Tetrahedron Vol. 37, No. 17, pp. 3005 to 3007, 1981
Printed in Great Britain

0040-4020/81/173005-03$02.00/0

RELATIVE STABILITIES OF 5-MEMBERED CYCLIC ALLYLAMINE/ENAMINE SYSTEMS

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(*Received in UK 19 February 1981*)

Abstract—Evidence bearing on the relative stabilities of 3- and 2-pyrrolines is reviewed. It is shown that 1-(indol-3-ylethyl)-3-pyrroline is only partially transformed into its enamine isomer by prolonged base treatment and it is concluded that within a 5-membered ring the allylamine is more stable than enamine.

We have previously demonstrated[1,2] the operation and utility for alkaloid synthesis of the methoxide- or acetic acid-catalysed isomerisation of 4 - acyl - 1,2,5,6 - tetrahydropyridines **1a** to their enamine isomers, 4 - acyl - 1,4,5,6 - tetrahydropyridines **2a**. Under more vigorous basic conditions (t-BuOK-DMSO-90°) we[2] and others[3] showed that 6-membered cyclic allylamines **1b**, even without a conjugated CO group, can be isomerised and the isomer **2b** thus generated utilised[2] in their capacity as enamines for the construction of complex skeleta. Complimentarily we also showed[2] that in the kinetic protonation of the allylic anion formed by irreversible abstraction of a proton from C-2 in **1c**, some enamine **2c** together with unchanged allylamine (1:2), was formed, though the process was far from efficient for the interconversion, since initial deprotonation occurred mainly at C-5.

When the 6-membered cyclic allylamine **1d** was isomerised and the resulting enamine treated, without isolation, with aqueous acetic acid, the tetracycle **3** was obtained[2] in good yield *via* β-protonation of the enamine **2d** and intramolecular Mannich cyclisation to the indole α-position. Further study of this sequence has now shown that aqueous work-up after the strong base treatment leads in high yield to a stable dimer **4**. Since the dimer was amorphous and since moreover its mass spectrum showed no ion higher than that corresponding to the enamine **1d** monomer, it was characterised by NMR (two coincidental NH signals at τ 1.85, two indole-α-proton signals at τ 3.00 and 3.30, but only one olefinic signal at τ 4.14) and chemical transformation. Thus, in anticipation of obtaining a straightforward dihydro-derivative by reduction of the enamine system, **4** was treated with $NaBH_4$. In the event, a seco-derivative **5a** was obtained, in which the presence of a secondary amine was confirmed by mono-acetylation to **5b**. An analogous cleavage had been earlier reported[4] in the catalytic hydrogenolysis-hydrogenation of the N,N-dimethyl-analogue of **4** to a tetrahydro-derivative. We envisage the reductive cleavage of **4** as involving hydride trapping of a seco-immonium species **6** formed probably reversibly from **4** by reaction with BH_3.

The significance of the dimer **4** is that it could be handled and was stable *and yet* on treatment with aqueous acetic acid led cleanly to the tetracycle **4**. This suggested to us that all cyclic enamines (including, for example, 5-membered analogues the instability of which has been commented on more than once),[5-7] might conveniently be handled if *allowed to dimerise*, the potential enamine character later to be called forth by acid treatment.

The potential wide applicability of 2-pyrrolines has been well canvassed[9] and well illustrated;[6-9] in what follows we describe an investigation which sought to elaborate an alternative method for the generation of such species. To test the possibility of producing a 2-pyrroline and/or its dimer, by the allylamine → enamine isomerisation, now within a 5-membered ring, we chose to synthesise **10**, the N-substituent being chosen to give a sufficiently large molecular weight to facilitate the handling of the pyrroline and also to provide an intramolecular nucleophilic centre, the indole, as a means for trapping protonated 2-pyrroline should it be generated. Successful operation of the sequence would provide a convenient synthesis, analogous to our preparation of **3**, of the tetracycle **7** which was the key intermediate in Harley-Mason's syntheses of tubifoline,[8a] geissoschizoline,[8b] fluorocurarine,[8c] and related bases.[8]

Some but not all previous evidence encouraged us to believe that a cyclic 5-membered allylamine could be isomerised. 1-Methyl[10a] and 1 - benzyl - 3 - pyrrolidinone[10b] underwent Friedlander reactions implying base-catalysed enolisation away from the nitrogen; further, a study[5] of the enolisation of cyclic and acyclic α-aminoketones showed that equilibrative enolisation (0°-lithium hexamethyldisilazide-THF) of N - benzyl - 3 - pyrrolidinone occurred away from the nitrogen and so predominantly (2:1) did kinetic deprotonation (−78°-lithium diisopropylamide-THF). However, 3 - pyrrolin - 2 - one **8** reacts[11] as an electrophile in organic acid solution bringing about substitution of reactive aromatic substrates; the effective electrophile is **9** and the transformation of **8** into **9** is directly analogous to the proton-catalysed allylamine → enamine isomerisations which we have observed[1a,c] in 4 - acyl - 1,2,5,6 - tetrahydropyridine systems **1a**. Secondly, MINDO-3[12] calculations[13] suggested that there was a very similar difference in thermodynamic stabilities between the N - Me - 6- and -5-membered allylamine/enamine pairs (6.95 and 5.87 kcal mol^{-1} respectively) and thus that what had been achieved[2,3] in the 6-membered system would also be possible in the smaller ring system.

The 3-pyrroline **10a** was straightforwardly prepared by $LiAlH_4$ reduction of the amide **10b** resulting from interaction of ethyl indol - 3 - ylglyoxylate[14] and 3-pyrroline.[15]

As anticipated, the allylamine **10a** was completely unchanged in refluxing aqueous acetic acid. In turning to strong base (t-BuOK-DMSO) treatment it soon became clear that isomerisation was far from being as easy as in the 6-membered system, mostly starting material being recovered after 24 hr at 90° under N_2. Abandoning the

plan to try and isolate an enamine dimer, the material resulting from base treatment at 90° under N_2 for 2 weeks was straight away subjected to aqueous acetic acid yielding three products in a ratio of 3:1:1—the major product was unchanged starting material. One of the minor products was the pyrrole **11** readily spectroscopically identified, and the other, the target tetracycle **7** identified by its spectra and by m.p.[8a]

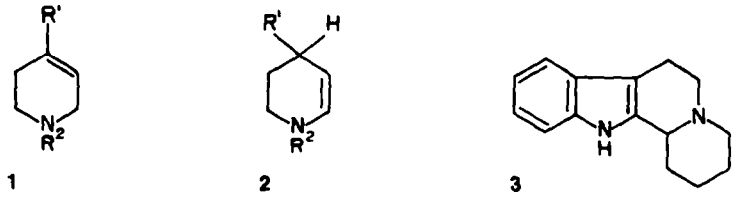
The experiment demonstrates the greater stability of the 5-membered cyclic allylamine isomer under these conditions for after this extended reaction time, excluding the oxidised material, only one quarter of the material was present as enamine. It seems then that the generation of 2-pyrrolines from 3-pyrrolines by strong base-catalysed isomerisation is not a viable method for the generation of these synthetically useful enamines.

That the formation of **11** almost certainly involved traces of oxygen which must have entered the system over the extended heating period despite out best efforts to exclude it, was supported by the easy and clean dehydrogenation of **10a** to **11** in DMSO at 90°, with or without the presence of base, but with the deliberate introduction of air.

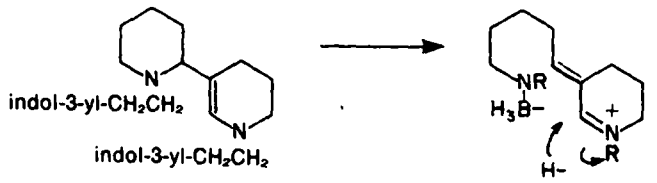
EXPERIMENTAL

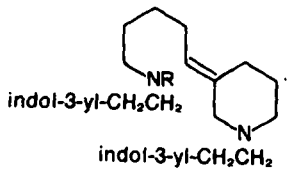
Treatment of 6-membered allylamine **1d** *with base*

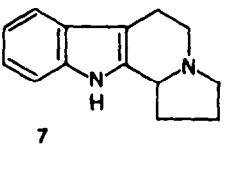
Isolation of dimer **4**. **1d**[16] (418 mg) in DMSO (dry, 10 ml) was stirred under N_2 for 1 hr, then t-BuOK (resublimed, 510 mg) was

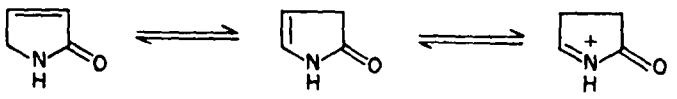


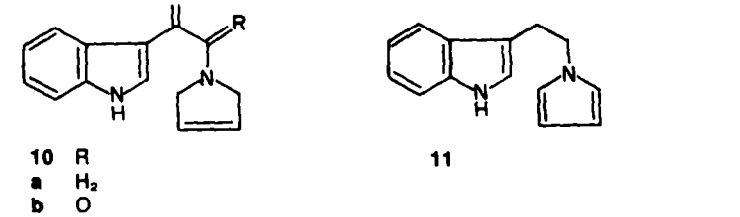
	R'	R^2
a	CO.R	R^2
b	H	R^2
c	H	CH_3
d	H	indol-3-ylethyl











added. The soln was stirred at 95° for 20 hr then the cooled soln poured into water and the organic material extracted with EtOAc to give after drying and evaporation **4** (410 mg) as a white foam, ν_{max} 1655 s cm^{-1}; τ ($CDCl_3$) 1.85 (2H, bs, 2 × NH), 2.10–3.10 (8H, m, HAr), 3.00 and 3.30 (2 × 1H, s, 2 × indole - α - H), 4.14 (1H, bs, CH:C), 6.50–8.80 (23H, m); *m/e* 226(25%), 144(15), 143(16), 130(20), 98(80) and 96(100).

Reduction of dimer **4** *to dihydro-derivative* **5a**. **4** (72 mg) in MeOH (3 ml) was reduced with excess $NaBH_4$ during 0.5 hr. The mixture was diluted with water and the product (62 mg) isolated with EtOAc as a gum, τ ($CDCl_3$) 1.62 (2H, bs, 2 × NH), 2.20–3.10 (8H, m, HAr), 3.02 (2H, s, 2 × indole - α - H), 4.75 (1H, m, CH:C), 8.25 (1H, bs, D_2O-exchangeable, NH), 6.70–8.70 (24H, m); *m/e* 454.3096 (M^+, 5%, $C_{30}H_{38}N_2$ requires 454.3089), 324(30), 226(8), 193(12), 144(60), 130(100) and 96(90).

Acetylation of dihydro-dimer **5a** *to* **5b**. The reduced dimer **5a** (10 mg) was treated with Ac_2O (1 ml) at 90° for 3 min. After addition of water and basification the product was isolated, using EtOAc, as a gum (8 mg), *m/e* 496.3201 (M^+, 10%, $C_{32}H_{40}N_4O$ requires 496.3183), 366(100), 233(9), 144(40), 130(20), 98(15) and 96(12).

Preparation of amide **10b**. 3-Pyrroline hydrochloride[15] (10 g) was partitioned between 40% NaOH aq and ether. The ether layer was dried, mixed with ethyl indol - 3 - ylglyoxylate[14] (10 g) and the ether carefully distilled. The resulting mixture was then refluxed for 11 hr and the excess pyrroline evaporated to give the amide which was recrystallised from EtOH to give **10b** (7.6 g), m.p. 222–224°, λ_{max}(EtOH), 210, 248, 266 and 314 nm (log ϵ 4.24, 3.86, 3.83 and 3.86); ν_{max}(Nujol) 3170 m, 1630 s and 1600 s cm^{-1}; τ (d_6-Me_2CO) – 1.00 (1H, bs, NH), 1.75 (1H, s, indole - α - H), 1.75–2.75 (4H, m, HAr), 4.10 (2H, s, CH:CH), 5.70 (4H, m, NCH_2C:C); *m/e* 240 (M^+, 2%), 212(5), 144(100), 116(19), 89(14) and 68(12) (Found: C, 67.2; H, 4.9; N, 11.1% $C_{14}H_{12}N_2O_2 \cdot \frac{1}{2}H_2O$ requires: C, 67.4; H, 5.2; N, 11.2%).

Preparation of pyrroline **10a**. To a suspension of **10b** (2.98 g) in THF (300 ml) under N_2 was added at 0° $LiAlH_4$ (2.25 g) and the mixture then brought to reflux for 7 hr. To the ice-cooled mixture was added 2N NaOH aq (5 ml), water (15 ml) and ether (250 ml). The solids were filtered off, washed with EtOAc and the combined organic solns evaporated to give an oil (2.2 g) which was purified by chromatography over silica eluting with EtOAc; after crystallisation from petroleum ether (60–80°), the pyrroline had m.p. 110°, λ_{max}(EtOH) 223, 275 sh, 284 and 292sh nm (log ϵ 4.35, 3.57, 3.60 and 3.55); ν_{max}($CHCl_3$) 3480 s cm^{-1}; τ ($CDCl_3$) 1.60 (1H, bs, NH), 2.35–2.85 (4H, HAr), 3.00 (1H, s, indole - α - H), 4.20 (2H, s, CH:CH), 6.40 (4H, s, NCH_2C:C) and 5.70 (4H, bs, CH_2CH_2): *m/e* 212 (M^+, 76%), 144(24), 130(100), 82(100) and 55(100) (Found: C, 79.1; H, 7.7; N, 13.3% $C_{14}H_{16}N_2$ requires: C, 79.2; H, 7.6; N, 13.2%).

Treatment of **10a** *with t-BuOK-DMSO-95°*

Isolation of pyrrole **11** *and tetracycle* **7**. To a de-oxygenated soln of **10a** (50 mg) in DMSO (dry, 0.5 ml) was added freshly sublimed t-BuOK (109 mg) and the mixture was then heated at 90–110° for 2 weeks. Aqueous AcOH (50%, 1 ml) was added and the mixture heated at 95° for 4 hr. The cooled mixture was basified with K_2CO_3 and extracted with EtOAc to give a gum (64 mg) the components of which were isolated by preparative tlc (silica; MeOH/EtOAc, 1:1) to give starting material (15 mg) together with **11** (6 mg), as the least polar component, λ_{max}(EtOH) 222, 274 sh, 285 and 292 sh (log ϵ 4.33, 3.63, 3.64 and 3.61); ν_{max}($CHCl_3$) 3480 s cm^{-1}; τ ($CDCl_3$) 2.24 (1H, bs, NH), 2.45–3.00 (4H, m, HAr), 3.20 (1H, d, J 2 Hz, indole - α - H), 3.45 (2H, dd, J 3 Hz, pyrrole - α - H), 3.85 (2H, dd, J 3 Hz, pyrrole - β - H), 5.85 (2H, t, J 7 Hz, CH_2-N) and 6.80 (2H, t, J 7 Hz, CH_2); *m/e* 210.1152 (M^+, 30%, $C_{14}H_{14}N_2$ requires 210.1157) 130(100), 103(5) and 80(8) and the tetracycle **7** (5 mg), m.p. (Et_2O–C_6H_{14}) 164–167° (lit.[8a] 174–176°), λ_{max}(EtOH) 226, 275 sh, 284 and 241 nm; ν_{max}($CHCl_3$) 3470 cm^{-1}; τ ($CDCl_3$) 2.10 (1H, bs, NH), 2.50–2.85 (4H, m, HAr), 5.68 (1H, bs, indole - CH - N), and 6.65–8.10 (10 H, m); *m/e* 212.1306 (M^+, 62%, $C_{14}H_{16}N_2$ requires 212.1313), 211(74), 184(23), 170(10), 169(10) and 156(15).

Acknowledgement—WRA thanks the SRC for a maintenance grant.

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