Formation of Aziridinones (α-Lactams) from Hydroxamic Derivatives

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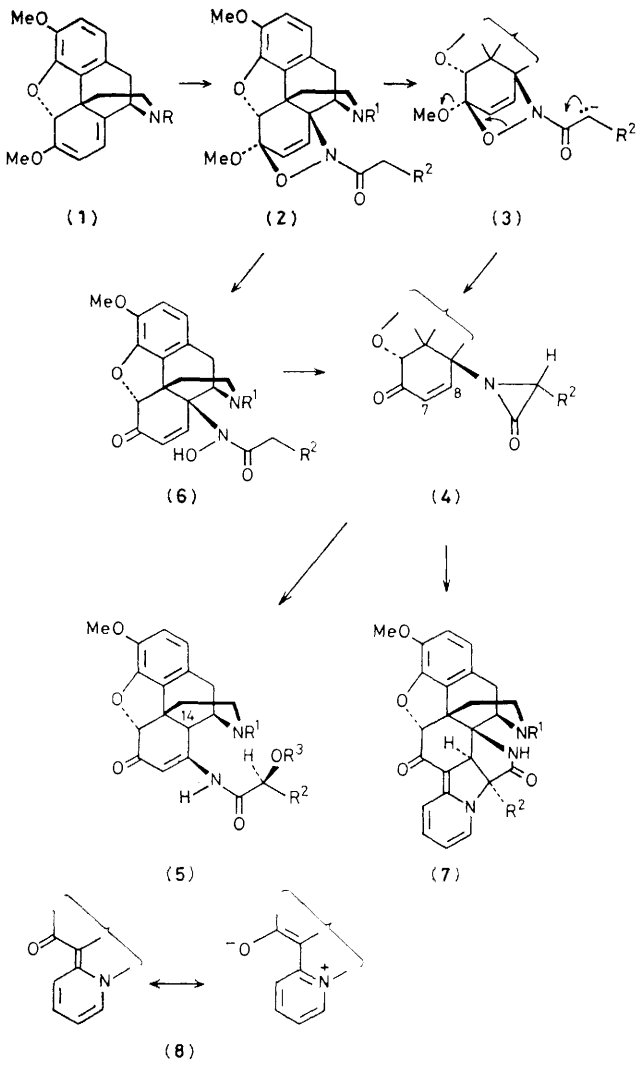
Various *NO*-disubstituted derivatives of chloroaceto- and phenylaceto-hydroxamic acid are shown to cyclise with base to give aziridinones with cleavage of the N–O bond, a process exemplified by an efficient synthesis of 1-t-butyl-3-phenylaziridin-2-one.

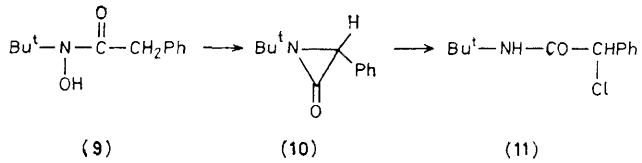
Thebaine (**1**; R = Me) readily forms cycloadducts [as (**2**)] with transient nitrosocarbonyl compounds generated *in situ* by oxidation of hydroxamic acids.[1] We now report reactions, believed to involve aziridinone (α-lactam) intermediates, which



occur when certain adducts of the type (**2**) are treated with alkoxides.

Treatment of *N*-t-butoxycarbonylnorthebaine (**1**; R = Bu^tOCO) with 2-chloroacetohydroxamic acid[2] and tetraethylammonium periodate, in the usual way,[1] gave the cycloadduct† (**2**; R^1 = Bu^tOCO, R^2 = Cl) (90%), m.p. 178—179 °C. This, with sodium ethoxide (4 mol. equiv.) in ethanol at room temperature, gave, unexpectedly, the diethyl acetal (**5**; R^1 = Bu^tOCO, R^2 = EtO, R^3 = Et) (20%), m.p. 205—206 °C. Similarly, the cycloadduct (**2**; R^1 = Me, R^2 = Ph),[3] m.p. 148—149 °C, with sodium methoxide (1 mol. equiv.) in methanol, gave the methyl ether (**5**; R^1 = R^3 = Me, R^2 = Ph) (37%), m.p. 179—180 °C. The structure and stereochemistry of this product were established unambiguously by an alternative synthesis from 14β-aminocodeinone[4] and (*S*)-α-methoxyphenylacetic acid[5] using *N*,*N*-dicyclohexylcarbodi-imide in dichloromethane. Conversion of the cycloadduct (**2**; R^1 = Me, R^2 = Ph) into the (*S*)-ether (**5**; R^1 = R^3 = Me, R^2 = Ph) must occur with high stereochemical control since the product was accompanied by only small amounts (<10%) of the diastereoisomer having the (*R*)-configuration in the amide side-chain. Furthermore, control experiments showed that slow epimerisation of the (*S*)-isomer (**5**; R^1 = R^3 = Me, R^2 = Ph), to give

† All new compounds (indicated by citation of m.p.) have been fully characterised spectroscopically and by elemental analysis.



approximately equal amounts of (*S*)- and (*R*)-forms, took place with extended reaction times.

The transformation of the acetals (**2**) into the ketones (**5**) under basic conditions, with concomitant attachment of a nucleophile at a remote site, appeared to imply the formation of aziridinones (**4**) as intermediates. Thus, formation of a carbanion (**3**), assisted by the α-substituent (R^2 = Cl or Ph), might be followed by intramolecular cleavage of the weak N–O bond to afford the aziridinone (**4**). Generation of the keto-group may be concerted, as shown, or take place by collapse of a hemi-acetal intermediate. The aziridinone ring would then be opened, at least in part, by attack by alkoxide at the α-carbon. We reasoned, therefore, that aziridinones should be formed with similar or greater facility from hydroxamic derivatives having electron-withdrawing groups attached to oxygen. Accordingly, the hydroxamic acid (**6**; R^1 = Me, R^2 = Ph), m.p. 167—169 °C, prepared by hydrolysis of (**2**; R^1 = Me, R^2 = Ph), was treated with toluene-*p*-sulphonyl chloride in dry pyridine at room temperature. The pyridine was evaporated off and the gummy residue was dissolved in methanol containing sodium methoxide (4 mol. equiv.). A golden-yellow product (**7**; R^1 = Me, R^2 = Ph) (30%), m.p. 285 °C (decomp.), slowly crystallised from the mixture which was kept at room temperature overnight. The presence of an anhydro-base moiety (**8**) in (**7**) accounted both for the latter's colour [λ_{max} 435 nm (ε 7150)], which was discharged by trifluoroacetic acid and regenerated by subsequent addition of alkali, and the abnormally low[6] carbonyl stretching frequency (1485 cm^{-1}) and carbonyl chemical shift (δ 178.3 p.p.m.). The remainder of the structure was deduced from spectroscopic and mechanistic considerations. We believe that the hydroxamic acid (**6**) is first converted, as predicted, into the aziridinone (**4**). Attack by the solvent pyridine on the aziridinone α-carbon then gives an intermediate pyridinium salt. Removal of the α-proton of the latter with base generates a pyridinium ylide which adds, as a 1,3-dipole, to the 7,8-double bond. Finally, dehydrogenation takes place to give the fully conjugated anhydro-base.

The simple hydroxamic acid (**9**)‡ was chosen as a model to clarify the role of aziridinones in the foregoing reactions. The reaction of (**9**) with toluene-*p*-sulphonyl chloride and triethylamine, in dichloromethane at room temperature, was monitored by i.r. spectroscopy. A band at 1850 cm^{-1}, attributed to the aziridinone (**10**), slowly appeared but began to diminish in intensity before all of (**9**) had been consumed. The chloro-compound (**11**) was isolated from the reaction mixture. However, when (**9**) was treated with trifluoromethanesulphonic anhydride and triethylamine in dichloromethane at −70 °C, the labile aziridinone (**10**)[7] was formed almost quantitatively and was isolated (97%) in crystalline form without difficulty.

Aziridinones[8] are most commonly prepared by 1,3-elimination of hydrogen halides, with strong bases, from α-halogeno-amides [as (**11**)]. Occasionally, elimination of hydrogen

‡ The hydroxamic acid (**9**), m.p. 129—130 °C, was prepared from *N*-t-butylhydroxylamine in chloroform by successive treatment with chlorotrimethylsilane and triethylamine and then phenylacetyl chloride and triethylamine; *cf.* P. F. Alewood, S. A. Hussain, T. C. Jenkins, M. J. Perkins, A. H. Sharma, N. P. Y. Siew, and P. Ward, *J. Chem. Soc., Perkin Trans.* 1, 1978, 1066, who cite m.p. 85—86 °C.

chloride from *N*-chloroamides has been employed.[7] To our knowledge, the formation of aziridinones from hydroxamic acid derivatives has not been described previously.

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