

Novel Synthesis of 3*H*-Pyrroles, and Novel Intermediates in the Paal–Knorr 1*H*-Pyrrole Synthesis: 2-Hydroxy-3,4-dihydro-2*H*-Pyrroles from 1,4-Diketones and Liquid Ammonia

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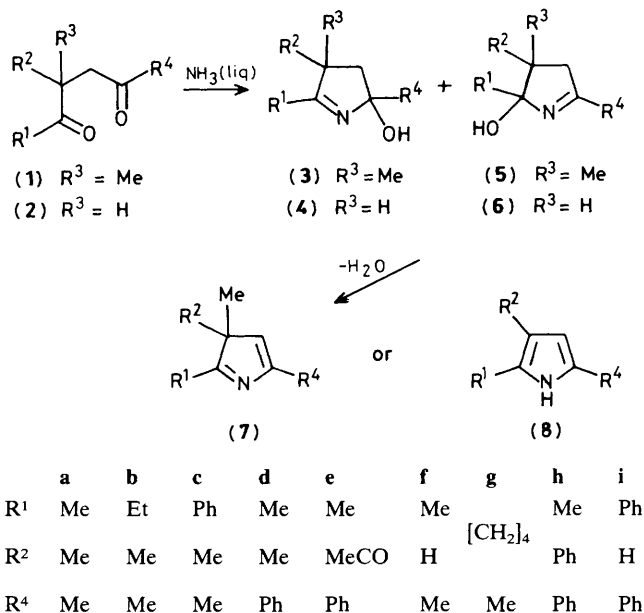
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Reaction of 2,2-dimethyl-1,4-diketones with liquid ammonia gives high yields of isolable 2-hydroxy-3,4-dihydro-2*H*-pyrroles (**3**) and (**5**) which are readily dehydrated to give separable mixtures of 3*H*-pyrroles and methylenedihydropyrroles, while less-substituted 1,4-diketones give analogous hydroxy-compounds (**4**) and (**6**) which are hitherto-unsuspected intermediates in the Paal–Knorr 1*H*-pyrrole synthesis.

3*H*-Pyrroles constitute a little-known ring system¹ with a potentially rich chemistry in terms of rearrangement, addition, and cycloaddition reactions. To date, no general synthetic approaches to these compounds have been reported.² We recently attempted to prepare 3*H*-pyrroles from 2-acyl-2-alkyl-1,4-diketones *via* the Paal–Knorr reaction, but obtained instead 1-acyl-1*H*-pyrroles by rearrangement, apparently *via* 2-hydroxy-3,4-dihydro-2*H*-pyrrole (hydroxypyrroline) intermediates.³ Believing the rearrangement to be mediated by the diketone 2-acyl substituent, we have now repeated the reaction using 2,2-dimethyl-1,4-diketones and have successfully isolated 3*H*-pyrroles.

1,4-Diketone (**1a**) (formed by Triton B-catalysed⁴ Michael addition of nitroethane to 4-methylpent-3-en-2-one, followed by Nef reaction⁵) on treatment overnight with a large excess of anhydrous liquid ammonia gave only the hydroxypyrroline (**5a**)^{†‡} (89%); m.p. 97 °C (from benzene–hexane) (Scheme 1). Hydroxypyrrolines of this type have been observed only rarely.^{3,6} Dehydration with basic Al₂O₃ in refluxing CH₂Cl₂ (8 h) with simultaneous removal of water (4Å molecular sieves; Soxhlet), gave a mixture (97%) of (**7a**), (**9a**), and (**10a**) in a ratio of 12:5:3 which was hydrolysed when subjected to Al₂O₃ or SiO₂ chromatography. However, the mixture on dissolution in ice-cold 1M HCl (1.5 mol) followed by immediate basification with ice-cold 0.4M Na₂CO₃ (0.9 mol) and ether extraction, gave on drying (MgSO₄) and evaporation essentially pure 3*H*-pyrrole (**7a**) [46% from (**5a**)].[‡] Hydration of (**9a**) and (**10a**) to (**5a**) (recoverable from the aqueous solution with CH₂Cl₂) is apparently much faster than hydration of (**7a**). Attempts to purify (**7a**) by distillation (49–50 °C; 29 mmHg) regenerated the above mixture of isomers. Diketone (**1b**) gave with ammonia a mixture of hydroxypyrrolines (**3b**) and (**5b**) (100% by ¹H n.m.r.), but dehydration yielded mostly the ethylenedihydropyrrole (**9b**)

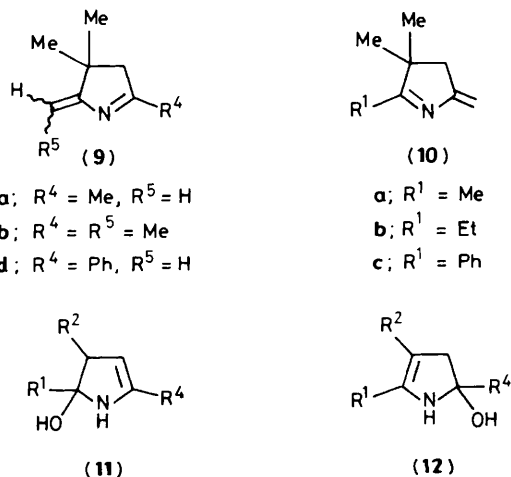
(85%), together with the 3*H*-pyrrole (**7b**) (15%) and no trace of the isomer (**10b**). In contrast, the diketone (**1c**) gave mostly the kinetic hydroxypyrroline isomer (**5c**) (85%),[‡] m.p. 147 °C (benzene–hexane); the thermodynamic isomer (**3c**),[‡] m.p. 112 °C, formed by rearrangement during recrystallisation of (**5c**), was recovered from the mother liquor. Isomeric hydroxypyrrolines were readily distinguished by ¹H n.m.r. signals for the R¹ or R⁴ Me groups. Both (**3c**) and (**5c**) on



Scheme 1

[†] Distinguished from (**3a**) by ¹H coupled ¹³C n.m.r. spectrum.

[‡] Satisfactory microanalyses could be obtained only for compounds (**5a**), (**3c**), (**5c**), and for (**7a**) picrate and (**7c**) HBF₄ salt. All new compounds were characterised spectroscopically [i.r., ¹H and ¹³C n.m.r. (CDCl₃)], e.g. (**3c**), ν_{\max} (Nujol): 3 180 (OH) and 1 605 cm⁻¹ (C=N); δ_{H} : 1.34 (3H, s), 1.44 (3H, s), 1.58 (3H, s), 1.97 and 2.13 (2H, ABq), and 7.2–7.8 (5H, m); δ_{C} : 27.47 (q), 28.33 (q), 29.96 (q), 50.87 (s), 54.01 (t), 97.57 (s), 128.17, 129.75, and 134.08 (Ph), and 179.2 (s); (**5c**), ν_{\max} (Nujol): 3 120 (OH) and 1 647 cm⁻¹ (C=N); δ_{H} : 0.37 (3H, s), 1.16 (3H, s), 1.71 (3H, s), 2.13 and 2.49 (2H, ABq), and 7.1–7.5 (5H, m); δ_{C} : 19.88 (q), 21.56 (q), 26.76 (q), 45.72 (s), 53.79 (t), 102.66 (s), 126.28, 126.82, 127.25, and 143.45 (Ph), and 178.88 (s); (**7a**), ν_{\max} (liq.): 1 635 (C=N), 1 585 (C=C), and 785 cm⁻¹; δ_{H} : 1.11 (6H, s), 2.08 (3H, d, *J* 1.5 Hz), 2.09 (3H, s), and 5.64 (1H, q, *J* 1.5 Hz); δ_{C} : 14.74 (q), 16.04 (q), 21.62 (q), 56.50 (s), 128.55 (d), 149.41 (s), and 188.31 (s); (**4f**), ν_{\max} (liq.): 3 290 (OH), 1 650 (C=N), and 1 110 cm⁻¹ (C=O); δ_{H} : 1.30 (3H, s), 1.97 (3H, s), 1.8–2.2 (2H, m), 2.4–2.7 (2H, m), and 4.54 (1H, br. s); δ_{C} : 17.93 (q), 26.33 (q), 35.22 (t), 36.79 (t), 84.79 (s), and 170.67 (s).



dehydration (basic Al_2O_3 ; refluxing benzene; 4.5 h), gave essentially pure 3*H*-pyrrole (**7c**)‡ (90%), b.p. 58 °C; 1.3 mmHg, coproduct (**10c**) being barely detectable by ^1H n.m.r. spectroscopy and readily removed by the above acid-base treatment. The isomeric diketone (**1d**) was converted (~100%) into a mixture of (**3d**) and (**5d**) (3:1) which was dehydrated to a 5:1 mixture of 3*H*-pyrrole (**7d**) and methylenepyrroline (**9d**).

When the 2-acyl-1,4-diketone (**1e**) was treated with liquid ammonia, we obtained not the expected intermediate (**5e**), but a mixture of acetamide, 1*H*-pyrrole (**8d**), and what appeared to be mixed diastereoisomers of the hydroxypyrroline (**6d**) [$\delta_{\text{H}}(\text{CDCl}_3)$ *inter alia* 1.17 (d, *J* 6 Hz), 1.35 (s), 1.58 (s), and 2.2–3.7(m)], which decomposed with concomitant formation of (**8d**) over a few days.§ The detection of (**6d**), formed apparently *via* C-acyl cleavage of (**1e**) with ammonia, suggested that compounds of this type might be isolable and hitherto unsuspected intermediates in the classical Paal-Knorr reaction between simple 1,4-diketones and ammonia, a reaction which is an important synthetic and biosynthetic route to 1*H*-pyrroles.

Treatment of hexane-2,4-dione (**2f**) with excess of anhydrous liquid ammonia did indeed give essentially pure hydroxypyrroline (**4f**)‡ as an unstable oil, containing no trace of (**1f**) by ^1H n.m.r. spectroscopy and contaminated with only a few percent of 1*H*-pyrrole (**8f**). After a few days at 25 °C the solution in the n.m.r. tube contained mostly (**8f**)§ and very little (**4f**). Likewise the diketone (**2g**) gave a mixture of the two diastereoisomers of (**4g**) and one of (**6g**) (probably with *cis*-fused rings) (δ_{H} 1.25, 1.44, and 1.98 respectively; Me groups), which was converted completely into (**8g**)§ after a few days at 25 °C, while (**2h**) gave just the two diastereoisomers of (**6h**) in a ratio of 12:7, the major one having R^1 and R^2 *cis* from the ^1H n.m.r. high-field Me signal, and the mixture decomposing as above into (**8h**).§ Under these conditions (**2i**) failed to react, being recovered unchanged after evaporation of the ammonia. In no case was any evidence of hydroxy-enamines (**11**) and (**12**) detected.

‡ ^1H N.m.r. spectra of 1*H*-pyrroles (**8**) matched literature data.

Only two other examples of hydroxypyrrolines (**6**) are known, having been prepared indirectly from oxime ethers, and in both cases having $\text{R}^1 = \text{R}^2 = \text{H}$.^{6c,d} Such structures do not appear to have been considered as intermediates in the Paal-Knorr 1*H*-pyrrole synthesis, discussions on the mechanism having concluded that the isomeric hydroxy-enamines related to (**11**) and (**12**) are the species involved, as is probably the case when primary amines are used in place of ammonia.⁷ The isolation of structures (**6**) suggests a number of different possible mechanisms for the Paal-Knorr synthesis with ammonia; these are now being explored.

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