3-Hydroxypyrroles [Pyrrol-3(2*H*)-ones]

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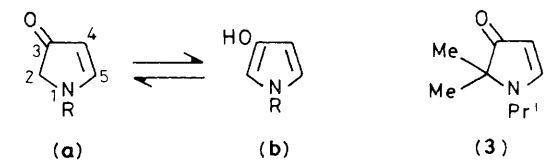
Simple 3-hydroxypyrroles are obtained by pyrolysis of appropriate aminomethylene Meldrum's acid derivatives: the unusual reactions of these compounds with acids, bases, and electrophiles is discussed.

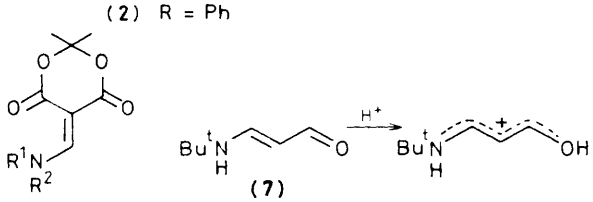
Despite the great importance in heterocyclic chemistry of the hydroxy (or oxo) function, simple examples in the pyrrole series are rare. Indeed, the only 3-hydroxypyrroles [pyrrol-3(2*H*)-ones] to be investigated in detail[1–3] are substituted at the potentially reactive 4- and 5-positions, and in just one study of *C*-unsubstituted derivatives the products were obtained only on a small scale, and were described as 'extremely unstable.'[4,5] In this paper, we extend our Meldrum's acid method[6] to the synthesis of (2),4,5-unsubstituted 3-hydroxypyrroles on a multi-gram scale and report some chemical properites of this fundamental heterocyclic system.

Thus, the *N*-alkyl compound (**1**) and the *N*-aryl compound (**2**)[5] are readily available in 38 and 63% yield respectively by flash vacuum pyrolysis (600 °C; 10^{-2} Torr) of the Meldrum's acid derivatives (**4**) and (**5**).† Although both hydroxypyrroles are somewhat sensitive to oxygen, they can be stored for long periods at −20 °C, and can be manipulated in air, without special precautions. For comparison, the 2,2-disubstituted compound (**3**)[7] is indefinitely stable in air at room temperature.



(a) (b) (3)

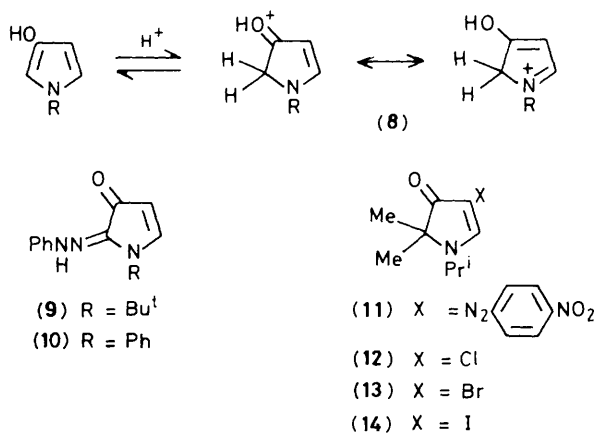
(**1**) R = Bu^t
(**2**) R = Ph



(**7**)

(**4**) R^1 = Me, R^2 = Bu^t
(**5**) R^1 = Me, R^2 = Ph
(**6**) R^1 = R^2 = Pr^i

† All new compounds are characterised by their spectra and by elemental analysis.

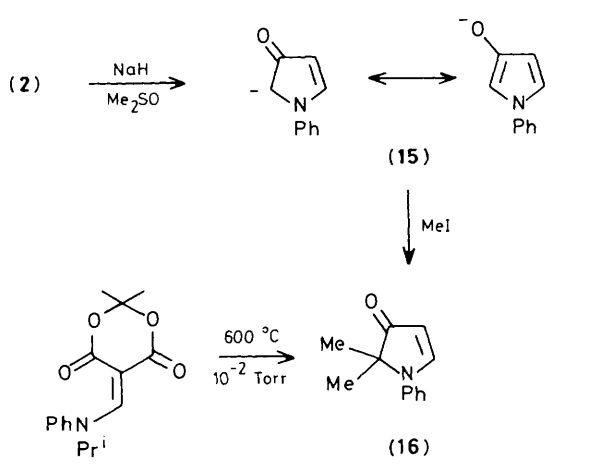


In accord with earlier work we have found that both (**1**) and (**2**)[4,5] exclusively adopt the keto tautomeric form (**a**) in non-polar solvents (*e.g.* $CDCl_3$), although in both cases the enol form (**b**) is predominant in polar solvents (*e.g.* CD_3SOCD_3) to the extent of 85—95%.

Pyrroles are notoriously sensitive to acids. In contrast, the hydroxypyrroles (**1**) and (**2**) dissolve in trifluoroacetic acid to give solutions which are unchanged after many days at room temperature. The ^1H and ^{13}C n.m.r. parameters of these solutions [and of the 2,2-dimethyl compound (**3**)] follow identical trends to those of the enaminal (**7**), which is known[8] to undergo *O*-protonation in acid. In the present case, such protonation generates a Wheland intermediate (**8**) for electrophilic substitution of the 3-hydroxypyrrole system, which is accordingly a stable species and directly observable under mild conditions. Its dynamic equilibrium with the neutral molecule is demonstrated by deuterium exchange reactions which show rapid incorporation at position 2 [(**1**): $t_{\frac{1}{2}} < 10$ min]. Remarkably, the exchange at position 4 is even faster ($t_{\frac{1}{2}} < 1$ min), whereas reaction at position 5 could not be detected *at all*, even after 24 h at 20 °C. This behaviour is reminiscent of the properties of the similar conjugated systems found in enaminones[9] and in 2,3-dihydro-1,4-diazepines.[10]

Other electrophilic reagents also react at positions 2 and 4. Thus (**1**) and (**2**) yield the 2-hydrazones (**9**) and (**10**) (50—60%) on treatment with benzenediazonium salts (*cf.* ref. 2). When this site is blocked, pyrrol-3(2*H*)-ones smoothly undergo diazo-coupling reactions to give 4-azo derivatives [*e.g.* (**11**) (63%)]. Similarly, the 4-halogeno-derivatives (**12**)—(**14**) are readily formed in 85—90% yield by reaction with *N*-halogenosuccinimides in methanol solution.

The reactions of 3-hydroxypyrroles with bases are complex, and result in reversible spectroscopic changes which are still



Scheme 1

under investigation. However, treatment of the *N*-phenyl derivative (**2**) with sodium hydride in dimethyl sulphoxide, then with an excess of iodomethane gave the 2,2-dimethyl derivative (**16**) as the major product (Scheme 1). Clearly, under these conditions, deprotonation of the hydroxypyrrole generates an anion (**15**) which behaves as an enolate rather than as an analogue of phenoxide. In agreement with this interpretation, 3-hydroxypyrroles are recovered unchanged after treatment with iodomethane–potassium carbonate in dimethylformamide, conditions which lead to quantitative *O*-alkylation of phenols.

We are grateful to the S.E.R.C. for a Research Studentship (to L. C. M.).

Received, 17th September 1984; Com. 1320

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