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CYCLIC ALLYLAMINE/ENAMINE SYSTEMS—6

SOME REACTIONS OF 4-(INDOL-2-YLCARBONYL)-, 4-(INDOL-3-YLCARBONYL AND 4-(INDOL-3-YLMETHYL)-1,2,5,6-TETRAHYDRO-1-METHYLPYRIDINES

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Abstract—Indol-3-yl 1-methyl-1,2,5,6-tetrahydropyridin-4-yl ketone (**1d**) can be isomerised to indol-3-yl 1-methyl-1,2,3,4-tetrahydropyridin-4yl- ketone but the protonated form of this enamine could not be cyclised to the indole α-position. Both indol-2-yl 1-methyl-1,2,5,6-tetrahydropyridin-4-yl ketone (**1c**) and its isomer (**1d**) were cyclised to 5-membered ketones by mineral acid catalysed Michael-type addition of indole β- and α-positions respectively onto the unsaturated ketone systems. Ketone (**1d**) was transformed to 1-acetylindol-3-yl 3-acetyl-1,4,5,6-tetrahydropyridin-4-yl ketone by hot acetic anhydride. Strong base treatment of indol-3-yl(1,2,5,6-tetrahydropyridin-4-yl) methane caused isomerisation of the double bond into conjugation with the indole rather than into the endocyclic enamine position.

In five previous papers[1-5] we have demonstrated the operation of base- or acid-catalysed isomerisation of 4 - acyl - 1,2,5,6 - tetrahydropyridines (**1a**) to their enamine isomers, 4 - acyl - 1,4,5,6 - tetrahydropyridines (**2a**), and that the latter are more stable[4] than the former. We have additionally illustrated the utility of this process for the construction of indole alkaloid skeleta in the subsequent use of the enamine isomer (**2a**) for C–C bonding either with an electrophilic centre at the enamine β-position[3] or with a nucleophilic centre at the enamine α-position after enamine-β-protonation.[1,2,4,5] More recently we[4] and others[6] have shown that 6-membered cyclic allylamines (**1b**) which do not have carbonyl conjugation at C-4 can likewise be isomerised to enamine isomer (**2b**) though more vigorous basic conditions are necessary. An analogous 5-membered system (**3**) could *not* be efficiently transformed into its enamine isomer **4** under comparable strong base conditions.[5]

The transformation of a compound of the form **1c** *via* **2c** into a tetracyclic system **5** formed the basis for our syntheses of the alkaloids dasycarpidone and 16-*epi*-dasycarpidone.[1] We hoped that an "upside-down" version of this process would enable us to transform **1d** into **6**, a tetracycle having four of the five carbocyclic rings of the akuammiline-type alkaloids[7,8] as well as potentially useful CO functionality at what was planned to be the alkaloid C-16.

Oxidation of the alcohol **1f**[5] to ketone **1d** with manganese dioxide proceeded only in 30% yield. Considerable effort failed to improve this yield: attempts to use Jones reagent,[9a] pyridinium dichromate,[9b] pyridinium chlorochromate,[9c] N-bromosuccinimide,[9d] N-bromoacetamide,[9e] DMSO-phosphoric acid-dicyclohexylcarbodiimide,[9f] DMSO-acetic anhydride,[9g] or potassium dichromate-sulphuric acid-chloroform[9h] led either to no reaction or to the formation of water-soluble products, only traces of the desired ketone being obtained in some cases.

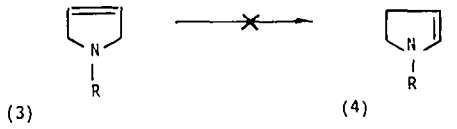
Treatment of the conjugated ketone **1d** with sodium methoxide in methanol transformed it into enamine **2d** characterised[4] by trapping with sodium borohydride producing a mixture of **7a** and **7b**. Disappointingly, heating **1d** at reflux in 50% aqueous acetic acid, conditions which readily transformed **1c** into **5**, led only to the enamine; none of the desired closure to **6** was observed. This failure can be attributed to the requirement in the present case to effect electrophilic substitution at an indole α-position (as opposed to a β-position for formation of **5**) compounded by the deactivating carbonyl conjugation. Attempts to ring close the ketones **8a** and **8b** (see below) in acetic acid also met with failure, either no reaction occurring or with acetic acid in the presence of *p*-toluenesulphonic acid, intractable tars being produced. These failures are in contrast to, for example, the reported transformations of **9** into **10**[10a] and of **11** into **12**.[10b]

On treatment of the conjugated ketone **1d** with hot 6M HCl an alternative mode of cyclisation was observed resulting in the formation of a new 5-membered ketone ring as in **13**, possibly by proton catalysed Michael-type addition of the indole to the unsaturated ketone. The α-substituted indole isomer **1c**[1] under comparable conditions produced **14**.

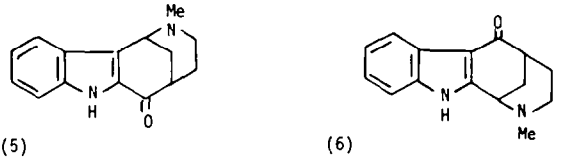
Since we knew[4,6] that allylamine→enamine isomerisation could be effected without 4-acyl conjugation an attempt was made to remove the CO deactivation by ketalisation, however only cleavage to indole itself was observed when the ketone **1d** was reacted with ethane-1,2-diol in hot benzene with *p*-toluenesulphonic acid. In other work[11] we had shown that it is possible to ketalise an N-acetyl-3-acylindole; to this end ketone **1d** was treated with acetic anhydride at reflux. In monitoring the reaction the rapid

(1) (2)

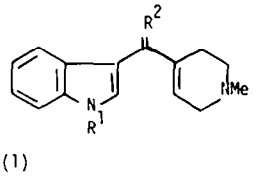
	R^1	R^2
a.	CO.R	R
b.	H	R
c.	indol-2-yl.CO	Me
d.	indol-3-yl.CO	Me



(3) (4)



(5) (6)



(1)

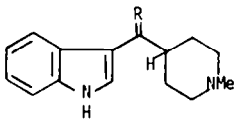
	R^1	R^2
d.	H	O
e.	Ac	O
f.	H	H,OH
g.	H	H_2

formation of the desired N-acetyl derivative **1e**, prepared in a separate experiment by acylation with sodium hydride-acetyl chloride, was followed by rapid conversion to a diacetyl derivative, assigned structure **8c** (see below). Attempted formation of the ethylene ketal of **1e** in the usual way again gave only indole itself.

The diacetylated derivative **8c** of ketone **1d** could be hydrolysed by aqueous potassium carbonate or triethylamine, with removal of the N-acetyl group and this product **8a** in turn could be re-acetylated to give the original diacetyl compound. That the second acetyl residue was attached to the piperideine moiety was clear from the mass spectra of both mono- and diacetyl-compounds which each had as base peak an ion at m/z 138 corresponding to a C-acetylated piperideine fragment (**A**).

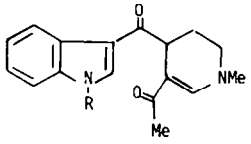
There are two positions at which it is reasonable to suppose the C-acetylation could have occurred: structure **8c** would result from a β-acetylation of enamine isomer produced *in situ*; structure **15** would result from γ-acetylation of dienol or dienol acetate the formation of which *in situ* would be entirely reasonable. Differentiation between these possibilities rests on the NMR spectrum of **8a** which showed a sharp singlet at τ2.38 for the alkene proton at C-2; the piperideine C-4 proton was represented by a multiplet at τ5.60 coupled to the protons giving rise to a multiplet at τ8.06 (C-5 protons) but not to the alkene proton. Chemical confirmation for the structural assignments **8a** and **8c** was provided by the reaction of the 1,4-diketone **8a** with hydrazine to produce the pyridazine **16** with isomerisation of the double bond.

In a final attempt to produce the ring system of **6** by the isomerisation of a cyclic allylamine, the piperideine **1g** was prepared by hydrogenolysis of the benzylic allylic alcohol **1f** with the sodium borohydride in hot ethanol. We anticipated that strong base catalysed isomerisation would produce enamine **17** and that the protonated enamine would close to the indole α-position in the absence of a deactivating 3-acyl group. However, on equilibration of **1g** with potassium t-butoxide the allylamine was transformed instead into the 3-vinylindole **18**. An exactly com-



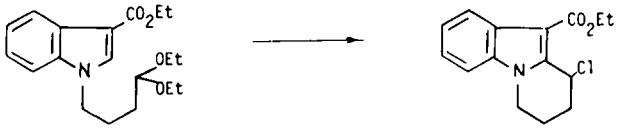
(7)

a. R = O
b. R = H,OH

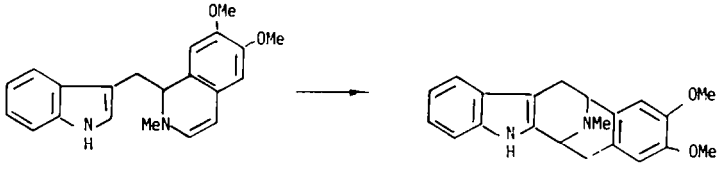


(8)

a. R = H
b. R = Me
c. R = Ac

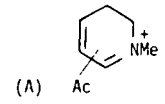


(9) (10)



(11) (12)

(13) (14)



(A)

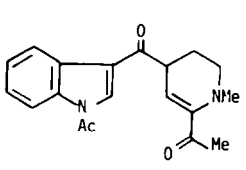
parable transformation of **19** into **20**, has recently been reported.[12]

EXPERIMENTAL

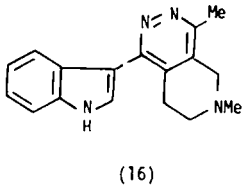
Indol-3-yl 1,2,5,6 - *tetrahydro* - 1 - *methylpyridin* - 4 - *yl ketone* (**1d**). Alcohol **1f** (2.5 g)[3] in dry $CHCl_3$ (200 ml) was oxidised with MnO_2 (10 g) with stirring for 2 hr. Filtration and evaporation gave crude **1d** (0.79 g) recrystallised from MeOH, m.p. 190–192°, λ_{max} (EtOH) 248, 269 sh, and 310 nm (log ϵ 4.00, 3.96 and 4.05), ν_{max} ($CHCl_3$) 3460s and 1620s cm^{-1}; τ (d_6-DMSO) – 1.80 (1H, bs, NH), 1.85 (1H, m HAr), 2.46 – 2.97 (3H, m, HAr), 2.09 (1H, s, indole-α-H), 3.51 (1H, m, CH=C), 6.90 (2H, bs, C : C . CH_2N), 7.50 (4H, m, CH_2CH_2N), and 7.68 (3H, s, NCH_3); *m/z* 240 M^+, 34%), 144 (35), 130 (11), 116 (12), 96 (100), 58 (27) and 43 (65) (Found: C, 74.5; H, 6.6; N, 11.0%. $C_{15}H_{16}N_2O$ Requires: C, 75.0; H, 6.6; N, 11.6%).

Ketone **13**. The unsaturated **1d** (50 mg) was heated in refluxing HCl aq (6M, 3 ml) for 4 hr. Na_2CO_3 was added to the cooled mixture and EtOAc used to extract crude product (33 mg) purified by PLC (silica; $CHCl_3$-MeOH-Et_3N; 80 : 20 : 1) to afford pure **14** (12 mg) as a pale yellow gum, λ_{max} (EtOH) 239, 262 and 294 nm; ν_{max} ($CHCl_3$) 3440s and 1675s cm^{-1}; τ (CD_3OD) 2.00–4.00 (4H, m, HAr), 6.37 (1H, m, CH . CO), 6.50–8.10 (7H, m, saturated CH), and 7.76 (3H, s, NCH_3); *m/z* 240 (M^+, 65%), 227 (33), 226 (27), 198 (75), 197 (43), 183 (37), 169 (33), 168 (75), 167 (100), 154 (30), 149 (28), 139 (41), 136 (28), 128 (22), 123 (21), 122 (40), 108 (63), 107 (52), 94 (28), 91 (27), 83 (63), 77 (73) and 58 (54) (Found: M by mass spectrometry 240.1248. $C_{15}H_{16}N_2O$ Requires: M 240.1262).

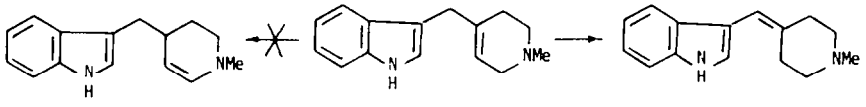
Ketone **14**. Indol-2-yl 1,2,5,6 - tetrahydro - 1 - methylpyridin - 4 -yl ketone[1] (30 mg) was heated at 95° in HCl aq (10M, 5 ml) for 0.5 hr. The cooled soln was made basic with K_2CO_3 and then extracted with EtOAc which gave a brown gum, purified by PLC (silica; EtOAc-Me_2CO-MeOH, 3 : 1 : 1) to give **14** (22 mg) as a pale brown gum, λ_{max} (EtOH) 206, 234 and 304 nm (log ϵ 4.20, 4.18 and 4.28); ν_{max} ($CHCl_3$)



(15)



(16)



(17) (1g) (18)

(19) (20)

3460m and 1685s cm^{-1}; τ ($CDCl_3$) 0.60 (1H, bs, NH), 2.20–3.02 (4H, m, HAr), 6.15 (1H, m, CH.CO), 6.54–8.20 (10H, m, including 7.78, 3H, s, NCH_3); *m/z* 240 (M^+, 100%), 225 (18), 197 (16), 183 (20), 168 (93), 154 (23), 143 (21), 115 (16), 85 (20), 70 (23), 96 (15), and 58 (70) (Found: M by mass spectrometry 240.1265. $C_{15}H_{16}N_2O$ requires: 240.1263).

1 - *Acetylindol* 3-*yl* 1,2,5,6 - *tetrahydro* - 1 - *methylpyridin* - 4 - *yl ketone* (**1e**). To a stirred suspension of **1d** (534 mg) in dry THF (50 ml) was added a suspension of NaH (80 mg) in dry THF (50 ml) and the mixture stirred for 20 min at room temp. Acetyl chloride (4.7 ml) was added and after a further 20 min stirring HCl aq (0.1 M, 50 ml) was added. After making the mixture basic with $KHCO_3$, EtOAc extracted the N-acetyl **1e** as a pale brown gum, λ_{max} (EtOH) 248 sh, 253 sh and 304 nm (log ε 4.08, 4.06 and 3.99); ν_{max} ($CHCl_3$) 1630s and 1720s cm^{-1}; τ ($CDCl_3$) 1.53–1.93 (2H, m, HAr), 2.50–2.80 (2H, m, HAr), 2.12 (1H, s, indole-α-H), 3.40 (1H, m, CH:C); 6.80 (2H, C:CCH_2N), 6.02–7.32 (4H, m, CH_2CH_2N), and 7.54 (3H, s, NCH_3); *m/z* 282 (M^+, 33%), 239 (10), 197 (8), 144 (30), and 96 (100) (Found: M by mass spectrometry 282.1370. $C_{17}H_{18}N_2O_2$ Requires: M, 282.1368).

Indol - 3 - *yl* 3 - *acetyl* - 1,2,5,6 - *tetrahydro* - 1 - *methylpyridin* - 4 - *yl ketone* (**8a**). The ketone **1d** (500 mg) was heated in refluxing Ac_2O for 5 min. Water was added to the cooled soln and the whole heated at 95° for 5 min. Cooling, basification and extraction with EtOAc produced a black gum (0.6 g). This was treated with Et_3N (1 ml) in MeOH (10 ml) at reflux for 10 min which produced a ppt of **8a** (132 mg), m.p. 270–272°, ν_{max} (EtOH) 241, 256 sh, and 302 nm (log ε 3.56, 4.06 and 4.56); ν_{max} (nujol) 1635s and 1615s cm^{-1}; τ (d_6-DMSO) 1.72 (1H, bs, NH), 1.65 (1H, d, indole-α-H), 1.85 (1H, m, HAr), 2.38 (1H, s, NCH: C.CO), 2.48–3.05 (3H, m, HAr), 5.60 (1H, m, CH.CO), 6.91 (3H, s, NCH_3), and 7.97 (3H, s, $COCH_3$); *m/z* 282 (M^+, 40%), 144 (28), 138 (100), 96 (20), 94 (25), and 43 (26) (Found: M by mass spectrometry 282.1368. $C_{17}H_{18}N_2O_2$ Requires: M, 282.1368).

1 - *Acetylindol* - 3 - *yl* 3 - *acetyl* - 1,2,5,6 - *tetrahydro* - 1 - *methylpyridin* - 4 - *ylketone* (**8c**). The diketone **8a** was heated with Ac_2O (3 ml) at 95% for 5 min. Water was added and after 0.5 hr at room temp the product was isolated by extraction with EtOAc to give **8c** (140 mg), as a pale yellow gum, λ_{max} (EtOH) 217, 227 sh and 301 nm (log ε 4.35 and 4.45); ν_{max} ($CHCl_3$) 1730s, 1660s and 1640s cm^{-1}; τ ($CDCl_3$) 1.20 (1H, s, indole-α-H), 1.50–1.84 (2H, m, HAr), 2.50–2.85 (2H, m, HAr), 2.58 (1H, s, NCH: C.CO), 5.42 (1H, m, CH.CO), 6.88 (3H, s, NCH_3), 7.23 (3H, s, N.CO.CH_3), 7.85 (3H, s, C: C.CO.CH_3), and 6.00–8.20 (4H, m, CH_2CH_2N); *m/z* 324 (M^+, 20%), 144 (33), 138 (100), 96 (35) and 94 (38) (Found: M by mass spectrometry, 324.1475. $C_{19}H_{20}N_2O_3$ Requires: M, 324.1474).

1 - *Methylindol* - 3 - *yl* 3 - *acetyl* - 1,2,5,6 - *tetrahydro* - 1 - *methylpyridin* - 4 - *yl ketone* (**8b**). Ketone **8a** (34 mg) was methylated with MeI (1 ml) in a vigorously stirred mixture of benzene (3 ml) and NaOH aq (50%, 4 ml) in the presence of tetra-n-butylammonium hydroxide at room temp for 1 hr. Separation of the layers gave **8b** (21 mg), purified by crystallisation from EtOH, m.p. 115–120°, λ_{max} (EtOH) 210, 246 and 303 nm (log ε 4.38, 4.06 and 4.41); ν_{max} (nujol) 1640s and 1610s cm^{-1}; τ ($CDCl_3$) 1.70 (1H, m, HAr), 1.80 (1H, s, indole-α-H), 2.60 (1H, s, C: CHN), 2.75–2.85 (3H, m, HAr), 5.50 (1H, m, CH.CO), 6.23 (3H, s, NCH_3), 6.92 (3H, s, NCH_3), and 7.88 (3H, s, CH_3CO); *m/z* 296 (M^+, 16%), 158 (63), and 138 (100) (Found: M by mass spectrometry, 296.1518. $C_{18}H_{20}N_2O_2$ Requires: 296.1525).

Indol - 3 - *yl* - 1,2,5,6 - *tetrahydro* - 1 - *methylpyridin* - 4 - *ylmethane* (**1g**). The alcohol **1f** (373 mg) was reduced with excess $NaBH_4$ in refluxing aqueous EtOH (95%, 10 ml) under N_2 during 1 hr. Evaporation of solvent and partitioning between water and EtOAc gave a colourless gum which was tributed with ether to give the reduced product (**1g**) (171 mg), m.p. 146–147°, λ_{max} (EtOH) 276 sh, 282 and 291 nm (log ε 4.03, 4.06 and 4.00); ν_{max} ($CHCl_3$) 3470s cm^{-1}; τ ($CDCl_3$) 1.80 (1H, bs, NH), 2.30–3.10 (4H, m, HAr), 3.02 (1H, s, indole-α-H), 4.53 (1H, m, C: CH), 6.54 (2H, s, CH_2), 6.90–8.00 (6H, m), and 7.62 (3H, s, NCH_3); *m/z* 226 (M^+, 4%), 182 (12), 168 (10), 154 (8), 130 (60) and 96 (100) (Found: M by mass spectrometry 226.1467. $C_{15}H_{18}N_2$ Requires: M, 226.1470).

3-*Vinylindole* (**18**). The allylamine **1g** (202 mg) was treated with t-BuOK (resublimed, 211 mg) in dry DMSO (3 ml) at room temp under N_2 for 1 hr and then at 95° for 15 hr and

finally at 120° for 48 hr. After cooling and adding water, product was extracted with EtOAc and obtained as a dark gum (162 mg). A portion (46 mg) was purified by PLC (silica; CH_2Cl_2-MeOH-Et_3N; 97.5: 1:1.5) to give **18** (27 mg) as a pale brown amorphous solid, λ_{max} (EtOH) 265, 280 and 290 nm; ν_{max} ($CHCl_3$) 3460s cm^{-1}; τ ($CDCl_3$) 1.27 (1H, bs, NH), 2.30–3.10 (4H, m, HAr), 3.00 (1H, s, indole-α-H), 3.68 (1H, s, C: CH), and 6.50–8.00 (11H, m, including 3H, s, NCH_3); *m/z* 226 (M^+, 100%), 225 (25), 182 (45), 168 (24), 167 (16), 154 (25), 143 (27), 130 (21), 109 (25) and 96 (46) (Found: M by mass spectrometry 226.1468. $C_{15}H_{18}N_2$ Requires: 226.1470).

Pyridazine (**16**). The diketone **8a** (115 mg) in EtOH (15 ml) was heated at reflux with hydrazine hydrate (60%, 5 ml) for 48 hr. The solvents were removed by evaporation *in vacuo* and the residue partitioned between water and $CHCl_3$. From the organic extract a brown oil was obtained which, after purification by PLC, gave **16** (10 mg), m.p. 175–181° (from EtOH), λ_{max} (EtOH) 217, 277 sh, 280, 288, 296 sh, 325 sh and 366 sh nm (log ε 4.41, 3.94, 3.95, 3.94, 3.87, 3.57 and 3.17); ν_{max} (nujol) 3200s cm^{-1}; τ ($CDCl_3$) 1.04 (1H, bs, NH), 2.01 (1H, d, J 8 Hz, HAr), 2.36 (1H, s, indole-α-H), 2.38 (1H, d, J 8 Hz, HAr), 2.76 (1H, t, J 8 Hz, HAr), 2.83 (1H, t, J 8 Hz, HAr), 6.47 (2H, s, $ArCH_2N$), 7.12 (2H, t, J 6 Hz, $ArCH_2CH_2N$), 7.37 (2H, t, J 6 Hz, $ArCH_2CH_2N$), 7.39 (3H, s, NCH_3), 7.39 (3H, s, NCH_3), and 7.48 (3H, s, $ArCH_3$); *m/z* 278 (M^+, 100%), 263 (24), 248 (13), and 236 (80) (Found: M by mass spectrometry, 278.1528. $C_{17}H_{18}N_4$ Requires: M 278.1531).

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