Tetrahedron Letters,Vol.26,No.35,pp 4245-4246,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

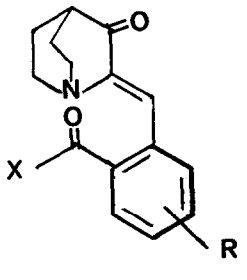
REARRANGEMENT OF 2-[1(3H)-OXODIHYDROBENZO[c]FURAN-3-YL] QUINUCLIDIN-3-ONES TO TETRAHYDROBENZO[b]QUINOLIZINES. A NOVEL SYNTHESIS OF BENZO[b]QUINOLIZINE RING SYSTEMS.

Jiban K. Chakrabarti* and David J. Steggles
Lilly Research Centre Limited, Windlesham, Surrey, GU20 6PH, England

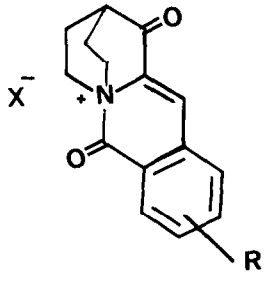
Abstract: A new two step synthesis of benzo[b]quinolizine ring systems via the rearrangement of 2-[1(3H)-oxodihydrobenzo[c]furan-3-yl] quinuclidin-3-ones is described.

A quinolizine skeleton and its benzoanalogues are found in many alkaloids. Some of these and their synthetic derivatives possess interesting pharmacological properties[1]. In view of our interest in certain benzo[b]quinolizine derivatives, we needed a scheme to provide an easy access to this ring system with built-in functionalities which should be amenable to further structural elaboration.

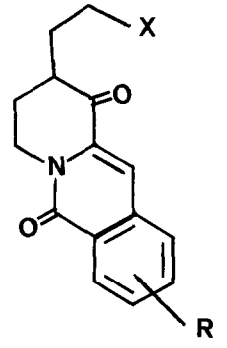
Since the nitrogen lone pair of electrons in quinuclidine is sp^3-hybridised and is free from steric hindrance, we envisaged an intramolecular quaternisation reaction at this nitrogen with a strategically placed group as shown in (1). A nucleophilic cleavage of the quaternary salt (2) would be expected to give the desired product (3). A similar rearrangement of benzylidene quinuclidinones to tetrahydropyridoindoles, reported previously[2], also lends support to the above. This report is concerned with the synthesis of 2-[1(3H)-oxodihydrobenzo[c]furan-3-yl]quinuclidin-3-ones (4) and their rearrangement to the corresponding tetrahydrobenzo[b]quinolizines (3).



1

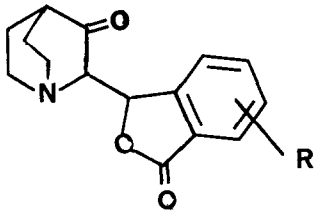


2

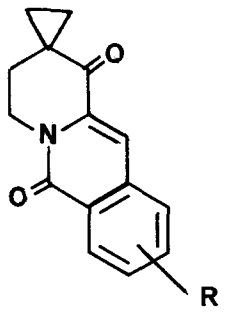


3

2-[1(3H)-Oxodihydrobenzo[c]furan-3-yl]quinuclidin-3-ones [4a, R=H; m.p. 157-8°C (ethanol)] and its dimethoxy analogue [4b, R = 3,4-OCH_3; m.p. 173-4°C (ethanol)] were obtained in good yields (~80%) from a reaction of quinuclidin-3-one with appropriate 2-carboxybenzaldehydes in the presence of sodium ethoxide in ethanol. (4) on treatment with PX_3 (X=Cl or Br) in refluxing benzene rearranged to the corresponding halides [3a, X = Cl, R = H; m.p. 116-8°C (ethylacetate-n-hexane); 3b, X = Cl, R = 3,4-OCH_3; m.p. 147-8°C (ethylacetate-n-hexane); 3c, X = Br, R = H; m.p. 131-2°C (ethanol)]. These haloethyl ketones undergo a facile 1,3 elimination under mild basic conditions to give cyclopropyl ketone [5, R = H, m.p. 126 - 8°C, (ethylacetate-n-hexane)].



4



5

The rearrangement probably involves a quaternary intermediate (2), which is cleaved by the halide ions (X^-) to give the product (3). The formation of (2) can be postulated by opening of the lactone ring under the influence of PX_3 to give an intermediate (1a, X = O^+HPX_2 X^-) which is set for an intramolecular elimination leading to (2). This would probably be a preferred route, although a reaction by the competing halide ions as nucleophiles resulting in a carbonyl halide (1b, X = Cl or Br) as an alternative precursor is also tenable.

Compounds (3), (4) and (5) were all characterised by using spectroscopic methods (ir, ^1H, ^{13}C-nmr and ms). Elemental microanalyses were within ±0.4% of the calculated values.

Acknowledgement

We thank Dr. D.M. Rackham and Mrs. S. Morgan for the spectroscopic characterisation and Miss J.E. Brown for mass spectra of the compounds.

References

1. R.K. Hill, Chemistry of the Alkaloids, ed. S.W. Pelletier, van Nostrand Reinhold, New York, p414 (1970).
2. D.L. Coffen, D.A. Katonak and F. Wong, J.Am.Chem.Soc., 96, 3966 (1974).

(Received in UK 17 June 1985)