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PALLADIUM ASSISTED ORGANIC REACTIONS

IV *. A NEW ISOQUINOLINE RING SYNTHESIS

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Summary

Ethyl *N*-methyl-*N*-(3,4-methylenedioxy)benzylglycinate is cyclopalladated regiospecifically at C(6) when treated with Li_2PdCl_4. The di-μ-chloro-bis(*N*,*N*-dialkylbenzylamine-6-C,N)dipalladium(II) complex that results undergoes an insertion reaction with methyl vinyl ketone, and the resultant β-aryl-α,β-unsaturated ketone is cyclised, as the methiodide, by K_2CO_3 in ethanol to the corresponding ethyl *N*,*N*-dimethyl-1,2,3,4-tetrahydroisoquinolinium-3-carboxylate. This sequence constitutes a new synthesis of the isoquinoline ring, with functionalised substituents at C(3) and C(4).

Introduction

The isoquinoline nucleus is present in a large number of alkaloids [2–4] and so for this, and other reasons, synthetic methods for the construction of this heterocyclic system have received considerable attention. Almost all of the useful methods that have been developed require a pre-formed benzenoid ring, and have been classified [5,6] into five main types (A–E), depending upon the bond or bonds that are made to close the nitrogen-containing ring.

Syntheses of type A are widely used, and substituent groups at C(1) are usually easily accommodated. Methods of type B, which have also been very popular, have been employed to prepare compounds with substituents at C(4) [5–7]. Because of the inaccessability of the precursors, syntheses of type C are almost unknown, yet in principle the method could be an attractive one since isoquinoline derivatives substituted at C(3) and C(4) could become available.

As part of a continuing programme in the utilisation of organopalladium compounds in the synthesis of alkoloids, and other heterocyclic systems of potential

* For part III see ref. 1.

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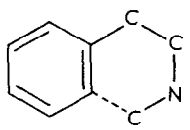
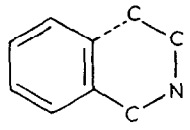


(A)



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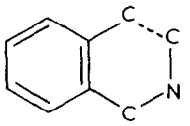

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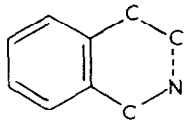

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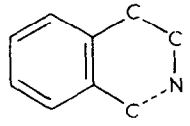
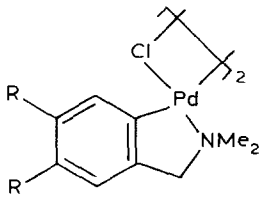


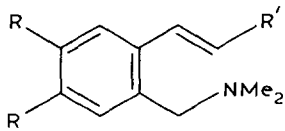
(E)

biological interest, it occurred to us that some insertion reactions of di-μ-chloro-bis(N,N-dialkylbenzylamine-2-C,N)dipalladium(II) complexes might provide the starting materials needed for a type C synthesis of the isoquinoline ring.

In 1968 Cope and Friedrick [8] reported that N,N-dimethylbenzylamine, and its p-methoxy and 3,5-dimethoxy derivatives, yielded cyclopalladated complexes of the type I when treated with Li_2PdCl_4 in methanol at room temperature. Such complexes have also been described by Thompson and Heck [9] and by Holton [10,11]. Tsuji [12] reported that I (R = H) reacted readily with styrene to give the insertion



(I)



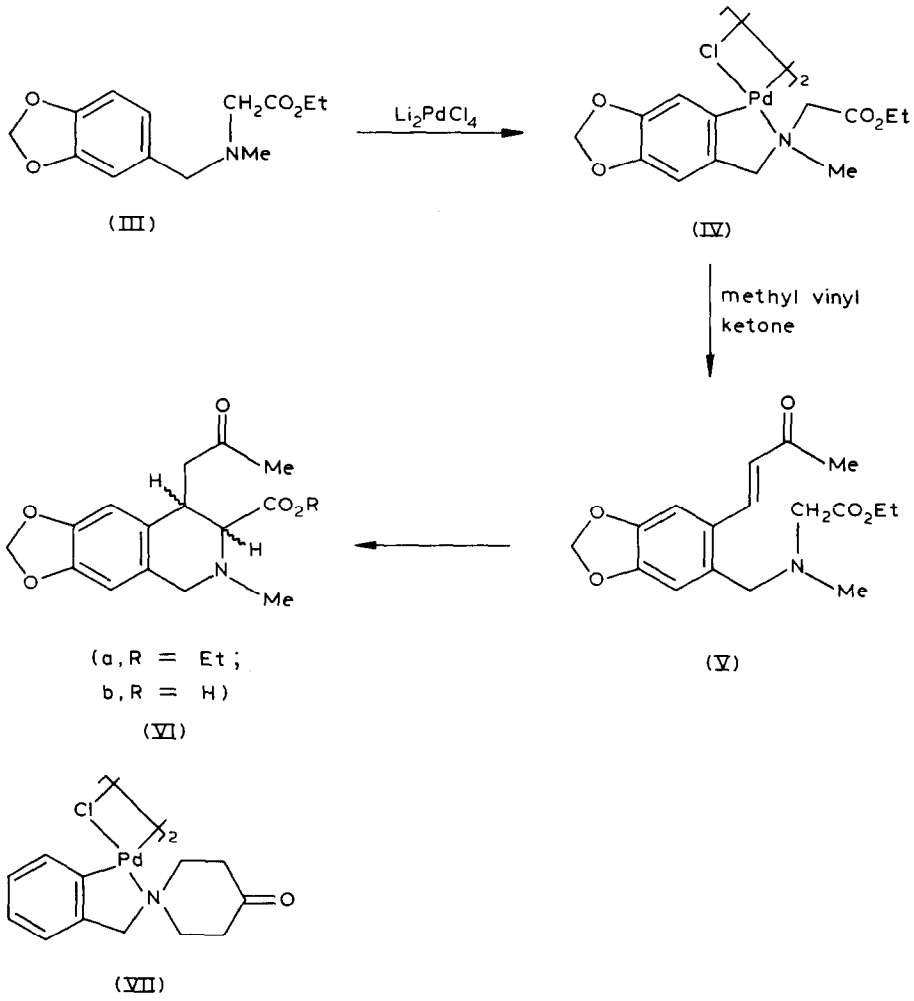
(II)

product II (R = H; R′ = C_6H_5). In part II of this series [13] we described the preparation of I (R = OMe) and its reaction with a number of styrene derivatives; in part III [1] a number of similar complexes is described. Holton [10] reported the insertion of methyl vinyl ketone into I (R = H) and I (2R = CH_2O_2) to give the ketones II (R = H, R′ = COMe) and II (2R = CH_2O_2, R′ = COMe), respectively, in good yield. In this paper we describe our attempts to realise the reactions summarised in III → VI (Scheme 1). Prior to this work the only functionalised cyclopalladated complex known was VII [14], but no chemical reactions have been reported for it.

Experimental

Melting points are uncorrected. ^1H NMR spectra were measured at 60 MHz (EM360L) or 100 MHz (JEOL PS100) on $CDCl_3$ solutions (unless otherwise stated). Chemical shifts are expressed in ppm downfield from internal TMS.

SCHEME 1



(III) (IV) (V) (VI) (VII)

Ethyl N-methyl-N-(3,4-methylenedioxy)benzylglycinate (III)

A mixture of *N*-methyl-(3,4-methylenedioxy)benzylamine (17.9 g, 0.109 mol), anhydrous sodium carbonate (17.1 g, 0.16 mol), ethyl chloroacetate (13.9 g, 0.113 mol) and dry benzene (100 ml) was heated under reflux for 24 h. The solids were removed by filtration and washed with CH_2Cl_2. The combined organic liquids and filtrate were filtered through a column of silica. Elution with ethyl acetate (200 ml) and evaporation of the eluate left *N*-methyl-(3.4-methylenedioxy)benzylglycinate as a pale yellow liquid (23.2 g, 84%). ^{1}H NMR ($CDCl_3$) 6.85 and 6.73 (3H, s, Ar–H); 5.88 (2H, s, CH_2O_2); 4.12 (2H, q, *J* 7.0 Hz,–CH_2CH_3); 3.57 (2H, s, Ar–CH_2–N); 3.22 (2H, s, N–CH_2CO_2Et); 2.35 (3H, s, NCH_3); 1.25 (3H, t, CH_3CH_2). Hydrochloride m.p. 155–156°C. (Found: C, 54.45; H, 6.4; N, 5.1. $C_{13}H_{18}ClNO_4$ calcd.: C, 54.3; H, 6.3; N, 4.9%). Methiodide m.p. 122–123°C. (Found: C, 43.1; H, 5.3; N, 3.6. $C_{14}H_{20}INO_4$ calcd.: C, 42,8; H, 5.1; N, 3.6%).

Di-μ-chloro-bis(ethyl N-methyl-N-(3,4-methylenedioxybenzyl)glycinate-6-C,N)dipalladium(II) (IV)

To an ice-cold solution of the above tertiary benzylamine (12.8 g, 51.0 mmol) in methanol (100 ml) was added 50 ml of 0.34 *M* Li_2PdCl_4 in methanol. After stirring at 0°C for 30 min the mixture was allowed to warm to room temperature and stirring was continued for 4 h. The solid was collected, washed with methanol and crystallised from $CHCl_3$/MeOH, m.p. 153–155°C (94% yield). ^{1}H NMR ($CDCl_3$): 6.65 (1H, s, Ar–H); 6.45 (1H, s, Ar–H); 5.83 (2H, s, CH_2O_2); 4.60–3.70 (6H, m); 3.10 (3H, s, NMe); 1.32 (3H, t, *J* 7.0 Hz, CH_3CH_2). (Found: C, 39.9; H, 4.2; N, 3.75. $C_{26}H_{32}Cl_2N_2O_8Pd_2$ calcd.: C, 39.9; H, 4.1; N, 3.6%).

Chloro-[ethyl N-methyl-N-(3,4-methylenedioxy)benzylglycinate-6,C,N]triphenylphosphinepalladium(II) (VIII)

A solution of the above chloride dimer (1.0 g, 1.28 mmol) and triphenylphosphine (0.67 g, 2.56 mmol) in CH_2Cl_2 (5 ml) was allowed to stand at room temperature for 1 h. Hexane was then added and the precipitated product was collected (1.27 g, 76.5%) m.p 159–160°C. ^{1}H NMR (CCl_4): 7.9–7.2 (m, 15H, PPh_3); 6.57 (s, 1H, Ar–H); 5.78 (d, 1H, *J*(P–H) 6.8 Hz, Ar–H); 5.60 (s, 2H, CH_2O_2); 4.20 (q, 2H, *J* 7.0 Hz, CH_2CH_3); 4.8–3.7 (m, 2H, $ArCH_2N$); 3.42 (s, 2H, N–CH_2CO_2Et); 2.97 (s, 3H, NMe); 1.27 (t, 3H, (CH_3–CH_2). Attempts to crystallise this compound for elemental analysis caused equilibration with IX, which was obtained pure (see below).

Chloro-[ethyl N-methyl-N-(3,4-methylenedioxy)benzylglycinate-6-C]-bis(triphenylphosphine)palladium(II) (IX)

A solution of the bridged chloride dimer (0.78 g, 1.0 mmol) and triphenylphosphine (1.1 g, 4.2 mmol) in CH_2Cl_2 (8.0 ml) was stood at 0°C for 30 min. Addition of sufficient hexane to cause cloudiness caused the product IX to crystallise (1.50 g, 82%). Recrystallisation from CH_2Cl_2/hexane at 0°C gave IX, m.p. 135–136°C (dec.). ^{1}H NMR (CCl_4): 7.65–7.0 (m, 30H, 2x Ph_3P); 6.30 (s, 1H, Ar–H); 5.87 (s, 1H, Ar–H); 5.50 (s, 2H, CH_2O_2); 4.10 (q, 2H, *J* 7.0 Hz); 3.52 (bs, 2H, Ar–CH_2–N); 3.27 (b.s., 2H, N–CH_2CO_2Et); 2.32 (b.s., 3H, NMe); 1.23 (t, 3H, *J* 7.0 Hz, CH_3CH_2). (Found: C, 64.3; H, 5.1; N, 1.6; Cl, 3.95. $C_{49}H_{46}ClNO_4P_2Pd$ calcd.: C, 64.2; H, 5.1; N, 1.5; Cl, 3.9%).

Insertion reaction between IV and methyl vinyl ketone

A mixture of the bridged chloride dimer IV (4.46 g, 5.68 mmol), methyl vinyl ketone (3.15 g, 45.0 mmol) and triethylamine (6.38 g, 63.7 mmol) was heated under reflux for 4.5 h in dry benzene (400 ml). After cooling, the mixture was filtered through a celite column and the column was then rinsed with CH_2Cl_2. The combined organic solutions were evaporated to small bulk, diluted with CH_2Cl_2 (50 ml), washed with water (to remove triethylamine hydrochloride), then with saturated NaCl solution and then dried (Na_2SO_4) and evaporated. The residual oil was dissolved in boiling hexane and the required insertion product, V crystallised upon cooling (72.5% yield) m.p. 63.5–64.5°C. ^{1}H NMR ($CDCl_3$), δ: 8.13 (1H, d, *J* 16 Hz) and 6.50 (1H, d, *J* 16 Hz, alkene hydrogens); 7.10 (1H, s, Ar–H); 6.83 (1H, s, ArH); 5.98 (2H, s, CH_2O_2); 4.17 (2H, q, *J* 7 Hz, $CO_2CH_2CH_3$); 3.73 (2H, s, $ArCH_2N$); 3.27 (2H, s, N–CH_2CO_2Et); 2.40 (3H, s, NCH_3 or CH_3CO–); 2.37 (3H, s, NCH_3 or CH_3CO): 1.27 (3H, t, *J* 7.0 Hz, CH_3CH_2–). (Found: C, 63.7; H, 6,6; N, 4.5.

$C_{17}H_{21}NO_5$ calcd.: C, 63.9; H, 6.6; N, 4.4%). Methiodide, m.p. 168–169°C from ethanol/ether. (Found: C, 47.0; H, 5.4; N. 2.9. $C_{18}H_{24}INO_5$ calcd.: C, 46.9; H, 5.2; N, 3.0%).

Cyclisation of V methiodide

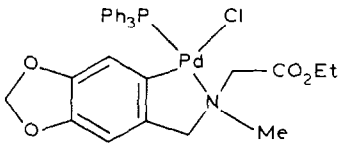
To a solution of the methiodide of V (0.85 g) in ethanol (20 ml) was added anhydrous potassium carbonate (0.35 g). The mixture was stirred overnight then filtered. A solution of potassium iodide (1.5 g) in water (25 ml) was added to the filtrate and the solution was then concentrated (rotatory evaporator). The residual liquid was brought to pH 7, filtered, then the filtrate was further concentrated as before. After standing overnight the crystals that had separated were collected, washed with a little absolute ethanol and dried (0.13 g; 15.3% yield). m.p. 219–220°C. (Found: C. 45.3; H, 4.8; N, 3.0; I. 27.2. $C_{18}H_{24}INO_5$ calcd.: C, 46.9; H, 5.2; N, 3.0; I, 27.5%) (Considerable difficulty was experienced in achieving combustion of this quarternary salt in the analysis).

Results and discussion

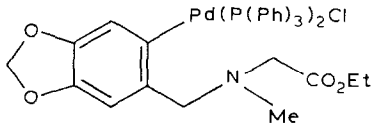
In the event, cyclopalladation of III occurred readily under the conditions described previously [1] and IV was obtained in 83% yield. That cyclopalladation had occurred regiospecifically at C(6) was evident from the ^{1}H NMR spectrum of IV which exhibited two one-hydrogen singlets at δ 6.68 and 6.46. Both methylene groups attached to nitrogen absorbed as AB quartets at δ 4.21 (J 14 Hz) and 4.0 (J 16 Hz). The *N*-methyl group appeared as a singlet at δ 3.12, compared with 2.38 in the base III itself. In previous work [1] it was found that the bridged chloride dimers such as IV are not very soluble in common organic solvents, but that the derived, monomeric triphenylphosphine complexes are. When IV was treated with 2 mol of triphenylphosphine the expected complex VIII was obtained. In the ^{1}H NMR spectrum (in CCl_4) the C(5)-H is substantially shielded by the new ligand and appears as a doublet (J(H–^{31}P) 6.8 Hz) at 5.78 δ. The upfield shift of this absorption, compared with its position in the bridged dimer IV is indicative of the *trans* relationship between the nitrogen and phosphorus groups, as depicted in VIII. When attempts were made to recrystallise VIII an equilibrium mixture of VIII and IX was produced. When IV was reacted with 4.2 mol of triphenylphosphine, IX could be isolated, purified and analysed. It is believed that this is the first time that a bis(triphenylphosphine) complex such as IX has been isolated and characterised. The geometry of IX could not be determined unambiguously.

The reaction IV with methyl vinyl ketone in benzene solution, in the presence of triethylamine gave the expected insertion product V in 73%. The ^{1}H NMR spectrum is diagnostic of this structure. When the bis(triphenylphosphine) complex IX was reacted similarly with methyl vinyl ketone, dichlorobis(triphenylphosphine)palladium(II) was the major product, together with a mixture of other complexes containing some VIII and some IX.

When the methiodide of V was treated, at room temperature, with anhydrous potassium carbonate in ethanol solution for 12 h, a mixture of quaternary salts was produced. By fractional crystallisation the expected product X (R = Et) was isolated as the iodide. Since this compound is insoluble in most common organic solvents ^{1}H and ^{13}C NMR spectra were difficult to record and it was not possible to make any



(VIII)



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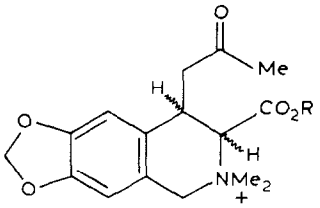

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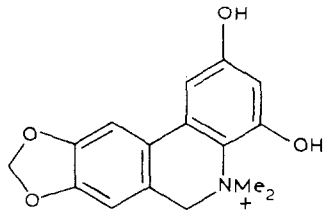

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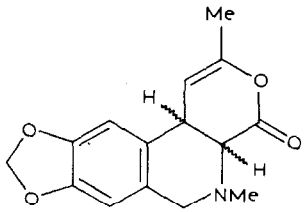

(XII)

comment about the stereochemistry at C(3) and C(4). That cyclisation had occurred was evident from the ^{1}H NMR spectrum since absorptions due to the alkene hydrogen atoms at low field in V had disappeared and been replaced by multiplet absorption in the 4.0–5.0 δ region. When X (R = Et) was exposed to aqueous HCl further reaction occurred to give what is believed to be XI, although elemental analyses of it were less than satisfactory.

When the base V itself was heated under reflux for 12 h with ethanolic sodium carbonate a mixture of VIa and VIb, together with unchanged V was obtained. It is possible that the amino acid VIb was formed via the enol lactone XII. Unfortunately VIa proved to be unstable, readily forming brown oils upon exposure to air. However, a mass spectral fragmentation pattern is consistent with the proposed structure, particularly in the light of the established fragmentations of other, related compounds in the series [15].

Further work is in progress to develop this new synthetic procedure for the isoquinoline ring system.

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