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PALLADIUM ASSISTED ORGANIC REACTIONS

V *. THE REACTIONS OF DI-μ-CHLORO-BIS(*N*,*N*-DIALKYLBENZYLAMINE-2-C,N)DIPALLADIUM(II) COMPLEXES WITH ACYL CHLORIDES

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Summary

The reactions between two di-μ-chloro-bis(*N*,*N*-dialkylbenzylamine-2-C,N)dipalladium(II) complexes, and two [ethyl di-μ-chloro-bis(*N*-methyl-*N*-benzyl-2-C,N)-glycinate]dipalladium(II) complexes with a variety of acyl halides have been studied. Regiospecific *ortho*-acylation occurs in good to high yields in most examples. The intermediate complexes of the type $[LPdCl_2]_2$ were characterised in two cases (L = *ortho*-acylbenzylamine derivative). No insertion reactions were observed with $(C_6H_5)_3C \cdot COCl$ or with $(CH_3)_3C \cdot COCl$. The cyclisations of two of the *ortho*-acylbenzylglycinates to isoquinoline derivatives are described, to illustrate the utility of these acylation reactions in synthetic nitrogen heterocyclic chemistry.

Introduction

In 1963, the first cyclometalled compound, formed by the reaction of azobenzene and nickelocene, was reported by Kleinmann and Dubeck [2]. Cope and Siekman [3] extended this study with azobenzene, and certain of its derivatives, forming cyclometallated compounds with palladium and platinum. Since then cyclometallation reactions have been observed with other transition metal complexes, and with other ligands, in particular with *N*,*N*-dialkylbenzylamines and benzalimines [1,4–6], but cyclopalladation seems to be the most facile, and, because of potentially useful catalytic processes, has been the most intensely studied. It has been found that the Pd–C bond in some of the cyclopalladated compounds can undergo a number of "insertion" reactions with, for example, carbon monoxide [7,8], electron deficient alkenes [9–11], alkynes [12], and acetyl or benzoyl chlorides [13]. Although such "insertion" reactions are regiospecific, and offer a potentially important sequence in

* For part IV see ref. 1.

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organic synthetic methodology, little research has been done in this area. We have been interested in these reactions of cyclopalladated benzylamines for the development of new synthetic routes to certain nitrogen heterocyclic compounds and in part IV of this series [1] we described a new synthesis of the isoquinoline ring system utilising the insertion of methyl vinyl ketone. In this paper are described the reactions of these types of complexes with some acyl chlorides, and the utilisation of the resultant *o*-acylbenzylamine derivatives in the preparation of 3,4-disubstituted isoquinoline derivatives.

Experimental

The palladium chloride was obtained from Johnson–Matthey Research Centre and was used without further purification. A solution of 0.25 *M* lithium tetrachloropalladate(II) in methanol was used in the preparation of the starting complexes. *N*,*N*-Dimethyl-3-methoxybenzylamine and *N*,*N*-dimethyl-3,4-dimethoxybenzylamine were prepared as outlined previously [14]. Ethyl *N*-3-methoxybenzyl-*N*-methylglycinate and ethyl *N*-3,4-dimethoxybenzyl-*N*-methylglycinate were prepared from *N*-3-methoxybenzyl-*N*-methylamine and *N*-3,4-dimethoxybenzyl-*N*-methylamine respectively and ethyl chloroacetate [15].

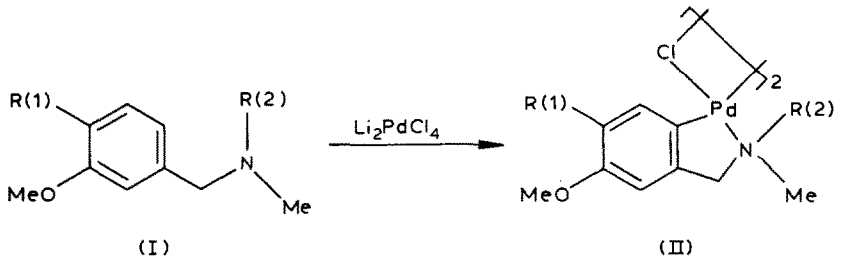
IR spectra were recorded using a Perkin–Elmer 598 spectrometer in the range 4000–200 cm^{-1}. Solid samples were scanned as Nujol mulls and oils as neat samples. ^1H NMR spectra were recorded using a Varian EM360L and a Bruker CXP-300 spectrometer operating at 300.0 MHz. Proton decoupled, and off-resonance ^{13}C NMR spectra were recorded on the Bruker CXP-300 spectrometer operating at 75.4 MHz. All NMR samples were dissolved in $CDCl_3$ using TMS as an internal reference and the NMR spectrometers were operated at ambient probe temperatures. Chemical shift values are in ppm with TMS taken as zero. ^1H–^1H couplings are in Hz. The gas chromatographs and mass spectra were obtained on a Carlo-Erba GC linked to a KRATOS MS25 mass spectrometer. The molecular weights of the organic compounds were recorded as the parent M^+ ion in the mass spectra, while the molecular weights of the palladium complexes were obtained by vapour pressure osmometry on samples dissolved in chloroform. High resolution mass spectral data were obtained using an A.E.I. MS902 mass spectrometer. Microanalyses were performed by the University of Queensland Microanalytical Laboratory and the Australian Microanalytical Service, Melbourne.

The di-μ-chloro-bis(*N*,*N*-dialkylbenzylamine-2-C,N)dipalladium(II) complexes IIa and IIb were prepared as previously described [14]. The complexes I–IV are depicted in Scheme 1.

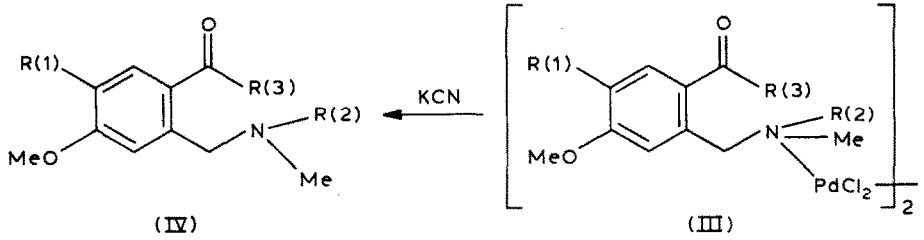
Preparation of the [ethyl di-μ-chloro-bis(N-methyl-N-benzyl-2-C,N)-glycinate]dipalladium(II) complexes IIc and IId

Complex IIc: a solution of ethyl *N*-3-methoxybenzyl-*N*-methylglycinate (12.0 g, 50.6 mmol) in methanol (100 ml) was added to 0.25 *M* lithium tetrachloropalladate(II) in methanol (100 ml) at room temperature and stirred for 16 h. The resulting yellow precipitate was removed by filtration and washed with methanol. The complex was recrystallised from chloroform/methanol to yield complex IIc (8.7 g, 92%).

Complex IId: this was prepared in a similar manner to IIc and was obtained in 62% yield.



	R(1)	R(2)
a	H	Me
b	OMe	Me
c	H	CH_2CO_2Et
d	OMe	CH_2CO_2Et



	R(1)	R(2)	R(3)
a	H	Me	CH_2Ph
b	H	Me	$CH{=}CHPh$
c	H	Me	CH_2CH_2Ph
d	H	Me	$CH(CH_3)Ph$
e	H	Me	$CHPh_2$
f	OMe	Me	CH_2Ph
g	OMe	Me	$CH{=}CHPh$
h	OMe	Me	$CH_2{-}CH_2Ph$
i	OMe	Me	$CH(CH_3)Ph$
j	OMe	Me	$CHPh_2$
k	H	CH_2CO_2Et	CH_2Ph
l	OMe	CH_2CO_2Et	CH_2Ph

SCHEME 1

Preparation of the dimeric complexes (IIIa–IIIl)

To a stirred solution of 5.0 mmol of one of the complexes IIa–IId in 120 ml of sodium-dried benzene under nitrogen at room temperature was added 25 mmol of the acid chloride. After stirring for 60 h, the brown to red precipitate was filtered, washed with benzene and dried in air. The yields of these complexes are listed in Table 2. They were too insoluble for recrystallisation, but reasonably accurate

TABLE 1

ANALYTICAL DATA

Compound	Molecular formula	Found (calcd.) (%)				
		C	H	Cl	N	Mol.wt. Found (calcd.)
IIc	$C_{26}H_{36}Cl_2N_2O_6Pd_2$	40.9 (41.3)	4.80 (4.80)	10.2 (9.4)	3.73 (3.71)	735 (756)
IId	$C_{28}H_{40}Cl_2N_2O_8Pd_2$	40.9 (41.2)	4.97 (4.94)	9.1 (8.7)	3.40 (3.44)	825 (816)
IIIk	$C_{42}H_{50}Cl_4N_2O_8Pd_2$	46.1 (47.3)	4.61 (4.73)		– –	1110 (1064)
IVa	$C_{18}H_{24}NO_2$	75.8 (76.3)	7.09 (7.47)		5.13 (4.94)	283 (283)
IVb	$C_{19}H_{21}NO_2$	76.9 (77.3)	7.39 (7.17)		5.02 (4.74)	295 (295)
IVc	$C_{19}H_{23}NO_2$	77.0 (76.7)	7.79 (7.79)		4.56 (4.71)	297 (297)
IVd	$C_{19}H_{23}NO_2$	76.6 (76.7)	7.67 (7.79)		4.82 (4.71)	297 (297)
IVe	$C_{24}H_{25}NO_2$	80.0 (80.2)	7.00 (7.01)		3.76 (3.90)	359 (359)
IVf	$C_{19}H_{23}NO_3$	72.0 (72.8)	7.24 (7.40)		4.48 (4.47)	313 (313)
IVg	$C_{20}H_{23}NO_3$	73.8 (73.8)	7.26 (7.12)		4.22 (4.31)	325 (325)
IVh	$C_{20}H_{25}NO_3$	72.5 (73.4)	7.57 (7.70)		4.22 (4.28)	327 (327)
IVi	$C_{20}H_{25}NO_3$	73.2 (73.4)	7.72 (7.70)		4.17 (4.28)	327 (327)
IVj	$C_{25}H_{27}NO_3$	76.4 (77.1)	6.88 (6.99)		3.80 (3.60)	389 (389)
IVk	$C_{21}H_{25}NO_4$	71.0 (71.0)	6.90 (7.09)		3.64 (3.94)	355 (355)
IVl	$C_{22}H_{27}NO_5$	68.9 (68.6)	7.00 (7.06)		3.67 (3.63)	385 (385)
Vb	$C_{22}H_{27}NO_5$	68.1 (68.6)	7.09 (7.06)		3.88 (3.63)	385 (385)

TABLE 2

IR DATA AND YIELDS (ν in cm^{-1})

Compound	ν(CO)	ν(Pd–Cl)		Yield [a] (%)
IIc	1740s	360w	260w	92
IId	1740s	346w	270w	62
IIIa	1668s	335m	–	97
IIIb	1647s	352w	337m	84
IIIc	1658s	350sh	337m	95
IIId	1660s	342w	330m	80
IIIe	1655s	345sh	335s	96
IIIf	1666s	347m	–	70
IIIg	1642s	347sh	338m	96
IIIh	1658s	344sh	333m	90
IIIi	1658s	345sh	335s	84
IIIj	1662s	335s	–	74
IIIk	1648s 1735s	338s	–	98
IIIl	1660s 1728s	345m	330m	95
IVa	1677s			98
IVb	1648m			87
IVc	1675s			91
IVd	1675s			85
IVe	1678s			91
IVf	1696s			84
IVg	1643m			88
IVh	1678s			77
IVi	1678s			80
IVj	1665s			91
IVk	1655s 1728s			93
IVl	1676s 1735s			95
Va [b]	1710 br			12
Va' [b]	1718s 1725s			12
Vb [b]	1720s			25

[a] Yields for the final products of type IV are based upon the intermediate complexes of type III. [b] Va, ν(OH) 3440br; Va', ν(OH) 3420br; Vb, ν(OH) 3420br.

analytical, and reliable NMR, data on one of these complexes (IIIk) were obtained. Pure samples of the complexes IIIb and IIIg were best prepared in methylene chloride, which eliminated the coprecipitation of the starting complex.

Preparation of the o-acyl-N,N-dimethylbenzylamines (IVa–IVj) and the ethyl o-acyl-N-methyl-N-benzylglycinates (IVk–IVl)

To a stirred suspension of 1.0 g of one of the complexes (IIIa–IIIl) in a mixture of chloroform (100 ml) and water (100 ml) was added potassium cyanide (1.0 g). The mixture was stirred until the solution had cleared, indicating that all of the palladium complex (III) had reacted. The organic layer was separated and washed with water, dried (sodium sulphate) and evaporated at reduced pressure to give a viscous oil. The yields of these oils are given in Table 2. These oils were found to be pure as shown by analyses, GC/MS and NMR spectral data. The oils could not be distilled as they discoloured rapidly on heating.

(Continued on p. 409)

TABLE 3

^{1}H NMR DATA

(δ in ppm; absorptions are singlets unless otherwise stated; J(H–H) (Hz) in brackets)

Compound	δ(NMe)	δ(ArCH$_2$N)	δ(OMe)	δ(N–CH$_2$CO)	δ(Ar)			Other
					2	4	5	
IVa	2.17	3.64	3.82	–	7.07d (2.6)	6.77dd (2.6, 8.5)	7.56d (8.5)	4.14 (PhC*H*$_2$)
IVb	2.18	3.61	3.85	–	7.05d (2.6)	6.83dd (2.6, 8.5)	7.48d (8.5)	7.14d and 7.35d (16.0) (CH=CH)
IVc	2.21	3.65	3.82	–	7.06d (2.7)	6.76dd (2.7, 8.5)	7.49d (8.5)	3.01–3.17m (–CH$_2$–CH$_2$Ph)
IVd	2.13	3.62d 3.51d (14.4)	3.78	–	7.00d (2.7)	6.65dd (2,7, 8.5)	7.30d (8.5)	1.52 and 4.41q (6.9) (CH$_3$CH)
IVe	2.11	3.64	3.80	–	7.10d (2.6)	6.78dd (2.6, 8.6)	7.51d (8.6)	5.8 (Ph$_2$CH)
IVf	2.16	3.57	3.91 3.83	–	7.00	–	7.01	4.14 (PhCH$_2$)
IVg	2.18	3.55	3.95 3.90	–	7.03	–	7.03	7.31d and 7.15d (16.1) (CH=CH)
IVh	2.19	3.58	3.92 3.84	–	6.93	–	7.02	3.14t and 3.03t (7.7) (PhCH$_2$CH$_2$)

IVi	2.14	3.58d 3.46d (14.2)	3.88 3.68	–	6.71	–	6.96	1.53d and 4.34q (6.9) (CH_3CH)
IVj	2.13	3.61	3.89 3.66	–	6.94	–	7.07	5.75 (Ph_2CH)
Ic	2.48	3.48	3.80	3.34	6.84		7.37m	1.27t and 4.17q (7.1) (CH_3CH_2O)
IIc	3.13	4.52d 4.08d (14.3)	3.73	4.07d 3.92d (16.7)	6.47	–	7.10m	1.31t and 4.22q (7.1) (CH_3CH_2O)
Id	2.39	3.61	3.86 3.89	3.22	6.94d (1.5)	6.78–6.85m		1.27t and 4.17q (7.2) (CH_3CH_2O)
IId	3.14	4.51d 4.08d (14.0)	3.87 3.79	3.91d 4.08d (16.7)	6.48	–	6.64	1.32t and 4.22q (7.1) (CH_3CH_2O)
IVk	2.29	3.88	3.82	3.16	7.14d (2.6)	6.77dd (2.6, 8.5)	7.59d (8.5)	1.24t and 4.14q (7.1) (CH_3CH_2O–) 4.15 ($PhCH_2$–)
IIIk	3.21	3.98	3.98	3.64	7.68d (2.6)	7.08dd (2.6, 8.9)	8.06d (8.9)	1.25t and 4.10q (7.1) (CH_3CH_2O); 4.34 ($PhCH_2$)
IVl	2.31	3.84	3.84 3.92	3.15	7.06	–	7.15	1.25t and 4.15q (7.1) (CH_2CH_2O); 4.16 ($PhCH_2$–)

TABLE 4

^{13}C NMR SPECTRAL DATA

(δ in ppm)

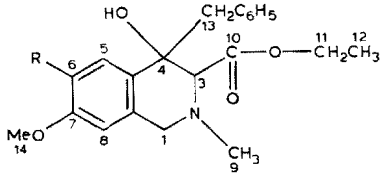
Compound	δ(NMe)	δ(OMe)	δ(Ar–C(=O)–)	δ(–C(=O)–O)	δ(Ar–CH_2N)	δ(Ar)	Other
IVa	45.2	55.3	200.6	–	61.6	111.0–162.0	48.6 (CH_2Ph)
IVb	44.9	55.4	194.8	–	61.3	111.0–161.0	130.4 (PhCH=CH) 143.1 (PhCH=CH)
IVc	45.2	55.3	202.6	–	61.6	111.0–161.0	30.5 (Ph–CH_2–); 43.2 (CH_2–CH_2–Ph)
IVd	45.2	55.2	203.8	–	61.6	111.0–161.0	18.7 (Ph–C(–CH_3)–); 50.9(CH–C(–CH_3)–Ph)
IVe	45.2	55.4	201.0	–	61.5	111.0–160.0	62.2 (Ph_2CH)
IVf	45.2	56.1 56.3	200.9	–	61.3	112.0–135.0 [a]	49.1 (Ph–CH_2–)
IVg	44.8	56.1 56.3	195.1	–	61.0	112.0–151.0	143.7 (CH=CH–Ph); 130.2 (Ph–CH=CH–)
IVh	45.2	56.2 56.3	202.9	–	61.3	111.0–130.0 [a]	43.6 (–CH_2CH_2Ph); 30.8 (Ph–CH_2–CH_2)
IVi	44.9	56.0 56.3	203.9	–	61.2	111.0–151.0	18.5 (Ph–CH(–CH_3)–) 51.6 (Ph–CH(–CH_3)–)
IVj	45.2	56.0 56.0	201.0	–	61.1	112.0–151.0	62.7 (Ph_2CH)

IVk	42.0	55.3	200.7	171.1	60.2	111.0–162.0	14.3 (CH_3CH_2–) 57.9 [b] (–CH_2CH_3); 48.4 ($C_6H_5CH_2$) 58.6 [b] (N–CH_2CO)
IVl	42.1	56.1 [b] 56.3 [b]	200.7	171.1	60.2	112.0–171.0	14.3 (CH_3–CH_2–); 57.8 [b] (–CH_2CH_3); 58.2 [b] (N–CH_2CO) 49.0 (PhCH_2CO)
Ic	42.1	55.2	–	170.7	60.9	111.0–159.0	14.1 (CH_3CH_2–) 57.5 [b] (–CH_2CH_3) 60.2 [b] (N–CH_2CO)
Id	42.1	55.8 [b] 55.8 [b]	–	170.8	60.7	111.0–149.0	14.1 (CH_3CH_2–) 57.3 [b] (CH_2–CH_3) 60.0 [b] (N–CH_2–CO)
IIc	49.7	55.3	–	167.0	69.7	108.0–158.0	14.2 (CH_3–CH_2) 61.3 [b] (–CH_2CH_3) 61.8 [b] (NCH_2CO)
IId	49.7	56.1 [b] 56.3 [b]	–	166.9	69.7	106.0–147.0	14.1 (CH_3CH_2) 61.2 [b] (–CH_2CH_3) 61.7 [b] (NCH_2CO)
IIIk	42.7	55.4	c	c	61.0	117.0–134.0 [a]	14.0 (CH_3CH_2) 57.3 [b] (CH_2CH_3) 63.3 [b] (NCH_2CO) 47.2 (PhCH_2)
IIIl	42.3	55.3 56.4	c	c	63.4	b	14.0 (CH_3–CH_2) 58.1 [b] (CH_2CH_3) 60.5 [b] (NCH_2CO) 47.8 (PhCH_2)

[a] The aromatic carbon bearing OMe groups not detected. [b] Assignment uncertain. [c] Not visible.

TABLE 5

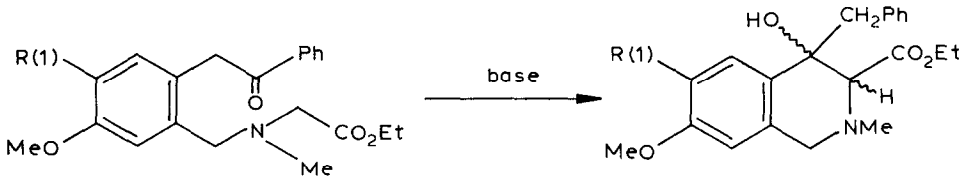
NMR DATA FOR THE ISOQUINOLINE DERIVATIVES (J(H–H) (Hz) in brackets)



Compound		1	3	4	5	6	8	9	10	11	12	13	14	15 (R = OMe)
Vb	^{1}H	3.28q (13.4)	3.86 bs	–	6.85	–	6.24	2.64	–	4.51q (7.1)	1.19t (7.1)	3.42	3.75	3.83
	^{13}C	60.4	67.4	74.2	←	No assignment	→	43.5	172.2	52.6	14.4	48.5	56.15	55.9
Va	^{1}H													
	(a)	3.13 (13.8)	3.84	–	7.45d (8.5)	6.77dd (2.6,8.5)	6.54d (2.6)	2.62	–	4.3q (7.0)	1.16t (7.0)	3.4	3.78	–
	(b)	3.08	3.81	–	7.48d (8.7)	6.82dd (2.5,8.7)	6.55d (2.5)	2.50	–	4.5q (7.0)	1.16t (7.0)	3.68q (15.7)	3.78	–

Preparation of ethyl 2-methyl-6,7-dimethoxy-4-benzyl-4-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (Vb)

Ethyl *N*-3,4-dimethoxy-6-phenylacetylbenzyl-*N*-methylglycinate, (IVl) (1.0 g, 2.6 mmol), was stirred with a solution of sodium ethoxide (0.2 g, 3.0 mmol) in dry ethanol (20 ml) under nitrogen for 24 h. After acidification with dilute acetic acid, the solution was evaporated in vacuo, diluted with water, extracted with methylene chloride (3 × 20 ml), washed, dried and evaporated to yield a dark oil. GLC analysis (SE 30/200°C) showed two main components, the original glycine ester (IVl) (ca. 45%) and the isoquinoline derivative (Vb) (*r* 0.72 rel. to IVl; ca. 45%) as well as other



(IVk, IVl) (Va, R(1) = H; Vb, R(2) = OMe)

components of lower retention times. Column chromatography (Silica gel, Woelm 02747, Activity 1) of the original dark oil mixture, using mixtures of ethyl acetate/cyclohexane of increasing polarity, yielded Vb as a light yellow gum which was further purified for analyses by TLC (Merck Silica gel, 20 × 20 cm, 0.25 mm, ethyl acetate/cyclohexane 2/5). Analytical and spectral data for Vb are summarised in Tab. 1–5.

Preparation of ethyl 2-methyl-7-methoxy-4-benzyl-4-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (Va)

Ethyl *N*-3-methoxy-6-phenylacetylbenzyl-*N*-methylglycinate (IVk) was cyclised under similar conditions as IVl, and after chromatography yielded two isoquinoline derivatives as light yellow gums. Both compounds showed the same mass spectral fragmentation pattern, indicating that they are geometrical isomers. Analytical and spectra data for Va are summarised in Tab. 1–5.

Results and discussion

When the cyclopalladated complex IIc was reacted with phenylacetyl chloride in benzene solution at room temperature, the initial yellow colour of the solution changed to reddish-brown during 60 h, and a solid was formed. In the IR spectrum of this dried solid strong bands at 1660 (ketone carbonyl) and 1730 cm^{-1} (ester carbonyl) were present, together with two palladium–chlorine stretching frequencies at 335 and 345 cm^{-1}. Both of these bands are associated with terminal palladium–chlorine bonds; bands due to bridging Pd–Cl bonds, which normally occur at about 300 and 260 cm^{-1} [16], were absent from the spectrum. The material was not sufficiently soluble to be fully characterised, but ^{1}H and ^{13}C NMR spectra (see tables) were obtained. These data are consistent with structure IIIk, formed by "insertion" of the carbonly group of the acid chloride into the Pd–carbon bond of IIc, leaving the nitrogen atom still bonded to palladium. Molecular weight determination confirmed that the new complex is dimeric. The positions of the two

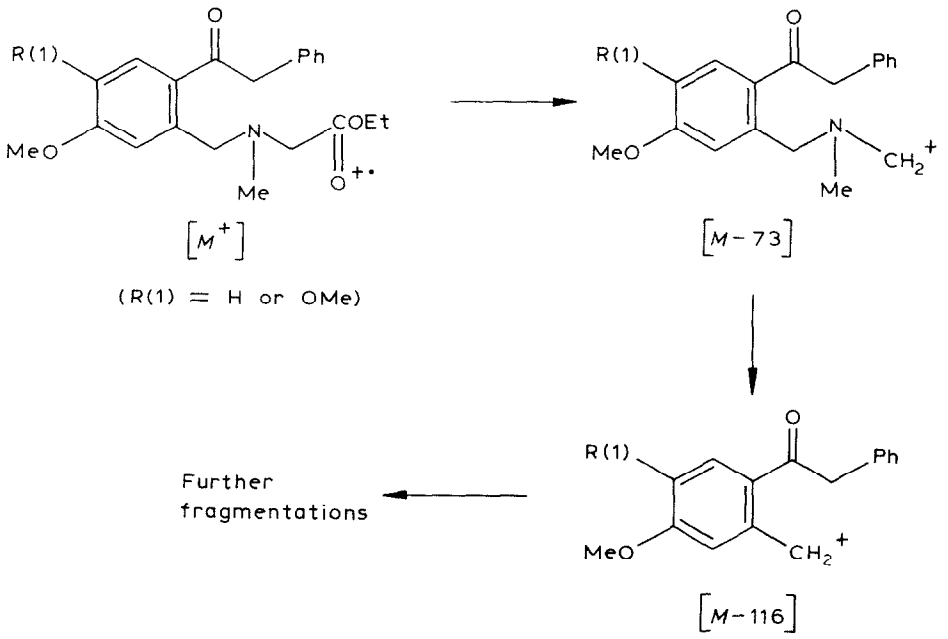
Pd–Cl frequencies in the IR suggests [16] that the complex has the *cis* configuration, although it has not proved possible to confirm this.

The reaction of the cyclopalladated complex IId with phenylacetyl chloride gave a similar result leading to the complex IIIl (see tables for NMR data).

When the complex IIIk was reacted at room temperature with aqueous KCN solution it decomposed, liberating the keto-amine IVk in high overall yield. The structural assignment rests upon IR, ^{1}H and ^{13}C NMR spectral data (see tables), the mass spectral fragmentation pattern and elemental analyses. The keto-amine IVl was similarly obtained from IIIl and similarly characterised.

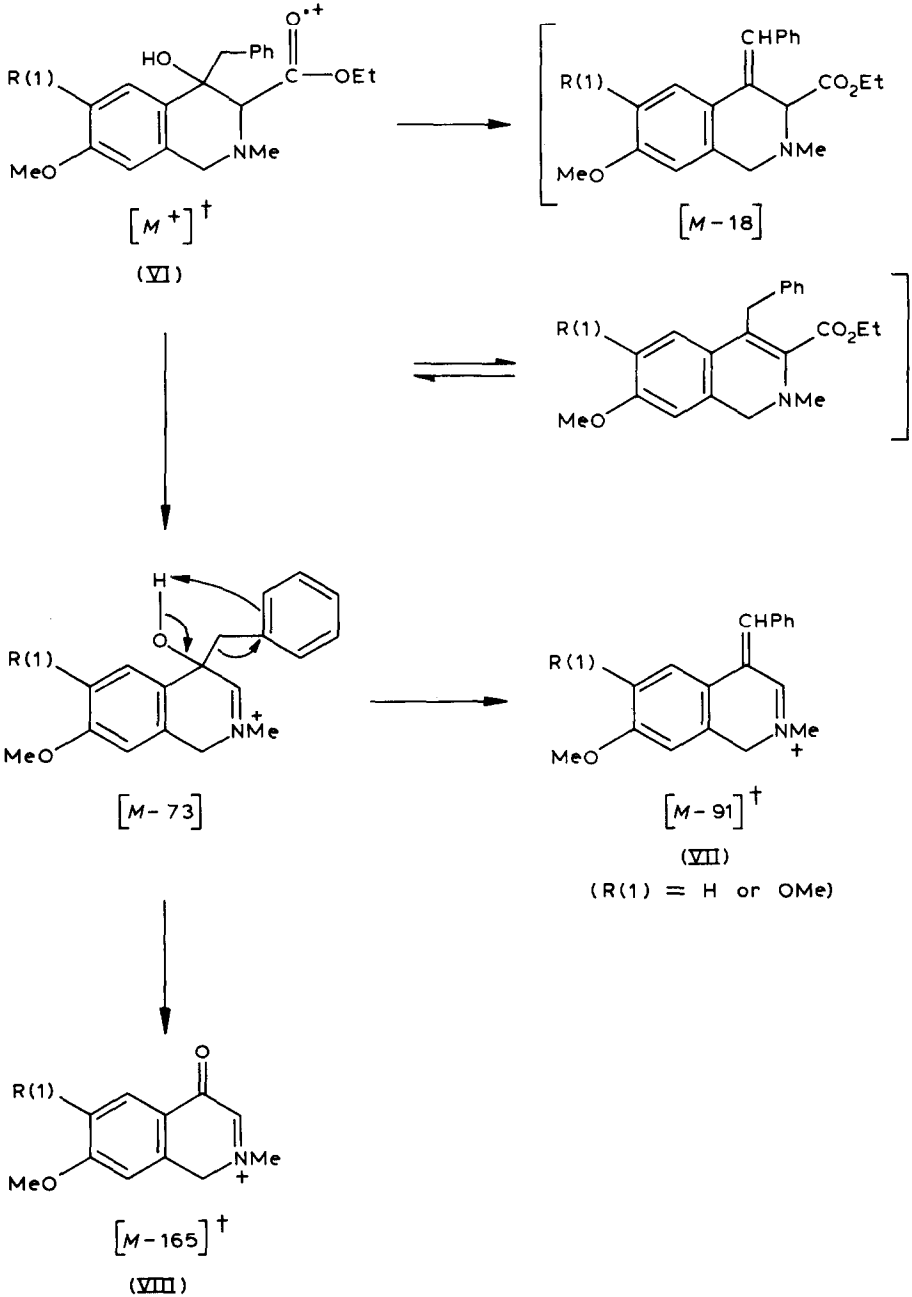
The scope of this regiospecific *ortho* acylation reaction was tested by successfully reacting the cyclopalladated complexes IIa and IIb with phenylacetyl, cinnamoyl, 3-phenylpropionoyl, 2-methylphenylacetyl and diphenylacetyl chlorides. In all cases the intermediate complex of the type III was too insoluble for full characterisation, but reaction with aqueous KCN gave good overall yields of the ketoamines of the type IV, which were fully characterised (see tables). Neither triphenylacetyl nor pivoyl chlorides reacted with IIa or IIb. Investigations are proceeding to determine whether these sterically hindered acyl chlorides fail to undergo oxidative addition to the palladium or whether it is the "insertion" that fails. Whereas cinnamoyl chloride reacted satisfactorily with IIa and IIb to give ultimately the *trans* *o*-acylbenzylamines, acrylyl chloride and crotonyl chloride did not. Further investigations are proceeding to determine the nature of these products.

The successful reactions described above seem to be in contrast to those described by Holton and Natalie [13], who did not observe the intermediate palladium complexes of type III.



SCHEME 2

Treatment of the *o*-phenacetylbenzylamine IVl with NaOEt/EtOH for 24 h at room temperature, followed by GLC analysis of the mixture formed showed that about 45% of IVl had cyclised to Vb. The only other main component present was IVl itself, together with a few, unidentified minor components of lower molecular



SCHEME 3

TABLE 6

HIGH RESOLUTION MASS MEASUREMENTS ON IONS IN SCHEME 3

Compound	Molecular formula	Found (calcd.)
VI R = H	$C_{21}H_{25}NO_4$	355.1802 (355.1783)
VII R = H	$C_{18}H_{18}NO$	264.1381 (264.1388)
VIII R = H	$C_{11}H_{12}NO_2$	190.0857 (190.0868)
VI R = OMe	$C_{22}H_{27}NO_5$	385.1895 (385.1889)
VII R = OMe	$C_{19}H_{20}NO_2$	294.1515 (294.1494)
VIII R = OMe	$C_{12}H_{14}NO_3$	220.0963 (220.0973)

weight. Column chromatography of the original reaction mixture over silica led to the isolation of IVl in 30% yield as a yellow oil, which could not be crystallised. From elemental analysis, high resolution mass spectral measurements and other spectral evidence the structure was assigned as that of ethyl 2-methyl-6,7-dimethoxy-4-benzyl-4-hydroxy-1,2,3,4,-tetrahydroisoquinoline-3-carboxylate (IVl) [17]. Similar treatment of the glycine ester IVk with base led to the isolation of Va as an almost equimolar mixture of geometric isomers. The mass spectral fragmentation patterns of Va and Vb showed distinctive features when compared with those of the parent compounds IVk and IVl respectively. The *o*-phenacetylbenzylamines IVk and IVl fragment by predominately α-cleavage (Scheme 2) leading to a base peak of $M - 116$. By contrast, the cyclised compounds Va and Vb exhibited weaker molecular ions, small $M - 18$ peaks and a base peak at $M - 165$. The fragmentation patterns of these tetrahydroisoquinolines (Scheme 3) are supported by high resolution mass measurements on those ions indicated (†) in the scheme (see Table 6).

The equilibrium mixtures of IVk/Va and IVl/Vb which are obtained from these attempted base-catalysed cyclisation reactions are presumably due to two main factors. Firstly the C–H bond α to the ketone carbonyl of IVk and IVl may be expected to undergo de-protonation instead of the required C–H bond α to the ester function; this would give rise to a conjugated enolate anion which cannot undergo cyclisation, and secondly, the products of cyclisation, IVl and Vb seemingly are resistant to the dehydration reaction which would drive the reaction to completion.

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17 We are indebted to Dr J.P. Bartley of this department for elucidating the fragmentation pathways in the mass spectra of the compounds described here.