·0 g.), b.p. 120—124°/0·05 mm., m.p. 83—85° (MeOH) (Found: C, 79·0; H, 9·0; O, 11·9. $C_{18}H_{24}O_2$ requires C, 79·4; H, 8·9; O, 11·75%); in the n.m.r. spectrum (CCl_4) the vinylic proton resonance was found at δ 4·95 p.p.m.

2-(2,5-*Xylyl*)*cyclohexylideneacetic Acid* (III; $R^1 = H$, $R^2 = CO_2H$).—A mixture of the acetate (IIIc) (0·5 g.), ethanol, and sodium hydroxide (0·3 g.), in water (the relative amounts of ethanol and water were adjusted to keep a homogenous solution) was heated under reflux for 3 hr. Ethanol was then removed under reduced pressure, more water was added and the solution was washed with ether. From the alkaline layer, on acidification, the crude *acid* was isolated (0·35 g.), and purified by recrystallisation from methylcyclohexane, m.p. 204—206° (Found: C, 78·4; H, 8·2; O, 13·2. $C_{16}H_{20}O_2$ requires C, 78·65; H, 8·25; O, 13·1%); in the n.m.r. spectrum (CCl_4) the vinylic proton signal was found at δ 4·95 p.p.m.

Ethyl 2-*Phenylcyclohexylideneacetate*.—To the solution of the carbanion formed by dropwise addition of diethyl ethoxycarbonylmethylphosphonate (VI) (22·4 g.) into the suspension of sodium hydride (2·4 g.) in dry dimethoxyethane (50 ml.), 2-phenylcyclohexanone (17·4 g.) in dimethoxyethane (20 ml.) was added. After the usual work up the acetate was isolated by distillation (7·5 g.), b.p. 125—130°/0·25 mm. Trituration with hexane gave the crystalline acetate, m.p. 42—45°; $\nu_{max.}$ (in $CHCl_3$) 1720 cm.$^{-1}$ (conjugated ester C=O); in the n.m.r. spectrum the vinylic proton resonated at δ 5·10 p.p.m.

Without further purification, the acetate was hydrolysed with alkali to yield 2-*phenylcyclohexylideneacetic acid*, m.p. 172—174° (from methylcyclohexane) (Found: C, 77·8; H, 7·6; O, 14·55. $C_{14}H_{16}O_2$ requires C, 77·75; H, 7·7; O, 14·8%).

2-(2,5-*Xylyl*)*cyclohexylidenecyanoacetamide*(IIId).—A mixture of 2-(2,5-xylyl)cyclohexanone (5·0 g.), cyanoacetamide (2·1 g.), ammonium acetate (3·3 g.), acetic acid (9 ml.), and dry benzene (50 ml.) was heated under reflux for 24 hr., the water produced being removed with an azeotropic collector. The cooled solution was filtered from unchanged cyanoacetamide, washed with dilute sodium carbonate solution until slightly alkaline, dried (Na_2SO_4), and the solvent was removed. The oily residue was chromatographed on a column of basic alumina (Merck) (140 g.). Elution with benzene–chloroform (1 : 2) gave the product (2·5 g.), m.p. 138—140° (from methylcyclohexane–hexane) (Found: C, 76·0; H, 7·4; N, 10·15. $C_{17}H_{20}N_2O$ requires C, 76·1; H, 7·5; N, 10·4%). In the n.m.r. spectrum the benzylic proton resonance appeared at δ 4·13 p.p.m.

The Reaction of 2-(2,5-*Xylyl*)*cyclohexanone with Ethyl Cyanoacetate*.—A mixture of 2-(2,5-xylyl)cyclohexanone (10·0 g.), ethyl cyanoacetate (5·7 g.), ammonium acetate (0·8 g.), acetic acid (0·5 ml.), and dry benzene (30 ml.) was heated under reflux for 20 hr., the water produced being removed with an azeotropic collector. The cooled solution was washed with water, followed by dilute sodium carbonate solution until slightly alkaline, dried (Na_2SO_4), and the solvent removed. The resulting viscous oil was distilled under reduced pressure and the fraction boiling at 125—135°/0·03 mm. (9·5 g.) was redistilled affording the product, b.p. 134—136°/0·04 mm. (Found: C, 76·4; H, 7·6; N, 4·5. $C_{19}H_{23}NO_2$ requires C, 76·7; H, 7·8; N, 4·7%); $\nu_{max.}$ (in $CHCl_3$) 2200 cm.$^{-1}$ (conjugated C≡N), 2240 cm.$^{-1}$ (non-conjugated C≡N); two v.p.c. peaks with retention time of 9·6 and 11·6 min. (carrier-gas pressure 30 lb./sq. in., column temp. 168°) were observed.

A sample of the product (1·1 g.) in ethanol was hydrogenated in the presence of platinum oxide (0·12 g.) at room temperature. After hydrogen uptake ceased, the solution was filtered, the solvent was removed, and the residue was analysed by v.p.c. Two peaks with retention times of 9·6 and 12·6 min. were observed under the same conditions as described above. The residue was hydrolysed with a mixture of hydrochloric acid (2 ml.) and glacial acetic acid (6 ml.), then esterified with diazomethane as described for the similar conversion of compounds of type (III) (see below). V.p.c. of the product showed the presence of three compounds, two of them corresponding to the methyl esters of *cis*- (I) and *trans*- (II) acids (in a ratio of 9 : 1) and the third one to the ester of the unsaturated endocyclic acid (VIII).

Conversion of Compounds of Type (III) *into* cis- (I) *and* trans- (II) *Acids*.—(*a*) The unsaturated acetate (IIIc) (0·5 g.) in ethanol (50 ml.) was hydrogenated in the presence of platinum oxide (0·05 g.) at room temperature. After consumption of the theoretical amount of hydrogen, the catalyst was filtered off, potassium hydroxide (0·3 g.) in water was added, and the mixture was heated under reflux for 2 hr. The ethanol was then removed under reduced pressure, the residue was diluted with water and then extracted with ether. The aqueous layer was acidified with dilute hydrochloric acid, and the resulting precipitate was taken up in ether. Evaporation of the dried ether solution gave a crystalline residue (0·28 g.), m.p. 140°. V.p.c. of a sample, after esterification with diazomethane, showed the presence of the *cis*- (I) and *trans*- (II) acids in a ratio of 1 : 1 (see Table 2).

(*b*) Each of the unsaturated nitriles (IIIa), (IIIb), or (IIId) (1·2 g.) in ethanol (50 ml.) was hydrogenated in the presence of platinum oxide (0·12 g.) at room temperature. Hydrogenation was stopped after consumption of 1 mol. of hydrogen. The catalyst was filtered off, the solvent was evaporated, and the residue was heated in a mixture of hydrochloric acid (2 ml.) and glacial acetic acid (6 ml.) for 3 days at 100°. After the volatile acids had been removed under reduced pressure, ether was added and the solution was extracted with N-sodium hydroxide. Acidification of the alkaline layer, re-extraction with ether, followed by evaporation of the dried ether solution gave a crystalline residue. The ratio of the *cis*- (I) and *trans*- (II) acids present in the product was determined in each case by v.p.c. of an esterified sample (see Table 2).

2-(2,5-*Xylyl*)*cyclohex*-1-*enylacetic Acid* (VIII).—A mixture of either of the αβ-unsaturated compounds (III) (0·5 g.), conc. hydrochloric acid (1 ml.), and glacial acetic acid (4 ml.)

was heated at 100° for 3 days. The work up was similar to that described for the preparation of the same compound in Part III,[2] and the products from the different experiments were found to be identical (i.r., n.m.r., v.p.c.) regardless of the starting compound used.

Catalytic Hydrogenation of Acid (VIII).—The unsaturated acid (VIII) (0·5 g.) was hydrogenated in glacial acetic acid (50 ml.) at 60—70° at an initial hydrogen pressure of 55 lb./sq. in. in the presence of 10% palladised carbon (0·05 g.). After 24 hr. the solution was filtered, fresh catalyst was added (0·05 g.), and the hydrogenation was continued for an additional 40 hr. The catalyst and solvent were then removed and a sample of the residue was esterified with diazomethane. V.p.c. analysis showed that about 70% of the starting acid had been reduced to a mixture containing *cis*- (I) and *trans*- (II) acids in a ratio of 82 : 18.

cis-*Hexahydrohomophthalic Acid*.—*cis*-Acid (I) (1·1 g.) was esterified with ethereal diazomethane, the solvent was replaced by methanol (25 ml.), and the resulting solution was ozonised exhaustively for 25 hr. at room temperature. Most of the solvent was then removed, hydrogen peroxide (30%; 10 ml.) was added, and the mixture was stirred for 40 hr. at room temperature. A 5% sodium carbonate solution was added to the cooled mixture until it was slightly alkaline reaction, after which the mixture washed with ether. The alkaline layer was acidified with cold dilute hydrochloric acid and extracted with ether. Evaporation of the dried (Na_2SO_4) ether extract gave an oily residue (0·57 g.). A part of this oil (0·30 g.), methanol (10 ml.), and 20% sodium hydroxide solution (5 ml.) was kept at room temperature for 5 days. After the usual work up, the crude acid (0·15 g.) was isolated. After repeated recrystallisation from water the pure *cis*-hexahydrohomophthalic acid, identical in m.p., mixed m.p., and spectral properties with an authentic sample prepared from dimethyl homophthalate,[8] was obtained.

[8/312 *Received, March 4th,* 1968]