Tetrahedron Letters,Vol.22,No.48,pp 4839-4842,1981
Printed in Great Britain

0040-4039/81/484839-04$02.OC

2-[2-(1,4-BENZODIOXANYL)]-2-IMIDAZOLINE HYDROCHLORIDE

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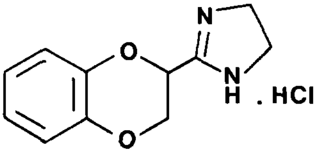
A new synthesis of 2-[2-(1,4-benzodioxanyl)]-2-imidazoline hydrochloride from 2-cyano-benzodioxan is described and the previously claimed route to this compound is shown to give a formula isomer, ie. 2-methyl--2-[2-(1,3-benzodioxolyl)]-2-imidazoline hydrochloride.

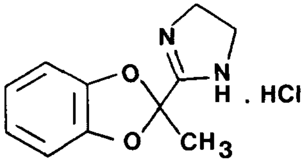
The title compound (1) was first claimed to possess antihypertensive activity by Krapcho and Lott in a US Patent[2] to the Olin Mathieson Chemical Corporation in 1961. More recently a publication[3] has appeared confirming the hypotensive activity for this claimed structure (1) which had been prepared following the original patent[2] procedure.



(1)

The imidazoline (1)[4] was prepared in our laboratories, by a different experimental route, as part of an investigation into potential centrally acting agents, and the observed melting point of 205-207° (crystallisation from isopropanol) differed significantly from the previously reported[2] melting point of ~ 243° (decomp. crystallisation from isopropanol).

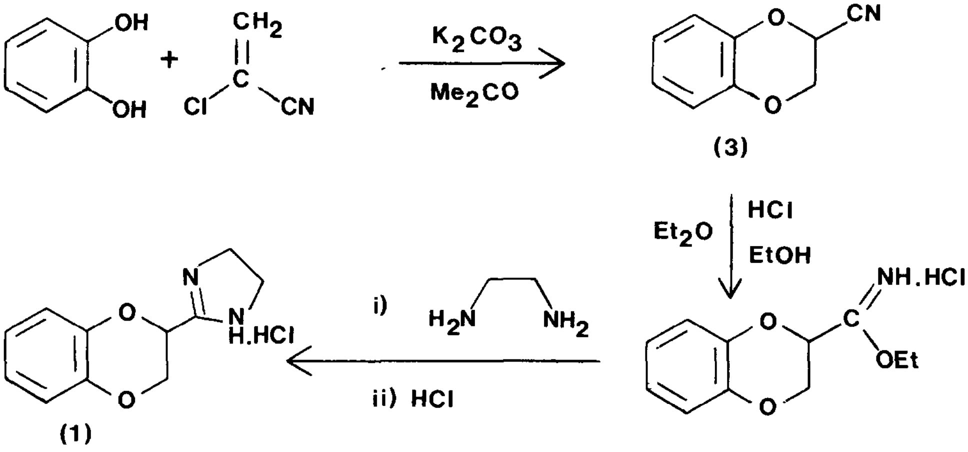
Re-examination of the patented procedure[2] indeed produced a compound with the claimed melting point of ~ 243° but its ^{1}H-NMR spectrum clearly shows that the correct structural representation is (2), i.e. a formula isomer of (1). Thus a 3H singlet at τ 7.8 corresponding to the methyl group in (2) is the dominant feature of the spectrum. In contrast the imidazoline (1) shows the dioxan ring protons as two distinct multiplets in the region τ 4.4 and 5.4.



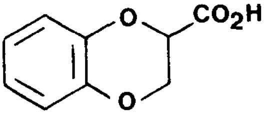
(2)

Comparison of our synthetic route to (1) with that published can explain the formation of different products: thus a conventional "Pinner-Type"[5] Synthesis with the nitrile (3), obtained from catechol and chloroacrylonitrile (Scheme 1), gives (1) in high yield (overall yield from catechol ~ 50%) using relatively mild experimental conditions.

SCHEME 1



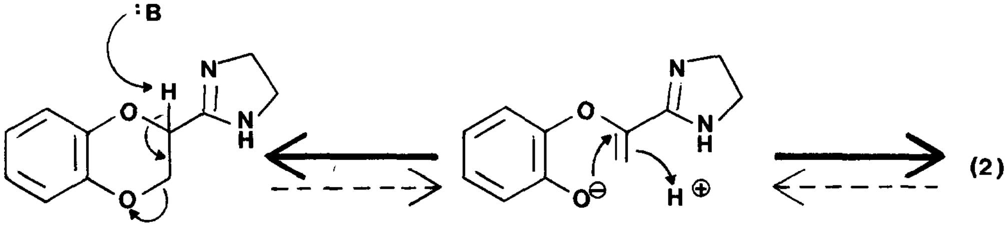
In contrast, preparation of the patented example[2] involves reaction of the acid (4) with excess ethylenediamine at elevated temperatures (~120° for $>$24 hours followed by a vacuum distillation (b.p. ~160°/0.1mm); we have shown, by the use of HPLC, that the product (2) is formed during the distillation and consequently this step is an integral part of the reaction process. Under these conditions it is possible to visualise formation of the 1,3-benzodioxole structure (2) from (4) probably by base catalysed ring-opening followed by an alternative mode of ring closure and this has been



(4)

confirmed by dry distillation of (1) at such temperatures when some conversion to (2) occurs. It would seem that at high temperatures the benzodioxole ring system (i.e. 2) is the thermodynamically more stable isomer. A mechanistic scheme involving the base catalysis for the interconversion of (1) ⟶ (2) is shown in Scheme 2.

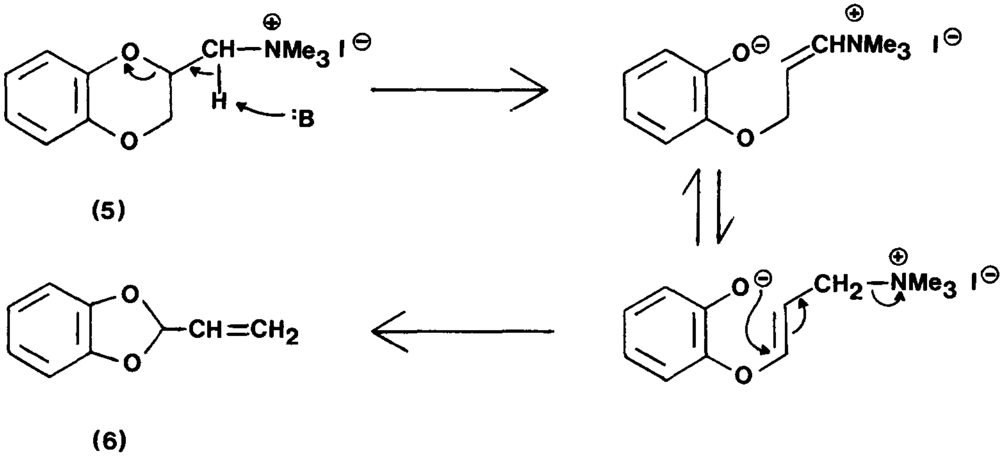
SCHEME 2



(1)

Precedence for this type of ring contraction also exists in the literature; thus Katritzky and co-workers[6] have reported that the benzodioxan amine (5) undergoes conversions to the corresponding benzodioxole (6) under Hoffman elimination conditions (Scheme 3).

SCHEME 3



Biologically the benzodioxan-imidazoline (1) differs substantially from its structural isomer (2) and has been the subject of further investigations, the results from this work will be reported elsewhere.

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(Received in UK 7 September 1981)