

Selective Reduction of Pyridazin-3-ones and Ring Contraction to Pyrrolidin-2-ones and 3-Pyrrolin-2-ones

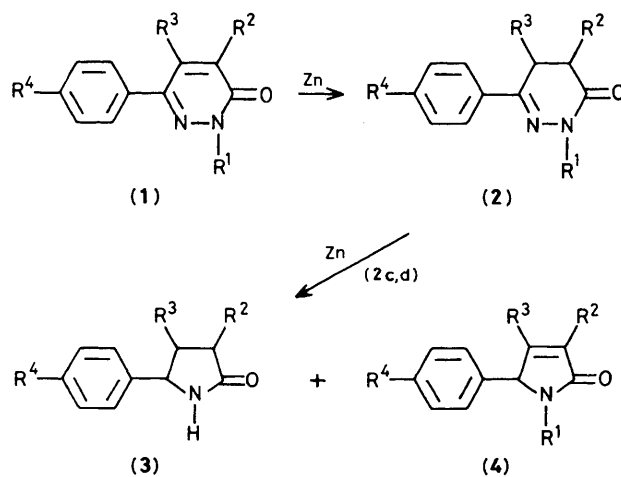
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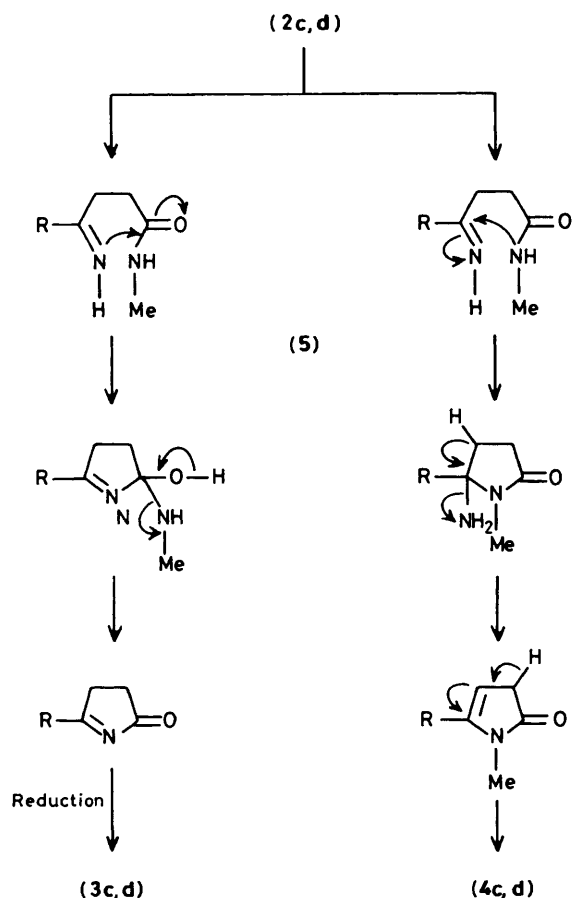
Reduction of pyridazin-3-ones (**1a—d**) with zinc dust in acetic acid affords selectively 4,5-dihydropyridazin-3-ones (**2a—d**), but *N*(2)-substituted (**1**) react further with excess of zinc to give equal amounts of pyrrolidin-2-ones (**3**) and 3-pyrrolin-2-ones (**4**).

Pyridazin-3-ones are of considerable interest as potential new medicines for the treatment of diseases of the heart, blood vessels, and circulation.¹ 4,5-Dihydropyridazin-3-ones possess much greater biological activity than the corresponding aromatic pyridazin-3-ones.² This communication describes the scope of a selective reduction of pyridazin-3-ones (**1**) to the more valuable derivatives (**2**) and embraces a novel selective ring contraction.

Reduction of pyridazin-3-ones with LiAlH₄ removes³ both ring double bonds, together with the carbonyl group. With NaCNBH₃ only the C=N moiety is reduced.⁴ Catalytic reduction affords mixtures and aromatic rings are partially reduced.⁴ We report that reaction of (**1a—d**) (1 mol) with zinc dust (1 mol) in boiling MeCO₂H during 3 h gives (**2a—d**) in yields of 75–85%, after chromatography on silica gel. The reaction was not affected by variation of the ring substituents (**1a—d**) at the available 2, 4, 5, and 6 substitution positions. Structures were supported by characteristic microanalyses and mass spectra, and had ¹H n.m.r. signals with the correct multiplicity and coupling for 4,5-dihydro derivatives. In (**2b**) where R² and R³ were both not H, ¹H n.m.r. showed that mixtures of isomers were present.



- a; R¹ = R³ = H; R² = PhCH₂; R⁴ = MeCONH
 b; R¹ = H; R² = PhCH₂; R³ = Me; R⁴ = MeCONH
 c; R¹ = R³ = Me; R² = H; R⁴ = MeCONH
 d; R¹ = Me; R² = R³ = R⁴ = H



Scheme 1

When the reaction was carried out during 6 h with Zn (3 mol), the acidic pyridazinones (**1a,b**) were reduced as before. In contrast the *N*(2)-substituted derivatives (**1c,d**) underwent a novel ring contraction to give two products [(**3c,d**) 50% and (**4c,d**) 50%]. The structure of (**3c**) (m.p. 220 °C; m/z 231, M^+) was assigned by ^1H n.m.r. and an alternative synthesis from the corresponding benzoylpropionic acid by reductive amination with NaCNBH_3 and MeCO_2NH_4 . The structure of (**4c**) (m.p. 170 °C; m/z 245, M^+) was deduced by ^1H n.m.r. and its 3,4-double bond was not reduced by further reaction with Zn.

A similar ring contraction of phthalazinones by zinc has been described⁵ and subsequently examined⁶ by polarography. Polarographic reduction⁶ of a number of diazoheterocycles suggests that in some cases N–N bond cleavage can take place without reduction of the azomethine moiety and that this occurs when phthalazinones undergo reductive ring contraction. We thus speculate that the mechanism of pyridazinone ring contraction involves N–N bond cleavage to give the intermediate azomethine (**5**). Two distinct ring closure pathways could thereby lead to the five member ring products (Scheme 1) which were isolated.

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References

- 1 J. Griess, H. König, R. Kretzschmar, J. Kunze, R. O. Lehmann, D. Lenke, and M. Thyges, *J. Med. Chem.*, 1983, **26**, 800.
- 2 W. V. Curran and A. Ross, *J. Med. Chem.*, 1974, **17**, 273.
- 3 R. Y. Levina, N. K. Mamaeva, Y. S. Shabarov, and N. I. Vasilev, *Zh. Obshch. Khim.*, 1963, **33**, 1206.
- 4 M. L. C. Carter, S-S. P. Chou, S. N. Ege, D. F. Ortwine, and J. F. Richman, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1252.
- 5 S. Racine, *Justus Liebigs Ann. Chem.*, 1887, **239**, 78.
- 6 H. Lund, *Faraday Discuss. Chem. Soc.*, 1968, **45**, 193.