

Addition Reactions of Conjugated Double Bonds. Part IV.¹ The Stereochemistry of Cyanide Ion Addition to Some $\alpha\beta$ -Unsaturated Ketones and Their π -Allylpalladium Derivatives²

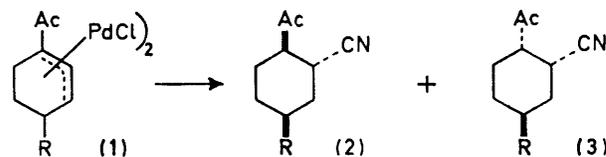
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The stereochemistry of cyanide ion addition to 1-acetyl-4-*t*-butylcyclohexene involves preferred axial attack of the nucleophile. This ketone and related ones give π -allylpalladium derivatives in which the acetyl group is preferentially *syn*-substituted[†] on a terminal atom of the allylic system. The π -allylpalladium compounds react with cyanide ion to give mixtures of β -cyano-ketones similar to those given by the parent $\alpha\beta$ -unsaturated ketones.

THE nucleophilic addition of cyanide ion to $\alpha\beta$ -unsaturated ketones is a reaction capable of wide synthetic application. $\alpha\beta$ -Unsaturated ketones can be readily converted into π -allylpalladium compounds,³⁻⁵ whose reactions with cyanide ion we have investigated as a potentially useful variant of the parent reaction.

π -Allylpalladium Compounds.—A series of cyclic $\alpha\beta$ -unsaturated ketones were prepared and treated with sodium chloropalladite in ethanol. 1-Acetylcyclohexene and 1-acetyl-4-*t*-butylcyclohexene gave π -allyl compounds (1; R = H and Bu^t) in which the acetyl group appeared as a *syn*-substituent[†] on the terminal carbon

atom of the allylic system. The *t*-butyl compound appeared to be a single diastereoisomer (single spot on t.l.c.) but its stereochemistry could not be assigned.



1-Acetyl-2-methylcyclohexene was treated with sodium chloropalladite to determine whether the π -allyl system

² Preliminary report, C. W. Alexander, M. S. Hamdam, and W. R. Jackson, *J.C.S. Chem. Comm.*, 1972, 94.

³ I. I. Moiseev, E. A. Federovskaya, and Y. K. Syrkin, *Zhur. neorg. Khim.*, 1959, **4**, 2941 (*Chem. Abs.*, 1960, **54**, 13,933).

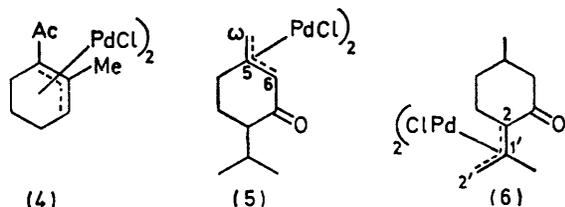
⁴ A. Kasahara, K. Tanaka, and K. Asamiya, *Bull. Chem. Soc. Japan*, 1967, **40**, 351.

⁵ R. W. Howsam and F. J. McQuillin, *Tetrahedron Letters*, 1968, 3667.

[†] *I.e.*, *syn* to the hydrogen atom or substituent on the central carbon atom; see M. L. H. Green in 'Organometallic Compounds,' vol. 2, Methuen, London, 1968, p. 42.

¹ Part III, H. Ferres, M. S. Hamdam, and W. R. Jackson, *J. Chem. Soc. (B)*, 1971, 1892.

preferred to form *endo* or *exo* to the six-membered ring. Only the *endo*-structure (4) was formed. Kashara and his co-workers⁴ have shown that endocyclic carbonyl compounds, e.g. 2,5,5-trimethylcyclohexen-1-one, form *exo*-



π -allyl systems in preference to the *endo*-isomers. Similarly we found that 6-isopropyl-3-methylcyclohex-2-en-1-one (piperitone) gave the *exo*- π -allyl compound (5), again of unknown stereochemistry. The preference in all of these compounds is to form the π -allyl compound in which the carbonyl group is *syn*-substituted on the terminal atom of the allyl system. On this basis the π -allyl palladium compound from 2-isopropylidene-5-methylcyclohexanone (pulegone) was assigned structure (6).

Cyanide Addition Reactions (Hydrocyanation).—The reactions of the parent $\alpha\beta$ -unsaturated ketones with cyanide ion were carried out by use either of calcium cyanide in *N*-methyl-2-pyrrolidone⁶ or of a mixture of potassium cyanide and ammonium chloride in dimethylformamide.⁷ 1-Acetylcyclohexene gave almost equal amounts of two isomeric β -cyano-ketones by either procedure and the isomers were separated by preparative g.l.c. The first eluted isomer had a large vicinal coupling constant ($J_{1,2}$ 10 Hz) consistent with axial-axial proton coupling and was assigned the *trans*-structure (2; R = H) whereas the more strongly adsorbed *cis*-compound had $J_{1,2}$ 3 Hz. The individual isomers were found to equilibrate under the reaction conditions. The reaction of 1-acetyl-4-*t*-butylcyclohexene with calcium cyanide gave two isomers in the ratio 2 : 1 which were separated by g.l.c. Their coupling constants were obtained from spectra observed with secondary irradiation at τ 8.0, *i.e.*, with decoupling of the protons on C-2 and C-6. The values were 1.5 Hz for the more abundant and 4.0 Hz for the less abundant isomer, indicating that neither isomer had 1-H and 2-H *trans*-diaxial. The individual isomers equilibrated under the reaction conditions to give an isomer mixture similar in composition to that formed in the cyanide addition reaction; no new isomers were obtained. Equilibration thus appears to involve epimerisation at only the carbon atom bearing the most acidic proton. This is almost certainly the carbon atom

⁶ H. B. Henbest and W. R. Jackson, *J. Chem. Soc. (C)*, 1967, 2465.

⁷ W. Nagata, M. Yoshioka, and S. Hirai, *Tetrahedron Letters*, 1962, 461.

⁸ H. O. House, 'Modern Synthetic Reactions,' Benjamin, New York, 1965, p. 154.

⁹ H. Booth, *Tetrahedron Letters*, 1965, 411; N. S. Bhacca and D. H. Williams, 'Applications of N.M.R. Spectroscopy in Chemistry,' Holden-Day, San Francisco, 1964, p. 144; R. J. Abraham, L. Cavalli, and K. G. R. Pachler, *Mol. Phys.*, 1966, 11, 471.

bearing the acetyl group, as acetone (pK_a 20)⁸ is a stronger acid than acetonitrile (pK_a 25).⁸ If we assume that the cyclohexane ring prefers a chair conformation, with the *t*-butyl group equatorial, the isomers, both of which must have an axial cyano-group, can be assigned the structures (2) and (3) (R = Bu^t). The more abundant isomer, with $J_{1,2}$ 1.5 Hz was tentatively assigned structure (3) and the minor isomer with $J_{1,2}$ 4.0 Hz structure (2). Compound (3), which has a cyano-group *trans*-coplanar with the 1-proton could be expected to have a smaller value of $J_{1,2}$ than isomer (2), which has no electron-withdrawing groups *trans*-coplanar with either 1-H or 2-H.⁹ This result is in agreement with the proposal of Abramovitch and his co-workers,¹⁰ who suggested that in the absence of exceptional steric factors axial nucleophilic attack on a conformationally rigid cyclohexene ring was preferred.

The reaction of piperitone with potassium cyanide gave two isomeric cyano-ketones, which were separated by preparative g.l.c. but whose stereochemistry was not assigned. Pulegone under similar conditions also gave two isomeric cyano-ketones but on attempted separation by preparative g.l.c. the cyano-group reacted, presumably to form a cyclic anhydramide as first formulated by Clarke and Lapworth.¹¹

The π -allylpalladium compounds from 1-acetylcyclohexene, 1-acetyl-4-*t*-butylcyclohexene, piperitone, and pulegone reacted with potassium cyanide and ammonium chloride in dimethylformamide at 100°. In all cases the products were the same mixtures of cyano-ketones as were obtained from reactions of the parent $\alpha\beta$ -unsaturated ketones under similar conditions. It thus appears that the parent $\alpha\beta$ -unsaturated ketones are intermediates in these reactions. In contrast, previous workers have shown that treatment of π -allylpalladium compounds from $\alpha\beta$ -unsaturated ketones with sodium cyanide in methanol gave conjugated dienones.¹²

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. Analytical g.l.c. was carried out with a Perkin-Elmer F11 gas chromatograph (2 m column of fluorosilicone oil on Chromosorb W). Preparative g.l.c. was carried out with an Aerograph Autoprep A 700 [20 m column of silicone fluid (20%) on Chromosorb W]. Alumina refers to Spence grade H deactivated with 5% of aqueous acetic acid (10% v/v). Fractions from column chromatography were tested for homogeneity by t.l.c. on 20 × 20 cm plates of Chromaluy silica gel, with mixtures of chloroform, ether, and light petroleum as solvent systems. Calcium cyanide was purified *via* its ammonia complex.¹³ N.m.r. spectra, except where stated otherwise, were recorded by R. Spratt and

¹⁰ R. A. Abramovitch and D. L. Struble, *Tetrahedron Letters*, 1966, 289; R. A. Abramovitch, M. M. Rogic, S. S. Singer, and N. Venkateswaron, 158th Amer. Chem. Soc. National Meeting, New York, 1969, Abstract Org. 99.

¹¹ R. W. L. Clarke and A. Lapworth, *J. Chem. Soc.*, 1906, 89, 1869.

¹² I. T. Harrison, E. Kimura, E. Bohme, and J. Fried, *Tetrahedron Letters*, 1969, 1589.

¹³ L. J. Christmann and A. G. Houpt, U.S.P. 2,386,434/1945 (*Chem. Abs.*, 1946, 40, 684).

I. Jack with a Varian HA 100 spectrometer for solutions in deuteriochloroform with tetramethylsilane as internal standard. I.r. spectra were recorded for potassium bromide discs for solid samples with a Perkin-Elmer Model 457 spectrometer.

Hydrocyanation of 1-Acetylcyclohex-1-ene.—1-Acetylcyclohex-1-ene (10.0 g), b.p. 85—88° at 22 mmHg (lit.,¹⁴ 63—64° at 6 mmHg) and calcium cyanide (18 g) were dissolved in *N*-methylpyrrolidone (50 cm³), and the solution was stirred for 3 days at ambient temperature. The neutral product (8.1 g, 65%) was shown to contain two compounds in the ratio 55 : 45 by analytical g.l.c. at 110°. Preparative g.l.c. at 170° gave *trans*-2-acetylcyclohexanecarbonitrile (2; R = H) as an oil (Found: C, 71.1; H, 8.8; N, 8.0. C₉H₁₃NO requires C, 71.5; H, 8.6; N, 8.2%); τ 7.24 (m, 2-H), 7.50 (m, 1-H), 7.76 (s, Ac), and 7.8—8.8 (m, CH₂); τ (C₆D₆) 7.57 (sextet, 2-H), 7.90 (sextet, 1-H) 8.23 (s, Me), and 8.4—9.4 (m, CH₂) ($J_{1,2}$ 10 Hz), followed by the *cis*-isomer (3; R = H) (Found: C, 71.0; H, 8.9; N, 7.9%); τ 6.77 (m, 2-H), 7.60 (m, 1-H), 7.80 (s, Ac), and 7.9—8.8 (m, CH₂) ($J_{1,2}$ ca. 3 Hz).

Equilibration. The cyano-ketone (2; R = H) (90 mg) was stirred with calcium cyanide (180 mg) in *N*-methylpyrrolidone (5 cm³) for 2 days at ambient temperature. The neutral product (68 mg) was shown to contain the isomers (2) and (3) in 1 : 1 ratio by analytical g.l.c.

Hydrocyanation of 1-Acetyl-4-*t*-butylcyclohex-1-ene.—(i) 1-Acetyl-4-*t*-butylcyclohex-1-ene (10 g), b.p. 130—132° at 10 mmHg (lit.,¹⁵ 135—137° at 14 mmHg) and calcium cyanide (15 g) were dissolved in *N*-methylpyrrolidone (50 cm³) and the solution was stirred at ambient temperature for 3 days. The neutral product (4.3 g, 37%) was isolated in ether and shown by qualitative g.l.c. at 150° to consist of a mixture of two components in the ratio 2 : 1. Preparative g.l.c. at 220° first gave the major isomer, *c*-2-acetyl-*t*-5-*t*-butylcyclohexane-*r*-1-carbonitrile (3; R = Bu^t), m.p. 46—48° (Found: C, 75.1; H, 10.4; N, 6.6. C₁₃H₂₁NO requires C, 75.3; H, 10.1; N, 6.8%); ν_{\max} 2280, 1725, 1370, and 1150 cm⁻¹; τ 6.47 (m, 2-H), 7.20 (m, 1-H), 7.82 (s, Ac), 9.17 (s, Bu^t), and 7.8—8.5 (m, CH₂) ($J_{1,2}$ 1.5 Hz); 2,4-dinitrophenylhydrazine, m.p. 157°. The minor component *t*-2-acetyl-*t*-5-*t*-butylcyclohexane-*r*-1-carbonitrile (2; R = Bu^t) was eluted as an oil (Found: C, 75.0; H, 10.4; N, 6.4%); ν_{\max} 2280, 1740, 1380, 1260, and 1190 cm⁻¹, τ 6.65 (m, 2-H), 7.60 (m, 1-H), 7.82 (s, Ac), 9.15 (s, Bu^t), and 7.3—9.0 (m, CH₂) ($J_{1,2}$ 4 Hz).

(ii) A mixture of the ketone (10 g), potassium cyanide (9 g), and ammonium chloride (5 g) in dimethylformamide (150 cm³) and water (35 cm³) was kept at 90—100° for 12 h with stirring. The neutral product (8.5 g, 72%) was isolated in chloroform and shown to contain the isomers (2) and (3) (R = Bu^t in the ratio 60 : 40).

Equilibration. The cyano-ketone (3; R = Bu^t) (100 mg) was heated with potassium cyanide (50 mg) and ammonium chloride (25 mg) in dimethylformamide (5 cm³) and water (1 cm³) for 4 h at 90—100°. The neutral product (70 mg) was shown to contain the isomers (2) and (3) in the ratio 55 : 45.

Hydrocyanation of 6-Isopropyl-3-methylcyclohex-2-en-1-one.—Treatment of the (\pm)-ketone (4.06 g) with potassium cyanide (3.4 g) and ammonium chloride (2.12 g) in di-

methylformamide (60 cm³) and water (16 cm³) at 90—100° for 12 h followed by isolation of the product in chloroform gave a mixture of *cis*- and *trans*-1-methyl-4-isopropyl-3-oxocyclohexanecarbonitriles (4.25 g, 88%) (Found: C, 74.0; H, 10.0; N, 8.2. Calc. for C₁₁H₁₇NO: C, 73.7; H, 9.6; N, 7.8%). Analytical g.l.c. on a Carbowax column showed the two compounds were present in the ratio 30 : 70. Preparative g.l.c. on Carbowax 1500 at 150° gave pure samples of the isomeric cyano-ketones. The first eluted had m.p. 62—66°, ν_{\max} 2225 and 1705 cm⁻¹, τ 8.52 (s, 1-Me), 7.30 and 7.61 (ABq, 2-H₂), 9.06 (d, Me), and 9.09 (d, Me) ($J_{2,3}$ 14, $J_{H,Me}$ 6.5 Hz). The second was a gum, ν_{\max} (film) 2225 and 1710 cm⁻¹; τ 8.58 (s, 1-Me), 7.31 and 7.51 (ABq, 2-H₂), 9.07 (d, Me), and 9.11 (d, Me) ($J_{2,3}$ 14, $J_{H,Me}$ 6.5 Hz) (lit.,¹⁶ ν_{\max} 2240 and 1708 cm⁻¹ for a mixture of the two diastereoisomers).

Hydrocyanation of 2-Isopropylidene-5-methylcyclohexanone.—A mixture of the (+)-ketone (7.5 g; [α]_D +22°), potassium cyanide (6.0 g), and ammonium chloride (4.0 g) in dimethylformamide (100 cm³) and water (25 cm³) was stirred at 90—100° for 12 h. 2-Methyl-2-(4-methyl-2-oxocyclohexyl)propionitrile (4.9 g, 56%), b.p. 130° at 3 mmHg (lit.,¹⁷ 120—125° at 1.4 mmHg) was isolated in dichloromethane. Analytical g.l.c. at 130° showed that two compounds were present in the ratio ca. 9 : 1. Attempted preparative g.l.c. separation at 140° gave a solid product which showed no C \equiv N i.r. absorption.

π -Allylpalladium Compounds.—A modification of McQuillin's procedure⁵ was used. Sodium chloropalladite (1 g, 3.3 mmol) was dissolved in ethanol (25 cm³) and a slight excess of the ketone (5 mmol) added. The solution was stirred under nitrogen for 3 h at ambient temperature and then poured into water (50 cm³). The solution was extracted with chloroform (3 \times 50 cm³); the combined extracts were washed with water, dried (MgSO₄), and evaporated to give a crude product which was chromatographed on silica gel.

Di- μ -chloro-bis-[1,2,3-trihapto-(1-acetylcyclohexene)palladium(II)] (1; R = H). Elution with ether-light petroleum (1 : 1) gave acetylcyclohexene. Elution with ether gave the *product* (1; R = H), m.p. 114° (decomp.), ν_{\max} 1680 cm⁻¹, τ 3.95 (d, 2-H), 4.55 (sextet, 3-H), 7.65 (s, Ac), and 8.13, 8.3, and 8.8 (multiplets) ($J_{2,3}$ 7 Hz) (Found: C, 35.0; H, 4.0. C₁₆H₂₂Cl₂O₂Pd₂ requires C, 36.2; H, 4.2%). The analysis was not improved by several recrystallisations from ether and the compound slowly darkened in air.

Di- μ -chloro-bis-[1,2,3-trihapto-(4-*t*-butyl-1-acetylcyclohexene)palladium(II)] (1; R = Bu^t). Elution with light petroleum-ether (9 : 1) gave 4-*t*-butyl-1-acetylcyclohexene (650 mg, 73%). Elution with light petroleum-ether (1 : 1) gave the *product* (1; R = Bu^t) (143 mg, 9.5%) as yellow needles, m.p. 167—168° (decomp.) (from ether-light petroleum) (Found: C, 44.9; H, 6.5. C₂₄H₃₈Cl₂O₂Pd₂ requires C, 44.8; H, 5.9%), ν_{\max} 1680 cm⁻¹, τ 4.0 (d, 2-H), 4.67 (d, 3-H), 7.67 (s, Ac), 9.07 (s, Bu^t), and 7.8—9 (m) ($J_{2,3}$ 7 Hz).

Di- μ -chloro-bis-[1,2,3-trihapto-(2-methyl-1-acetylcyclohexene)palladium(II)] (4). 1-Acetyl-2-methylcyclohexene, b.p. 85° at 12 mmHg (lit.,¹⁸ 98—98.5° at 22 mmHg) was purified *via* its semicarbazone, m.p. 210—212° (lit.,¹⁸ 213°) and

¹⁴ J. H. Saunders, *Org. Synth.*, 1955, Coll. Vol. III, p. 22.

¹⁵ M. S. Newman and P. H. Goble, *J. Amer. Chem. Soc.*, 1960, **82**, 4098.

¹⁶ W. A. Ayer and W. I. Taylor, *J. Chem. Soc.*, 1955, 2227.

¹⁷ N. Mayer and G. E. Gantert, Ger. Pat. 1,085,871/1960 (*Chem. Abs.*, 1962, **56**, 4640).

¹⁸ E. A. Braude, E. R. H. Jones, H. P. Koch, R. W. Richardson, F. Sondheimer, and J. B. Toogood, *J. Chem. Soc.*, 1949, 1890.

treated as above. Elution with ether gave the *product* (4) (70 mg, 6%), m.p. 120—121° (decomp.) (from ether—light petroleum) (Found: C, 37.8; H, 4.2. $C_{16}H_{26}Cl_2O_2Pd_2$ requires C, 38.6; H, 4.7%), ν_{max} 1670 cm^{-1} , τ 4.9 (m, 3-H), 7.51 (s, Me), 7.68 (s, Ac), and 8.0—8.5 (m, CH_2).

Di- μ -chloro-bis- $[\omega,5,6$ -trihapto-1-methylene-2-isopropyl-5-methylenecyclohexanone]palladium(II) (5).—The product from a reaction of (\pm)-6-isopropyl-3-methylcyclohex-2-en-1-one with sodium chloropalladite was chromatographed on silica gel. The starting ketone was eluted with ether—light petroleum (1 : 5); elution with ether gave the *product* (5), (54 mg, 4%), m.p. 84—86° (from chloroform—light petroleum) (Found: C, 41.1; H, 5.4; Cl, 12.3. $C_{20}H_{30}Cl_2O_2Pd$ requires C, 40.9; H, 5.1; Cl, 12.1%), ν_{max} 1668 cm^{-1} , τ 5.94 (s, ω_{syn} -H), 6.08 (s, 6-H), 6.82 (s, ω_{anti} -H), and 9.0—9.2 (2 \times d, Pr^1), and 7—8 (m, CH_2).

Di- μ -chloro-bis- $[2,1',2'$ -trihapto-(2-isopropylidene-5-methylcyclohexanone)palladium(II)] (6). A reaction between sodium chloropalladite (0.6 g) and (+)-2-isopropylidene-5-methylcyclohexanone (1 g), $[\alpha]_D^{20} +22^\circ$ was carried out as already described in ethanol (20 cm^3); the product was chromatographed on silica gel. Elution with ether—light

petroleum (1 : 10) gave unchanged ketone. Elution with ether gave the *product* (6) (430 mg, 60%), m.p. 164—165° (from chloroform—ether), $[\alpha]_D +77.4^\circ$ ($CHCl_3$) (Found: C, 41.7; H, 5.1; Cl, 12.3. $C_{20}H_{28}Cl_2O_2Pd_2$ requires C, 41.1; H, 5.5; Cl, 12.1%), ν_{max} 1675 cm^{-1} , τ 5.96 (s, $2'_{syn}$ -H); 6.18 (s, $2'_{anti}$ -H), 7.84 (s, $1'$ -Me); 8.92 (d, 5-Me, J 6 Hz), and 7.0—8.5 (m).

Hydrocyanation of π -Allylpalladium Compounds.—Di- μ -chloro-bis- $[1,2,3$ -trihapto-(1-acetylcyclohexene)palladium(II)] (100 mg) was heated for 12 h at 90—100° with potassium cyanide (100 mg) and ammonium chloride (50 mg) in dimethylformamide (10 cm^3) and water (1 cm^3). The product was isolated in dichloromethane as an oil which was shown to be a mixture of *cis*- and *trans*-2-acetylcyclohexane-carbonitriles (3) and (2) (R = H) (42 mg, 85%) in the ratio 45 : 55 (analytical g.l.c.; i.r. and n.m.r. spectroscopy).

The π -allylpalladium compounds (1; R = Bu⁴), (5), and (6) similarly gave mixtures of the appropriate cyanoketones in moderate yield (50—75%). The products were analysed by g.l.c. and spectroscopic methods.

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