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A NOVEL RING CONTRACTION OF A PYRIDAZINONE TO A PYRAZOLE. A POSSIBLE PYRIDAZYNE INTERMEDIATE

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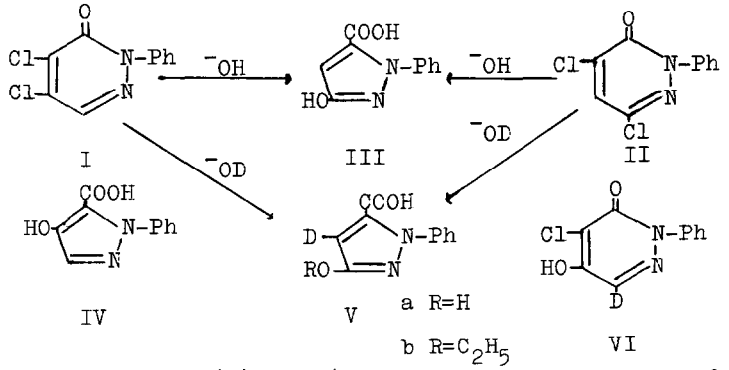
In previous papers[1] we have demonstrated that 2-phenyl-4,6-dichloro-3(2H)-pyridazinone(II) undergoes ring contraction to 2-phenyl-5-hydroxypyrazole-3-carboxylic acid(III) upon treatment with aqueous sodium hydroxide. Contrary to our expectation, it has been found that similar treatment of 2-phenyl-4,5-dichloro-3(2H)-pyridazinone(I) resulted in the formation of the same acid(III) instead of the expected product, 2-phenyl-4-hydroxypyrazole-3-carboxylic acid(IV).

In this communication we present evidence which leads us to propose a mechanism involving a new type of hetaryne intermediate for this unusual ring contraction.



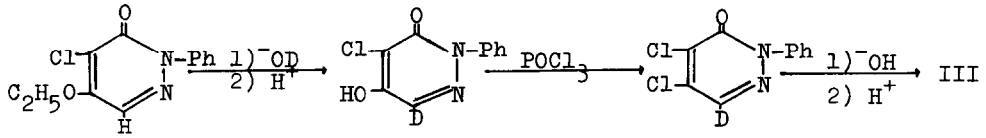
When a suspension of (I) in 5% NaOD-D_2O was heated to 130° for about 1.5 hr and the resulting clear solution was acidified with mineral acid, 4-d-carboxylic acid(Va), mp 270° dec., was obtained in 85% yield. The structure

of (Va) was established by NMR (absence of the C_4-H signal at τ 3.68 noted in the spectrum of (III)), and other physicochemical data. Careful chromatography accomplished the separation of 6-d-2-phenyl-4-chloro-5-hydroxy-3(2H)-pyridazinone(VI)(yield 7%) deuterated to the extent of about 15%[2] from the crude reaction product. (III) was found not to be converted to (Va) under the same conditions. Treatment of the reaction mixture with diethyl sulfate, without prior acidification, afforded 4-d-2-phenyl-3-ethoxycarbonyl-5-ethoxypyrazole (Vb), mp 93°, in 40% yield.

The 4,6-dichloro isomer (II) was also converted into (Va) in 90% yield under exactly the same conditions as the previous case.

These results provide good evidence that the ring contraction involves an enolizable intermediate and is accomplished solely by the action of alkali, the function of the acid being limited to the formation of the free acid (III) or (Va) from its salt.

When 2-phenyl-4-chloro-5-ethoxy-3(2H)-pyridazinone (VII) was treated with boiling 10% NaOD-D_2O for 30 hr, (VI) deuterated to the extent of about 75%[2] was obtained in 92% yield. (VI) was easily converted into 6-d-2-phenyl-4,5-dichloro-3(2H)-pyridazinone (VIII) with deuterium content of about 75% by the action of phosphorous oxychloride. Treatment of (VIII) with boiling 5% sodium hydroxide gave deuterium free (III).

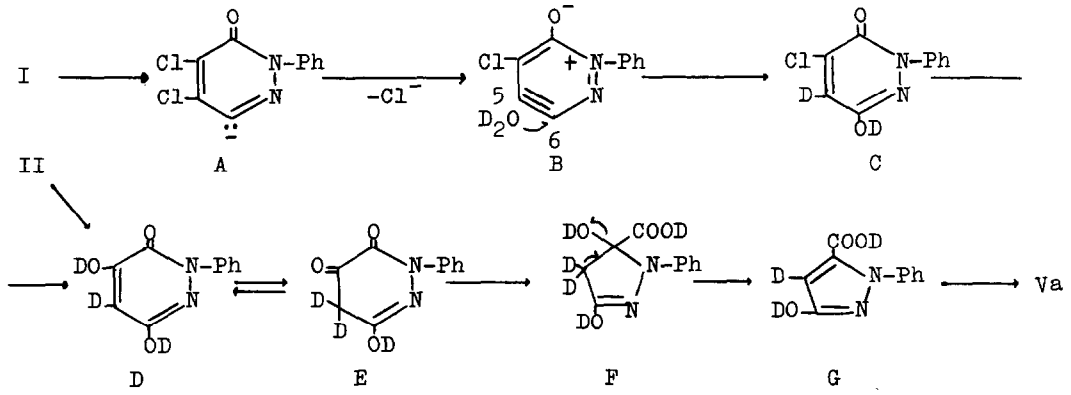


VII VI VIII

Although the nature of the 5 substituent and the conditions for the conversion of (VII) into (VI) are different from those of the ring contraction reaction, nevertheless the results demonstrate that the C_6-proton in this system is acidic[3]. Furthermore, the formation of deuterium free (III) from (VIII) again indicates that the ring contraction involves an enolizable intermediate.

From the above experimental results, we propose the mechanism of the ring

contraction (I) → (Va)(or III) shown in the scheme below. We cannot be sure whether or not the process (E) → (F) involves ring opening, however, it may be significant that no ring opened products could be isolated from the reaction mixture. In the case of (II) → (Va)(or III), the enolizable intermediate (D) can be derived from (II) via simple nucleophilic displacement of the C_4- and C_6-chlorines by deuteroxide ion. The course of the conversion (I) → (Va)(or III) involves an anomalous substitution leading to the formation of the key intermediate (D) from (I).



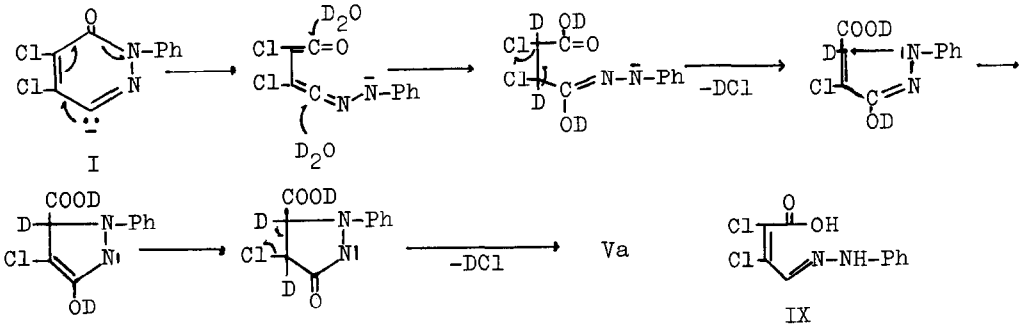
It seems most reasonable to propose that the anomalous substitution proceeds via an elimination - addition mechanism, the so-called hetaryne mechanism, as shown in the scheme. A pyridazyne intermediate (B) is generated via initial proton abstraction at the 5-position of (I) to form a carbanion (A) which then loses chloride ion.

Obviously, strong support for this hetaryne mechanism would be the isolation of an intermediate such as (C) or (D). Intermediate (C) was prepared independently. Upon subjecting it to the ring contraction conditions, it was converted very rapidly to the product (Va)(or III). Thus it would appear to be impossible to isolate such intermediates.

As mentioned previously, 5% NaOD-D_2O treatment of (I) gave the by-product (VI)(deuterium content 15%). Deuterium exchange of the C_6-proton in 2-phenyl-4-chloro-5-hydroxy-3(2H)-pyridazinone(cf. VI) required more drastic conditions (140-150°, 24 hr). Thus the deuterium content of (VI) suggests that (VI) is

formed both via the addition of deuterium oxide to the 5 position of the pyridazyne (B) and via simple nucleophilic displacement of the C_5-chlorine of (I) by deuteroxide ion.

Another conceivable mechanism for the unexpected ring contraction is the ring opening process as shown below.



This mechanism would also account for the observed labelling results. Although at present the evidence does not permit us to exclude completely this mechanism, the following facts make us favor the hetaryne mechanism rather than the ring-opening mechanism: 1) no ring opened products could be isolated. 2) mucochloric acid phenylhydrazone (IX) did not afford (Va)(or III) upon treatment with 5% NaOH or 5% NaOD.

Footnotes and References

1) Y.Maki and K.Obata, Chem.Pharm.Bull.(Tokyo), 12, 176 (1964), and preceeding papers.

2) The deuterium exchange ratios were determined by NMR spectroscopy by integration of the C_6 proton signals (C_6-H in V: τ 2.08; C_6-H in VII: τ 1.73) with those due to the aromatic protons.

3) Cf. A.R.Katritzky and I.Pojarlieft, J.Chem.Soc.(B), 873 (1968).