PERKIN 1

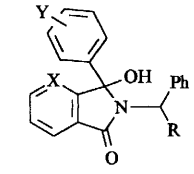
Formation of spiro indane derivatives from hydroxy lactams derived from *N*-(1-phenylethyl)-phthalimide and -pyridine-2,3-dicarboximide

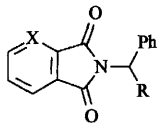
Abood A. Bahajaj and John M. Vernon*

Department of Chemistry, University of York, Heslington, York YO1 5DD, UK

Spiro[indane-1,7′-pyrrolo[3,4-*b*]pyridin]-5′-ones 18–22 are formed by acid-catalysed rearrangement from 7-aryl-7-hydroxy-6-(1-phenylethyl)-6,7-dihydropyrrolo[3,4-*b*]pyridin-5-ones. Further spiro indanes 39, 43 and 44 and spiro naphthalenes 41, 42, 45 and 46 are obtained from 3-(ω-phenylalkyl)-3-hydroxy-2-(1-phenylethyl)isoindolin-1-ones or from 7-(ω-phenylalkyl)-7-hydroxy-6-(1-phenylethyl)-6,7-dihydropyrrolo[3,4-*b*]pyridin-5-ones *via* α,α-cyclisation of *N*-acyliminium ion intermediates.

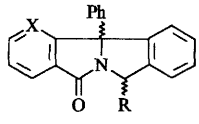
N-Benzyl hydroxy lactams **1** and **2** on heating in polyphosphoric acid (PPA) undergo cyclisation *via* *N*-acyliminium ion intermediates to give the fused tetracyclic products **15** and **16**, respectively.[1,2] However, lactam **3** containing the *N*-(1-phenylethyl) group reacts quite differently, rearranging to a 3:1 mixture of spiro lactams **18a,b** instead of the expected product(s) **17**.[3] This surprising result prompted us to study the behaviour of a series of compounds related to **1–3**, from which we have obtained a variety of products. We describe herein the formation of further spiro compounds related to **18** and in a subsequent paper fused-heterocyclic products related to **17**.



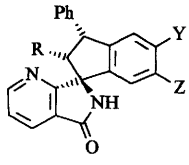


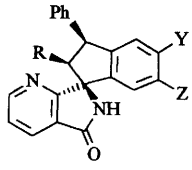
1 X = N, Y = R = H
2 X = CH, Y = R = H
3 X = N, Y = H, R = Me
4 X = N, Y = H, R = $CH_{(3-n)}D_n$
5 X = N, Y = H, R = Et
6 X = CH, Y = *p*-OMe, R = Me
7 X = N, Y = *p*-OMe, R = Me
8 X = N, Y = *m*-OMe, R = Me

9 X = N, R = H
10 X = CH, R = H
11 X = N, R = Me
12 X = N, R = $CH_{(3-n)}D_n$
13 X = N, R = Et
14 X = CH, R = Me



15 X = N, R = H
16 X = CH, R = H
17 X = N, R = Me





a **18** R = Y = Z = H **b**
19 R = D, Y = Z = H
20 R = Me, Y = Z = H
21 R = Z = H, Y = OMe
22 R = Y = H, Z = OMe

Results and discussion

Amines required for the synthesis of pyridine-2,3-dicarboximides **12** and **13** were made *via* Leuckart reactions from the appropriate aromatic ketones. In this way, the deuteriated imide **12** was obtained starting from [$^2H_3$]acetophenone, but most of the deuterium was lost, probably on account of tautomerism of the imine intermediate in the Leuckart reaction,

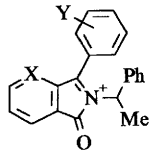
$$PhC(=NH)CD_3 \rightleftharpoons PhC(NH_2)=CD_2$$

so that **12** was found by mass spectrometry to contain only 31%[$^2H_2$] and 6%[^2H].

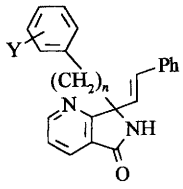
Grignard addition to imides **11–14** then afforded the hydroxy lactams **2–8**, all of which were obtained as mixtures of diastereoisomers (from ^{13}C NMR spectra). Separation of diastereoisomers was unnecessary, as the stereogenic centre bearing the OH group becomes planar in forming an *N*-acyliminium ion intermediate in the next step. As noted previously,[2,3] Grignard addition to pyridine-2,3-dicarboximides occurs predominantly or exclusively at the more reactive C-7 carbonyl group, so that the new hydroxy lactams obtained from imides **11–13** were the regioisomers **4**, **5**, **7** and **8**. The low-field position of the ^{13}C NMR signal for C-7a (δ_C 165) of these hydroxy lactams confirms the structural assignments.[2]

Hydroxy lactam **3** heated in PPA at 100–125 °C rearranges *via* the *N*-acyliminium ion (X = N, Y = H) **23** to the styrene derivative **24** (Y = H), which then undergoes cyclisation to a 3:1 mixture of diastereoisomeric spiro lactams **18a,b**.[3] If **3** is heated in trifluoroacetic acid (TFA), the intermediate **24** (Y = H) is isolable. From the partly deuteriated hydroxy lactam **4** in PPA the corresponding spiro lactam products were obtained in 61% overall yield and 72.5:27.5 ratio. They were separated chromatographically and both found to contain 13%[^2H] (by mass spectrometry). The expected value is 14%, if **4** contains the same distribution of deuterium as the imide **12** from which it is derived and if the spiro compounds **19a,b** are formed *via* the intermediate **24** (Y = H). ^2H NMR spectra of each of the spiro products showed two lines of equal intensity, because each of **19a,b** is accompanied by an equal amount of its C-2 epimer (at the deuteriated position).

From the hydroxy lactam **5** after heating in PPA, two diastereoisomeric spiro lactams were obtained in 59% overall yield and 3:1 ratio. The major product, which is also the more polar of the two, must have the same relative configuration at the spiro carbon centre and the indane 3-position as already established for **18a** by X-ray crystallography.[3] The coupling constant between vicinal hydrogens in the 5-membered ring (J 10.3 Hz) shows a *cis* relationship and established the stereochemistry of **20a**. However, the minor product obtained from **5** shows almost the same value for the coupling constant between the corresponding ring hydrogens (J 10.8 Hz).



23



24 $n = 0$
25 $n = 1$

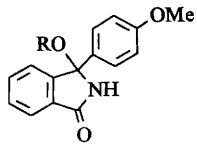
Therefore, the relative configuration at C-2 and C-3 is the same, but the spiro carbon has the opposite (relative) stereochemistry, and the structure is **20b**. Our earlier results[3] with ^{13}C-labelled **3** and **18a,b** are entirely consistent with structures **19a,b** and **20a,b** assigned to these new spiro products.

The *p*-methoxy group incorporated in the hydroxy lactams **6** and **7** was expected to stabilise the corresponding *N*-acyliminium ion intermediates **23** but not necessarily to alter the preference for rearrangement *via* a styrene derivative **24** (Y = *p*-OMe) rather than cyclisation to fused structures analogous to **16** or **17**. In fact, the only products obtained after heating **6** in PPA were 2-*p*-anisoylbenzamide (or its cyclic tautomer **26**) and the ethoxy lactam **27**, neither of which is the result of *N*-acyliminium ion cyclisation. (Formation of **27** is accounted for if **26** in the crude product reacts with the ethyl acetate used for chromatography, catalysed by traces of phosphoric acid remaining in the sample.) However, heating **7** in PPA afforded the spiro lactams **21a,b** in 26% yield, but incompletely separable. On the other hand, the *m*-methoxy group incorporated in the hydroxy lactam **8** was expected to activate the aryl ring position for spiro cyclisation of the intermediate **24** (Y = *m*-OMe). Accordingly, the spiro lactams **22a,b** were obtained from **8** in PPA at 100–110 °C in 53% overall yield, but they too were incompletely separable.

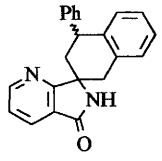
A further series of hydroxy lactams **29**–**33** was prepared in the same way as **3**–**8** by appropriate Grignard additions to imides **11** or **14**. Again, the formation of diastereoisomeric products was recognised from ^{13}C NMR signals for $CHCH_3$ of the 1-phenylethyl group, but mixtures of diastereoisomers were not separated. Compound **29** is a homologue of **3**, and if the same rearrangement involving the 1-phenylethyl group were to occur with **29**, the resulting structure **25** (Y = H) would present the opportunity for acid-catalysed cyclisation to the spiro naphthalene **28**. However, the only result of heating **29** in PPA was debenzylation and dehydration to give the benzylidene derivatives **34** in 32% overall yield and 73:28 ratio of *Z* and *E* stereoisomers. The stereochemistry was assigned by comparing the chemical shift of the ^{1}H NMR absorption for the lone alkene hydrogen, which was at lower field (δ_H 7.09) in the major stereoisomer (δ_H 6.66 in the minor stereoisomer) due to deshielding by the pyridine ring. These assignments from ^{1}H NMR spectroscopic evidence are the same as those made for the corresponding stereoisomers of **37**, for which the chemical shift values for the *exo* alkene hydrogen are δ_H 6.96 and 6.65 [but (*E*)-**37** corresponds to (*Z*)-**34** and *vice versa*].[4] The *Z* configuration of **34** is clearly less crowded in respect of the phenyl group. Analogous dehydration of hydroxy lactams has been noted previously, for example the formation of the enamide **35**.[2,5]

The series of hydroxy lactams **30**–**33** offered a different possibility for spiro cyclisation of an *N*-acyliminium ion intermediate **38** without requiring rearrangement of the 1-phenylethyl group. The latter might be expected to direct a diastereoselective spiro cyclisation, as has been achieved with intermolecular alkylation of *N*-acyliminium ions.[6]

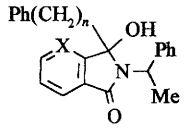
From the hydroxy lactam **30** the desired spiro cyclisation was achieved in refluxing TFA to give a 62% yield of **43**, accompanied by 10% of the debenzylated product **39**. From **32** in refluxing TFA the extent of debenzylation was greater, and



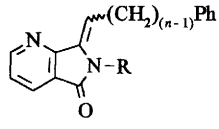
26 R = H
27 R = Et



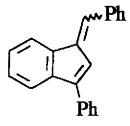
28



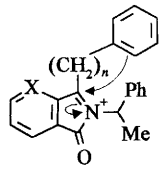
3 X = N, $n = 0$
29 X = N, $n = 1$
30 X = CH, $n = 2$
31 X = N, $n = 2$
32 X = CH, $n = 3$
33 X = N, $n = 3$



34 $n = 1$, R = H
35 $n = 1$, R = *o*-C_6H_4Ph
36 $n = 2$, R = H



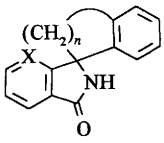
37



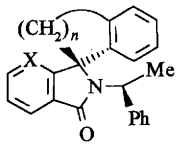
38

the products were the spiro lactams **41** (51%) and **45** (34%). Other hydroxy lactams **31** and **33** containing the fused pyridine ring required heating in PPA to effect reaction, and debenzylation was the predominant outcome. The products obtained from **31** were the enamide **36** (43%) (presumably the *Z* stereoisomer) and the spiro lactam **44** (9%), but none of **40** was detected; whereas **33** afforded the spiro lactams **46** (3.5%) and **42** (73%), with and without the *N*-(1-phenylethyl) group, respectively. The more forcing acidic conditions required for reaction of **31** and **33** in comparison with **30** and **32** may be attributable to the pyridine nitrogen atom: protonation at this site may make formation of the *N*-acyliminium ion intermediate **38** more difficult. The *N*-(1-phenylethyl) group is more easily lost under acidic conditions than *N*-benzyl or other *N*-substituents.[7]

^{1}H and ^{13}C NMR spectra showed the presence of two diastereoisomers for each of the spiro lactams **43**–**46**, in particular the signals for $CHCH_3$ of the 1-phenylethyl group, which indicated diastereoisomeric ratios between 68:32 for **43** and 80:20 for **45**. These mixtures were chromatographed unchanged. Moreover, it appears that the relative stereochemistry for the preferred course of 5-membered ring closure in **43** and **44** is opposite to that of the 6-membered ring closure in **45** and **46**. This conclusion is based on comparisons of ^{1}H NMR chemical shift values, for example in **43** the CH_3 resonance for the major diastereoisomer is at higher field but in **45** it is at lower field than that for the corresponding minor diastereoisomer. It also accords with our findings in respect of spiro cyclisations of the chiral bicyclic oxazolidines **47** and **48**, where the spiro indane **49** is formed from **47** preferentially with *R* configuration at the spiro stereogenic carbon centre, whereas the spiro naphthalene **50** is formed from **48** preferentially with the *S* configuration.[8] Therefore, we can infer the relative

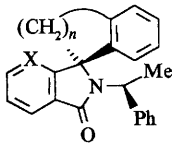


39 X = CH, *n* = 2
40 X = N, *n* = 2
41 X = CH, *n* = 3
42 X = N, *n* = 3

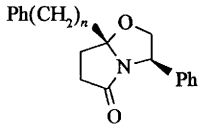


a

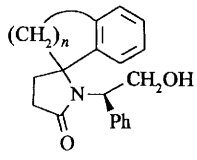
43 X = CH, *n* = 2
44 X = N, *n* = 2
45 X = CH, *n* = 3
46 X = N, *n* = 3



b



47 *n* = 2
48 *n* = 3



49 *n* = 2
50 *n* = 3

stereochemistry **a** for the major isomer of **43** and **44**, and **b** for the major isomer of **45** and **46**, although this has not been confirmed.

The stereoselectivity of spiro cyclisation is a matter of further work, but already it is clear that α,α-cyclisations[9] of *N*-acyliminium ion intermediates involving an aromatic ring as π-nucleophile provide a general approach to spiro structures.

Experimental

IR Spectra were recorded for Nujol mulls or for solutions in chloroform (Pye-Unicam SP3-200 or Perkin-Elmer 1420 spectrophotometers) and calibrated with polystyrene. ^{1}H NMR Spectra were recorded at 90 (JEOL-JNM-FX90Q) or 270 MHz (JEOL-JNM-FX270) and ^{13}C NMR spectra at 22.5 or 67.5 MHz (on the same instruments) for solutions in deuteriochloroform, unless stated otherwise, and with tetramethylsilane as internal standard. *J* Values are given in Hz. In NMR spectra of diastereoisomer mixtures, resonances attributed to the minor diastereoisomer are shown in brackets {}. Mass spectra were obtained by electron impact (EI) at 70 eV (VG Autospec). Chromatography was performed on MN-silica gel 60. Tetrahydrofuran (THF) was dried before use. Light petroleum refers to the fraction bp 40–60 °C.

Preparation of amines and imides

Deuteriated 1-phenylethylamine was obtained from [2,2,2-^{2}H$_3$]acetophenone (2.0 g) in a Leuckart reaction[10] with ammonium formate (4.0 g) and treated with pyridine-2,3-dicarboxylic anhydride, as described previously for imides **9**[2] and **11**,[3] to give the *N*-(1-phenylethyl)pyridine-2,3-dicarboximide **12** containing 31% [^{2}H$_2$] and 6% [^{2}H$_1$]. By the same procedures, 1-phenylpropylamine[11] was prepared from propiophenone and then converted into the *N*-(1-*phenylpropyl*)*pyridine*-2,3-*dicarboximide* **13** (59%), mp 111–113 °C (from ethanol) (Found: M$^+$, 266.1062. Calc. for $C_{16}H_{14}N_2O_2$: *M*, 266.1061); ν_{max}/cm^{-1} ($CHCl_3$) 1730 (CO); δ_H 0.97 (3 H, t, *J* 7.4, Me), 2.10–2.86 (2 H, m, CH_2), 5.29 (1 H, dd, *J* 7.7 and 9.2, CH), 7.24–7.64 (6 H, m, ArH), 8.10 (1 H, dd, *J* 1.5 and 7.7, 4-H) and 8.91 (1 H, dd, *J* 1.5 and 5.0, 2-H); δ_C 11.3 (Me), 24.0 (CH_2), 56.8 (CH), 127–131 (6 lines), 139.0, 151.0, 155.0, 165.9 and 166.1; *m*/*z* 266 (M$^+$, 44%), 237 (100), 209 (13), 118 (21) and 78 (23).

Phthalic anhydride (14.8 g) was heated with (±)-1-phenylethylamine (12.1 g) at 140 °C for 4 h. After cooling, a glassy material was obtained, which was dissolved in chloroform and shaken successively with dilute sulfuric acid, saturated aq. $NaHCO_3$ and water. After drying ($MgSO_4$), the mixture was evaporated and the residue recrystallised to give N-(1-*phenylethyl*)*phthalimide* (16.6 g, 66%), mp 51–52 °C (from toluene–light petroleum) (Found: M$^+$, 251.0946. *Calc. for* $C_{16}H_{13}NO_2$: *M*, 251.0946); ν_{max}/cm^{-1} 1780 and 1720 (CO); δ_H 1.93 (3 H, d, *J* 7.3, Me), 5.56 (1 H, q, *J* 7.3, CH) and 7.24–7.81 (9 H, m, ArH); δ_C 17.5 (Me), 49.6 (CH), 123–134 (6 lines), 140.3 and 168.2; *m*/*z* 251 (M$^+$, 100%), 236 (94), 208 (27), 130 (53), 104 (73) and 77 (63).

General procedure for preparation of hydroxy lactams

The imide (typically 1.0–1.5 g) was dissolved in THF (20–25 cm^3) and added rapidly to a stirred, ice-cold solution of the Grignard reagent (typically 3–4 equiv. to imide) freshly prepared from the appropriate aryl or phenylalkyl bromide and magnesium in THF (20–25 cm^3). After stirring at 0 °C for 3–4 h, the mixture was poured into saturated aq. NH_4Cl (150–200 cm^3), if necessary further acidified with a few drops of dilute sulfuric acid and extracted with chloroform (3 × 20 cm^3). The organic extracts were washed with water, dried ($MgSO_4$) and evaporated to dryness. The following products were isolated as mixtures of diastereoisomers after chromatography, eluting with mixtures of ethyl acetate–chloroform.

From imide **12** and phenylmagnesium bromide, the deuteriated hydroxy lactam **4** (75%), spectra as for **3**.[2]

From imide **13** and phenylmagnesium bromide, 7-*hydroxy*-7-*phenyl*-6-(1-*phenylpropyl*)-6,7-*dihydropyrrolo*[3,4-b]*pyridin*-5-*one* **5** (62%), mp 157–159 °C (from toluene–light petroleum) (Found: M$^+$, 344.1523. Calc. for $C_{22}H_{20}N_2O_3$: *M*, 344.1525); ν_{max}/cm^{-1} 3260 br (OH) and 1660 (CO); δ_H 0.55 {and 0.85} (3 H, t, *J* 7.5, Me), 1.80–2.60 (2 H, m, CH_2), 4.08–4.38 (1 H, m, CH), 4.90 {and 5.75} (1 H, s, OH) and 7.04–8.30 (13 H, m, ArH); δ_C 11.9 (Me), {25.8 and} 26.4 (CH_2), 59.9 (CH), 91.5 {and 92.3} (C), 124–129 (13 lines), 131.9 {and 132.0} (CH), 136.9 {and 137.5} (C), 141.0 {and 141.7} (C), 152.4 {and 152.7} (CH), {165.3 and} 165.5 (C) and 166.2 (C); *m*/*z* 344 (M$^+$, 0.3%), 210 (100), 182 (11), 154 (27), 134 (43) and 77 (33).

From imide **14** and *p*-anisylmagnesium bromide, 3-*hydroxy*-3-(p-*methoxyphenyl*)-2-(1-*phenylethyl*)*isoindolin*-1-*one* **6** (94%), mp 147–148 °C (from toluene–light petroleum) (Found: C, 77.1; H, 6.05; N, 3.9. $C_{23}H_{21}NO_3$ requires C, 76.9; H, 5.9; N, 3.9%); ν_{max}/cm^{-1} ($CHCl_3$) 3220w br (OH) and 1685 (CO); δ_H 1.86 (3 H, two overlapping d, *J* 7.2, Me), 3.08 {and 3.41} (3 H, s, OMe), 4.50 {and 4.73} (1 H, q, *J* 7.2, CH) and 6.64–7.78 (13 H, m, ArH); δ_C {19.7 and} 21.3 (Me), 49.5 (CH), {55.3 and} 55.5 (Me), 92.0 (C), 113–143 (12 lines), 148.8, 159.8 and 167.8; *m*/*z* 359 (M$^+$, 1%), 240 (25), 120 (100), 105 (13) and 77 (16).

From imide **11** and *p*-anisylmagnesium bromide, 7-*hydroxy*-7-(p-*methoxyphenyl*)-6-(1-*phenylethyl*)-6,7-*dihydropyrrolo*[3,4-b]*pyridin*-5-*one* **7** (90%), mp 161–163 °C (from toluene–light petroleum) (Found: C, 73.3; H, 5.7; N, 7.7. $C_{22}H_{20}N_2O_3$ requires C, 73.3; H, 5.6; N, 7.8%); ν_{max}/cm^{-1} ($CHCl_3$) 3200w (OH) and 1695 (CO); δ_H 1.42 {and 1.79} (3 H, d, *J* 7.1, Me), 3.76 {and 3.88} (3 H, s, OMe), 4.75 {and 5.15} (1 H, q, *J* 7.1, CH) and 6.66–8.67 (13 H, m, ArH and OH); δ_C 19.4 {and 21.5} (Me), 49.6 {and 52.4} (CH), 55.1 (OMe), 91.5 (C), 113–142 (14 lines), 149.6, 152.7, 160.1, 164.6, 165.5 and 166.6; *m*/*z* 360 (M$^+$, 2%), 344 (2), 241 (40), 135 (49), 120 (100) and 77 (19).

From imide **11** and *m*-anisylmagnesium bromide, 7-*hydroxy*-7-(m-*methoxyphenyl*)-6-(1-*phenylethyl*)-6,7-*dihydropyrrolo*[3,4-b]*pyridin*-5-*one* **8** (98%), mp 158–160 °C (from toluene–light

petroleum) (Found: M^+, 360.1471. Calc. for $C_{22}H_{20}N_2O_3$: *M*, 360.1474); ν_{max}/cm^{-1} ($CHCl_3$) 3300 br (OH) and 1700 (CO); δ_H($CDCl_3$–CD_3OD) 1.66 {and 1.85} (3 H, d, *J* 7.2, Me), {3.69 and} 3.79 (3 H, s, OMe), 4.62 (1 H, q, *J* 7.3, CH), 6.73–7.54 (10 H, m, ArH), 8.06 (1 H, dd, *J* 7.7 and 1.8, 4-H) and 8.51 (1 H, dd, *J* 4.9 and 1.7, 2-H); δ_C 18.2 {and 19.7} (Me), 52.4 {and 52.9} (CH), {55.2 and} 55.4 (OMe), 92.0 (C), 112–142 (22 lines), *152.9*, {159.5 and} 159.9, 165.9, 166.2 and 166.6; *m*/*z* 360 (M^+, 3%), 342 (1), 255 (2), 241 (41), 120 (93), 84 (79) and 49 (100).

From imide **11** and benzylmagnesium bromide, 7-*benzyl*-7-*hydroxy*-6-(1-*phenylethyl*)-6,7-*dihydropyrrolo*[3,4-b]*pyridin*-5-*one* **29** (62%), mp 172–174 °C (from ethanol) (Found: MH^+, 345.1595. Calc. for $C_{22}H_{21}N_2O_2$: *M* + H, 345.1603); δ_H 1.93 (3 H, d, *J* 7.3, Me), 3.29 and 3.55 (2 H, 2d, *J* 13.8, CH_2) {and 3.42 and 3.70 (2 H, 2d, *J* 14.2, CH_2)}, 4.92 (1 H, q, *J* 7.3, C*H*Me) overlapping 4.88 br (1 H, s, OH) {and 5.09 (1 H, q, *J* 7.3, CHMe) and 5.63 br (1 H, s, OH)}, 6.20 (1 H, dd, *J* 8.5 and 1.5), 6.72–7.39 (8 H, m, aryl H), 7.63–7.76 (3 H, m, aryl H) and 8.23 (1 H, dd, *J* 5.0 and 1.5, 2-H); δ_C 19.6 {and 21.3} (Me), {42.6 and} 42.8 (CH_2), 52.6 {and 53.2} (CH), {91.9 and} 92.2 (C-7), 124.3–134.1 (19 lines), 143.0 {and 143.1}, {151.3 and} 151.7, 164.5 {and 164.6} and 165.2 {and 165.6} (CO); *m*/*z* (M − CH_2Ph, 55%), 149 (66), 105 (100), 91 (27), 77 (19) and 65 (10); CI-MS *m*/*z* 362 (MNH_4^+, 8%) and 345 (MH^+, 100).

From imide **10** and 2-phenylethylmagnesium bromide, 3-*hydroxy*-2-(1-*phenylethyl*)-3-(2-*phenylethyl*)*isoindolin*-1-*one* **30** (100%), mp 179–181 °C (from toluene–light petroleum) (Found: M^+, 357.1727. Calc. for $C_{24}H_{23}NO_2$: *M*, 357.1715); δ_H 1.54–1.77 (2 H, m, CH_2), 1.92 (3 H, d, *J* 7.3, Me), 2.23–2.35 (2 H, m, CH_2), 3.18 (1 H, s, OH), 4.85 (1 H, q, *J* 7.3, CH), 6.44 (2 H, m, *o*-ArH) and 7.03–7.78 (12 H, m, ArH); δ_C 21.7 (Me), 30.0 (CH_2), 38.4 (CH_2), 52.7 (CH), 92.1 (C), 121–133 (6 lines), 140.5, 143.6, 145.8 and 167.7; *m*/*z* 357 (M^+, 4%), 339 (25), 248 (46), 235 (43), 148 (48), 120 (30), 105 (100), 91 (38) and 77 (19).

From imide **11** and 2-phenylethylmagnesium bromide, 7-*hydroxy*-6-(1-*phenylethyl*)-7-(2-*phenylethyl*)-6,7-*dihydropyrrolo*[3,4-b]*pyridin*-5-*one* **31** (73%), two diastereoisomers partially separated by chromatography and the front-running component characterised, mp 129–132 °C (from toluene–light petroleum) (Found: M^+, 358.1679. Calc. for $C_{23}H_{22}N_2O_2$: *M*, 358.1681); δ_H 1.98 (3 H, d, *J* 7.3, Me), 2.18–2.77 (4 H, m, $2CH_2$), 5.02 (1 H, q, *J* 7.3, CH), 5.24 (1 H, br s, OH), 6.91–7.73 (11 H, m, ArH), 7.89 (1 H, dd, *J* 1.5 and 7.7, 4-H) and 8.24 (1 H, dd, *J* 1.5 and 5.0, H-2); δ_C 18.4 (Me), 30.1 (CH_2), 37.9 (CH_2), 51.2 (CH), 91.6 (C), 124–142 (10 lines), 152.1, 164.7 and 165.0; *m*/*z* 358 (M^+, 3%), 340 (2), 254 (44), 149 (100), 120 (28), 105 (90), 99 (59) and 77 (44).

From imide **10** and 3-phenylpropylmagnesium bromide, 3-*hydroxy*-2-(1-*phenylethyl*)-3-(3-*phenylpropyl*)*isoindolin*-1-*one* **32** (96%), mp 153–155 °C (from toluene–light petroleum) (Found: M^+, 371.1870. Calc. for $C_{25}H_{25}NO_2$: *M*, 371.1885); δ_H(270 MHz) 0.66 (2 H, m, CH_2), 1.85 (3 H, d, *J* 7.1, Me), 1.94–2.09 (4 H, m, $2CH_2$), 3.65 (1 H, s, OH), 4.79 (1 H, q, *J* 7.3, CH), 6.68 (2 H, m, *o*-ArH) and 6.99–7.65 (12 H, m, ArH); δ_C 21.4 (Me), 25.6 (CH_2), 35.2 (CH_2), 36.2 (CH_2), 52.5 (CH), 92.3 (C), 121–132 (9 lines), 141.5, 143.7, 146.0 and 167.6; *m*/*z* 371 (M^+, 1%), 353 (2), 262 (27), 158 (57), 148 (38), 120 (30), 105 (100), 91 (25) and 77 (22).

From imide **11** and 3-phenylpropylmagnesium bromide, 7-*hydroxy*-6-(1-*phenylethyl*)-7-(3-*phenylpropyl*)-6,7-*dihydropyrrolo*[3,4-b]*pyridin*-5-*one* **33** (57%), mp 165–168 °C (from toluene–light petroleum) (Found: M^+, 372.1847. Calc. for $C_{24}H_{24}N_2O_2$: *M*, 372.1838); δ_H(270 MHz) {0.51, 0.71 (each 1 H, m) and} 0.87, 1.26 (each 1 H, m), 1.86 {and 1.93} (3 H, d, *J* 7.3, Me), 1.97–2.11 (2 H, m, CH_2), 2.31–2.45 (2 H, m, CH_2), {4.86 and} 4.96 (1 H, q, *J* 7.0, CH) overlapping 4.96 {and 5.26} (1 H, s, OH), 6.66 (1 H, dd, *J* 1.5 and 7.8, *o*-ArH), 6.99–7.68 (10 H, m, ArH), 7.88 {and 7.94} (1 H, dd, *J* 1.5 and 7.8, 4-H) and 8.35 {and 8.40} (1 H, dd, *J* 1.4 and 5.0, 2-H); δ_C 18.1 {and 21.4} (CH_3), 25.7 (CH_2), 35.2 {and 35.4} (CH_2), 35.7 (CH_2), 50.9 {and 53.0} (CH), 91.9 (C), 124–132 (6 lines), {141.4 and} 141.5, 143.3, 152.1, {164.5 and} 164.7, and 164.9 {and 165.7}; *m*/*z* 372 (M^+, 1%), 354 (6), 316 (8), 267 (21), 253 (26), 225 (25), 163 (13), 149 (56), 120 (54), 105 (100) and 91 (30).

General procedure for reactions in polyphosphoric acid (PPA): isolation and characterisation of spiro products

The hydroxy lactam was dissolved in polyphosphoric acid and heated, usually for 1 h at 100–110 °C. The hot mixture was poured onto crushed ice and extracted with chloroform (3 × 20 cm^3); the chloroform extracts were washed with aq. $NaHCO_3$ and water, dried ($MgSO_4$) and evaporated to dryness. Products were separated by chromatography, usually eluting with ethyl acetate–chloroform (1 : 4 v/v). The following spiro lactams and other products were obtained, in order of elution.

From hydroxy lactam **4** (0.43 g) and PPA (35 g) after heating for 1 h at 120–130 °C, the 3-phenylspiro[[2-^{2}H]indane-1,7′(6′*H*)-pyrrolo[3,4-*b*]pyridin]-5′-one diastereoisomers **19b** (71 mg, 17%) and **19a** (167 mg, 41%), both containing 13% [^{2}H], from comparison of mass spectra with those of **18a**,**b**.[2] ^{2}H NMR spectra (Bruker MSL300) showed 2 lines of equal intensity, δ_D 2.7 and 3.1 for **19a** and δ_D 2.6 and 3.1 for **19b**. Other spectra identical with those of **18a**,**b**.[2]

From hydroxy lactam **5** (0.44 g) and PPA (39 g) after 1 h at 120–130 °C, the 2-*methyl*-3-*phenylspiro*[*indane*-1,7′(6′H)-*pyrrolo*[3,4-b]*pyridin*]-5′-*one* diastereoisomers **20b** (92 mg, 22%), mp 229–231 °C (from toluene–light petroleum) (Found: M^+, 326.1430. Calc. for $C_{22}H_{18}N_2O$: *M*, 326.1429); δ_H 0.76 (3 H, d, *J* 6.8, Me), 1.81 (1 H, s, NH), 2.84 (1 H, dq, *J* 6.8 and 10.5, 2-H), 4.63 (1 H, d, *J* 10.5, 3-H), 7.04–7.48 (10 H, m, ArH), 8.15 (1 H, dd, *J* 1.6 and 7.7, 4′-H) and 8.66 (1 H, dd, *J* 1.6 and 4.9, 2′-H); *m*/*z* 326 (M^+, 46%), 297 (100), 221 (32), 92 (35), 91 (56) and 42 (71); and **20a** (275 mg, 66%), mp 206–208 °C (from toluene–light petroleum) (Found: C, 81.1; H, 5.6; N, 8.5. $C_{22}H_{18}N_2O$ requires C, 81.0; H, 5.6; N, 8.6%); ν_{max}/cm^{-1} ($CHCl_3$) 3440 (NH) and 1705 (CO); δ_H 0.85 (3 H, d, *J* 6.8, Me), 3.25 (1 H, dq, *J* 6.9 and 10.3, 2-H), 4.22 (1 H, d, *J* 10.2, 3-H), 6.65–7.49 (9 H, m, ArH), 7.71 (1 H, s, NH), 8.18 (1 H, dd, *J* 1.8 and 7.7, 4′-H) and 8.79 (1 H, dd, *J* 1.7 and 4.8, 2′-H); δ_C 10.8 (Me), 52.7 (CH), 56.7 (CH), 74.5 (C), 123–132 (10 lines), 141.8, 142.1, 147.7, 153.4, 167.9 and 168.3; *m*/*z* 326 (M^+, 34%), 297 (10), 221 (34), 149 (36), 92 (73) and 91 (100).

From hydroxy lactam **6** (0.10 g) and PPA (18 g) after 1.5 h at 140–150 °C, the crude product gave a single spot on TLC and was recrystallised directly to give 3-hydroxy-3-(*p*-methoxyphenyl)isoindolin-1-one **26** (34 mg, 48%), mp 159–161 °C (decomp.); ν_{max}/cm^{-1} 3320 and 3250 (OH and NH), 1720 and 1665 (CO); δ_H 3.77 (3 H, s, OMe), 6.37 (1 H, br s, NH), 6.81–7.55 (8 H, m, ArH) and 7.75 (1 H, br s, OH); *m*/*z* 255 (M^+, 38%), 238 (92), 237 (100) and 195 (98). In another experiment on a larger scale, chromatography of the crude product also afforded 3-*ethoxy*-3-(p-*methoxyphenyl*)*isoindolin*-1-*one* **27** (7%), mp 112–114 °C (decomp.) (from toluene–light petroleum) (Found: M^+, 283.1182. Calc. for $C_{17}H_{17}NO_3$: *M*, 283.1184); ν_{max}/cm^{-1} ($CHCl_3$) 3330w (NH) and 1725 (CO); δ_H 1.18 (3 H, t, *J* 7.0, Me), 3.08 and 3.49 (each 1 H, dq, *J* 7.0 and 9.1, CH_2), 3.77 (3 H, s, OMe), 6.72 (1 H, br s, NH) and 6.80–7.92 (8 H, m, ArH); δ_C 15.3 (Me), 55.3 (CH_2), 58.5 (OMe), 91.7 (C), 118.8, 123–133 (8 lines), 147.6, 159.8 and 169.7; *m*/*z* 283 (M^+, 3%), 238 (100), 195 (12) and 130 (33).

From hydroxy lactam **7** (0.42 g) and PPA (34 g) after 1 h at 100–110 °C, the 5-*methoxy*-3-*phenylspiro*[*indane*-1,7′(6′H)-*pyrrolo*[3,4-b]*pyridin*]-5′-*one* diastereoisomers **21a**,**b** (105 mg, 26%), incompletely separable. **21b** From early fractions had δ_H 2.54 (1 H, dd, *J* 9.0 and 12.9, 2α-H), 3.08 (1 H, dd, *J* 7.7 and 13.2, 2β-H), 3.67 (3 H, s, OMe), 4.94 (1 H, t, *J* 8.2, 3-H), 6.55–

6.83 (2 H, m, 4- and 6-H), 7.10 (1 H, br s, NH), 7.25–7.43 (7 H, m, ArH), 8.12 (1 H, dd, *J* 1.5 and 7.7, 4′-H) and 8.67 (1 H, dd, *J* 1.5 and 4.9, 2′-H); δ_C 48.3 (CH_2), 48.8 (CH), 55.4 (OMe), 71.2 (C), 110.6, 114.4, 123–133 (10 lines), 143.6, 148.5, 153.5, 161.0, 168.1 and 170.4. Fractional crystallisation of material from later fractions gave **21a**, mp 111–113 °C (decomp.) (from toluene–light petroleum) (Found: C, 77.3; H, 5.6; N, 8.1%; M^+, 342.1370. $C_{22}H_{18}N_2O_2$ requires C, 77.2; H, 5.3; N, 8.2%; *M*, 342.1368); ν_{max}/cm^{-1} ($CHCl_3$) 3200w (NH) and 1705 (CO); *m/z* 342 (M^+, 44%), 241 (33), 134 (53) and 119 (100).

From hydroxy lactam **8** (0.42 g) and PPA (45 g) the 6-*methoxy*-3-*phenylspiro*[*indane*-1,7′(6′H)-*pyrrolo*[3,4-b]*pyridin*]-5′-*one* diastereoisomers **22a**,**b** (0.30 g, 53%), incompletely separable. Fractional crystallisation of material from later fractions gave **22a**, mp 210–215 °C (from toluene–light petroleum) (Found: M^+, 342.1368. Calc. for $C_{22}H_{18}N_2O_2$: *M*, 342.1368). Spectra of **22a**,**b** mixtures: ν_{max}/cm^{-1} ($CHCl_3$) 3440 (NH) and 1700 (CO); δ_H 2.76 (1 H, dd, *J* 7.7 and 13.9, 2α-H), 3.06 (1 H, dd, *J* 9.6 and 13.9, 2β-H), {2.95–3.60 (2 H, m, CH_2)}, 3.56 {and 3.65} (3 H, s, OMe), 4.74 (1 H, dd, *J* 7.7 and 9.6, 3-H), {4.82–5.05 (1 H, m, 3-H)}, 6.14–7.45 {and 6.47–7.40} (8 H, m, ArH), 7.89 (1 H, s, NH), 8.04–8.19 (1 H, m, 4′-H) and 8.55–8.79 (1 H, m, 2′-H); *m/z* 342 (M^+, 100%), 327 (18) and 251 (33).

From hydroxy lactam **29** (0.44 g) and PPA (34 g), the 7-*benzylidene*-6,7-*dihydropyrrolo*[3,4-b]*pyridin*-5-*one* diastereoisomers **34**. (*E*)-Isomer (25 mg, 9%), mp 195–196 °C (from toluene–light petroleum); ν_{max}/cm^{-1} ($CHCl_3$) 3410br (NH) and 1710 (CO); δ_H[$CDCl_3$–$(CD_3)_2SO$] 6.66 (1 H, s, PhC*H*), 7.32–7.50 (6 H, m, ArH), 8.11 (1 H, dd, *J* 1.6 and 7.8, 4-H), 8.81 (1 H, dd, *J* 1.6 and 4.9, 2-H) and 10.38 (1 H, br s, NH); (*Z*)-Isomer (65 mg, 23%), mp 202–203 °C (from toluene–light petroleum) (Found: M^+, 222.0778. Calc. for $C_{14}H_{10}N_2O$: *M*, 222.0793); ν_{max}/cm^{-1} ($CHCl_3$) 3440br (NH) and 1710 (CO); δ_H[$CDCl_3$–$(CD_3)_2SO$] 7.09 (1 H, s, PhC*H*), 7.23–7.63 (6 H, m, ArH), 8.17 (1 H, dd, *J* 1.4 and 7.7, 4-H), 8.79 (1 H, dd, *J* 1.4 and 5.0, 2-H) and 9.81 (1 H, br s, NH); δ_C 109.1 (CH), 122–135 (9 lines), 153.6, 156.8 and 167.5; *m/z* 222 (M^+, 45%) and 221 (100).

From hydroxy lactam **31** (0.52 g) and PPA (39 g) after 1 h at 110–125 °C, the *N*-(1-phenylethyl) spiro indane lactam **44** (44 mg, 9%), viscous oil; *m/z* 340 (M^+, 10%), 325 (29), 236 (100), 207 (54), 191 (23), 105 (29), 91 (36) and 77 (44), and (Z)-7-(2-*phenylethylidene*)-6,7-*dihydropyrrolo*[3,4-b]*pyridin*-5-*one* **36** (147 mg, 43%), mp 165–167 °C (from toluene–light petroleum) (Found: M^+, 236.0938. Calc. for $C_{15}H_{12}N_2O$: M, 236.0949); δ_H 3.80 (2 H, d, *J* 8.2, CH_2), 3.94 (1 H, s, NH), 6.36 (1 H, t, *J* 8.2, alkene CH), 7.31 (5 H, m, ArH), 7.42 (1 H, dd, *J* 5.0 and 7.7, 3-H), 8.15 (1 H, dd, *J* 1.5 and 7.7, 4-H) and 8.72 (1 H, dd, *J* 1.5 and 5.0, 2-H); δ_C[$CDCl_3$–$(CD_3)_2SO$] 33.4 (CH_2), 110.5 (CH), 123–134 (6 lines), 139.0, 153.3, 155.9 and 167.4; *m/z* 236 (M^+, 100%), 207 (52), 180 (9), 131 (9), 104 (17) and 77 (16).

From the hydroxy lactam **33** (0.30 g) and PPA (20 g) after 1 h at 110–125 °C, the *N*-(1-phenylethyl) spiro naphthalene lactam **46** (10 mg, 4%) (Found: M^+, 354.1729. Calc. for $C_{22}H_{22}N_2O$: *M*, 354.1732); NMR spectra of poor quality due to small amount, but assignment supported by δ_C 20.0 (Me), 21.6 (CH_2), 29.0 (CH_2), 35.4 (CH_2), 51.6 (CH), 63.6 (C) and other lines 123–169; *m/z* 354 (M^+, 100%), 339 (13), 325 (17), 313 (9), 249 (13), 221 (33), 207 (28), 105 (51), 91 (23) and 77 (45); and *spiro*[3,4-*dihydronaphthalene*-1-(2*H*),7′(6′H)-*pyrrolo*[3,4-b]*pyridin*]-5′-*one* **42** (150 mg, 73%), mp 197–199 °C (from toluene–light petroleum) (Found: M^+, 250.1087. Calc. for $C_{16}H_{14}N_2O$: *M*, 250.1106); δ_H 2.02–2.52 (4 H, m, 2 × CH_2), 2.90–3.12 (2 H, m, CH_2), 6.62 (1 H, d, *J* 7.0, 8-H), 6.87–7.27 (3 H, m, 5-, 6- and 7-H), 7.34 (1 H, dd, *J* 5.0 and 7.7, 3′-H), 7.83 (1 H, s, OH), 8.11 (1 H, dd, *J* 1.5 and 7.7, 4′-H) and 8.63 (1 H, dd, *J* 1.5 and 5.0, 2′-H); δ_C 20.1 (CH_2), 29.4 (CH_2), 35.3 (CH_2), 63.9 (C), 123–139 (9 lines), 153.1, 168.2 and 171.6; *m/z* 250 (M^+, 100%), 221 (95), 209 (14), 193 (21), 91 (17), 84 (20) and 49 (29).

Reactions in trifluoroacetic acid (TFA): isolation and characterisation of spiro lactam products

Hydroxy lactam **30** (0.76 g) was dissolved in TFA (25 cm^3) and heated under reflux for 60 h until the reaction was complete (analysis by TLC). After cooling, the solution was poured portionwise into saturated aq. $NaHCO_3$ and the mixture extracted with chloroform. The extract was dried ($MgSO_4$) and evaporated and the residue chromatographed, eluting with ethyl acetate–chloroform (1:4 v/v) to obtain the 2′-(1-*phenylethyl*)*spiro*[*indane*-1,1′-*isoindol*]-3′-*one* diastereoisomers **43a**,**b** (0.447 g, 62%, 68:32 ratio), mp 200–203 °C (from toluene–light petroleum) (Found: M^+, 339.1626. Calc. for $C_{24}H_{21}NO$: *M*, 339.1623); δ_H 1.22 {and 1.30} (3 H, d, *J* 6.6, Me), 2.41–2.80 (4 H, m, 2 × CH_2), {2.92 and} 3.22 (1 H, unresolved 9, CH) and 6.59–7.94 (13 H, m, ArH); δ_C {18.1 and} 18.7 (Me), {34.8 and} 35.5 (CH_2), 43.0 {and 43.4} (CH_2), {59.4 and} 59.5 (CH), {73.0 and} 73.8 (C), 122–132 (22 lines), {139.4 and} 139.5, {142.9 and} 143.1, 146.0 {and 148.0}, 148.9 {and 150.2}, {170.3 and} 170.6; *m/z* 339 (M^+, 98%), 310 (25), 248 (100), 231 (47), 220 (44), 206 (28) and 91 (49); and spiro[indane-1,1′-isoindol]-3′-one **39** (51 mg, 10%), viscous oil; δ_H 2.54–2.61 (2 H, m, CH_2), 3.24 (2 H, m, CH_2), 6.84 (1 H, d, *J* 7.6, 7-H), 6.95–7.55 (6 H, m, ArH), 7.61 (1 H, s, NH) and 7.83 (1 H, dd, *J* 1.6 and 8.2, 4′-H); δ_C 30.4 (CH_2), 39.0 (CH_2), 71.9 (C), 121–133 (10 lines), 143.3, 152.0 and 170.2; *m/z* 235 (M^+, 44%), 206 (48), 146 (19), 132 (100), 105 (14) and 77 (22).

Hydroxy lactam **32** (0.887 g) in TFA (25 cm^3) was heated under reflux for 50 h, then worked up as before to afford 2′-(1-*phenylethyl*)*spiro*[3,4-*dihydronaphthalene*-1(2H),1′(2′H)-*isoindol*]-3′-*one* diastereoisomers **45a**,**b** (288 mg, 34%, 25:75 ratio), mp 234–237 °C (from toluene–light petroleum) (Found: M^+, 353.1782. Calc. for $C_{25}H_{23}NO$: *M*, 353.1780); δ_H {0.51 and} 0.82 (3 H, d, *J* 7.0, Me), 1.20–2.95 (7 H, m, 3 × CH_2 and CH), 6.38 (1 H, d, *J* 7.5, 8-H) and 6.79–8.04 (12 H, m, ArH); δ_C[$CDCl_3$–$(CD_3)_2SO$] 22.0 (Me), 23.5 (CH_2), 29.8 (CH_2), 39.1 (CH_2), 48.6 (CH), 65.7 (C), 122–133 (11 lines), 136.3, 137.7, 144.8, 152.4 and 168.9; *m/z* 353 (M^+, 55%), 324 (14), 248 (100), 232 (32), 220 (81), 206 (19), 193 (65), 165 (17), 105 (26) and 77 (20); and *spiro*[3,4-*dihydronaphthalene*-1(2H),1′(2′H)-*isoindol*]-3′-*one* **41** (303 mg, 51%), mp 241–243 °C (from toluene–light petroleum) (Found: M^+, 249.1141. Calc. for $C_{17}H_{15}NO$: *M*, 249.1153); δ_H 1.85–2.34 (4 H, m, 2 × CH_2), 2.90–3.08 (2 H, m, CH_2) and 6.64–7.92 (9 H, m, ArH and NH); δ_C 20.8 (CH_2), 29.5 (CH_2), 37.5 (CH_2), 62.8 (C), 122–133 (9 lines), 136.3, 137.5, 153.8 and 169.8; *m/z* 249 (M^+, 86%), 220 (100), 193 (69), 165 (16), 158 (11) and 76 (10).

Hydroxy lactam **8** (0.50 g) in TFA (14 cm^3) was heated under reflux for 72 h and worked up as before. Reaction was incomplete, and the spiro lactam **22b** (56 mg, 12%) was obtained, followed by **22a** incompletely separated from unchanged starting material.

Acknowledgements

A. A. B. was in receipt of a scholarship from the University of Aden and an ORS award.

References

1 M. Winn and H. E. Zaugg, *J. Org. Chem.*, 1968, **33**, 3779.
2 G. J. Hitchings and J. M. Vernon, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1757.
3 A. A. Bahajaj, G. J. Hitchings, M. H. Moore and J. M. Vernon, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1211.
4 F. Marcuzzi, U. Azzena and G. Melloni, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1957.
5 *Cf.* H. M. Walton, *J. Org. Chem.*, 1957, **22**, 315; Y. Gouriou, C. Fayat and A. Foucaud, *Bull. Soc. Chim. Fr.*, 1970, 2293.

6 R. P. Polniaszek, S. E. Belmont and R. Alvarez, *J. Org. Chem.*, 1990, **55**, 215; T. Kiguchi, Y. Nakazono, S. Kotera, I. Ninomiya and T. Naito, *Heterocycles*, 1990, **31**, 1525.
7 *Cf.* P. D. Bailey, K. M. Morgan, D. I. Smith and J. M. Vernon, *Tetrahedron Lett.*, 1994, **35**, 7115.
8 A. A. Bahajaj, P. D. Bailey, K. M. Morgan, M. H. Moore and J. M. Vernon, *J. Chem. Soc., Chem. Commun.*, 1994, 2511.
9 H. Hiemstra and W. N. Speckamp, *Tetrahedron*, 1981, **41**, 4367.
10 B. S. Furniss, A. J. Hannaford, V. Rogers, P. W. G. Smith and A. R. Tatchell, *Vogel's Textbook of Practical Organic Chemistry*, Longman, London, 4th edn., 1978, p. 568.
11 F. S. Crossley and M. L. Moore, *J. Org. Chem.*, 1944, **9**, 529.

Paper 5/06399J
Received 28*th September* 1995
Accepted 8*th January* 1996