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The Ring Contraction of Pyridazinones to Pyrazoles. VI.[1]

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Upon treatment of 2-phenyl-4,5-dichloro-3(2H)-pyridazinone (I) with sodium alkoxides, a ring contraction product, 1-phenyl-4-alkoxy-5-alkoxycarbonylpyrazole (III), was obtained as a major product. From the available data, a mechanism for the ring contraction was proposed. A most interesting finding is that formation of III does not involve an anomalous substitution as has been observed in the ring contraction of I to 1-phenyl-3-hydroxypyrazole-5-carboxylic acid (II) upon treatment with aqueous sodium hydroxide.

Previous work[3] in this series has shown that when a suspension of 2-phenyl-4,5-dichloro-3(2H)-pyridazinone (I) in aqueous sodium hydroxide is heated, it undergoes an unusual ring contraction leading to 1-phenyl-3-hydroxypyrazole-5-carboxylic acid (II). We have suggested a possible mechanism[4] for this remarkable ring contraction, involving initial C_6-carboanion formation followed by generation of pyridazyne intermediate, although the occurence of an alternative ring opening process after the C_6-carboanion formation can not be excluded completely (see Chart 1). The behavior of 2-phenyl-3(2H)-pyridazinones having 5-substituents other than chlorine against sodium hydroxide has also be examined. When these compounds were treated with sodium hydroxide, the unusual ring contraction has not been observed.[1]

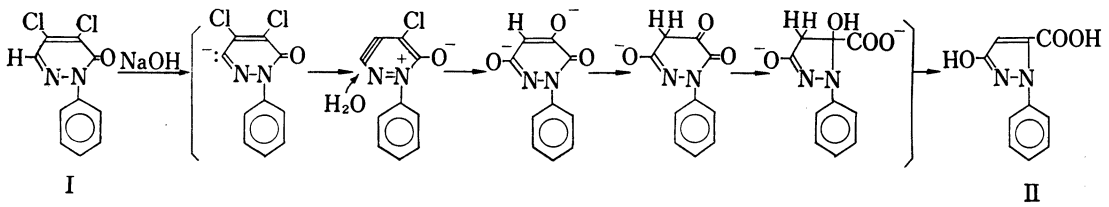


Chart 1

The present work was undertaken to determine whether the ring contraction of I would take place by employing sodium alkoxides instead of sodium hydroxide. It was found that treatment of I with alkoxide ion caused its ring contraction to 1-phenyl-4-alkoxy-5-alkoxycarbonylpyrazole (III) in a manner different from the previous case (I—II). This is a new type of ring contraction of a pyridazinones to a pyrazole.

We describe here this new observation and discuss a possible mechanism for the ring contraction.

A solution of I (1 mole) in ethanol containing sodium ethoxide (4 moles) was heated for 7 hr. Careful separation of the reaction products was carried out and six compounds were isolated: IIIa (30%), 2-phenyl-4,5-diethoxy-3(2H)-pyridazinone (IVa)[5] (20%), ethyl 1-chloro-

1) Part V: Y. Maki and M. Takaya, *Chem. Pharm. Bull.* (Tokyo), **19**, 1635 (1971).
2) Location: *a) Sakanoshita, Mitahora, Gifu*; *b) Yasu, Shiga.*
3) Y. Maki and K. Obata, *Chem. Pharm. Bull.* (Tokyo), **12**, 176 (1964).
4) Y. Maki, G.P. Beardsl ey and M. Takaya, *Tetrahedron Letters*, **1971**, 1507.
5) T. Takahashi and Y. Maki, Japan Patent, 42-4154 (1967).

2-formyl-2-ethoxyacrylate phenylhydrazone (Va) (15%), 2-phenyl-4-chloro-5-hydroxy-3(2H)-pyridazinone (VI) (5%), 2-phenyl-4-ethoxy-5-hydroxy-3(2H)-pyridazinone (VIIa) (8%), and 2-phenyl-4-chloro-5-ethoxy-3(2H)-pyridazinone (VIIIa) (7%) (see Chart 2).

The structure of the major product, IIIa (mp 101°), was fully confirmed by the comparison of its physicochemical data with those of the isomeric 1-phenyl-3-ethoxy-5-ethoxycarbonylpyrazole (IX) (mp 89°), prepared upon treatment of II with diethyl sulfate.[3] Both compounds showed an ester carbonyl band at 1730 cm^{-1} in their infrared (IR) spectra. In their nuclear magnetic resonance (NMR) spectra, the C_3-proton signal of IIIa (δ 7.26) appears in a downfield compared with the C_4-proton signal of IX (δ 6.41) as expected.

All physicochemical data for Va are consonant with the ring opened structure, *e.g.*, the presence of an NH grouping was supported by its IR spectrum (3300 cm^{-1}) and NMR spectrum (δ 10.59). Va was also obtained (together with IIIa, IVa, VI, and VIIa) upon treatment of VIIIa with boiling ethanol containing sodium ethoxide.

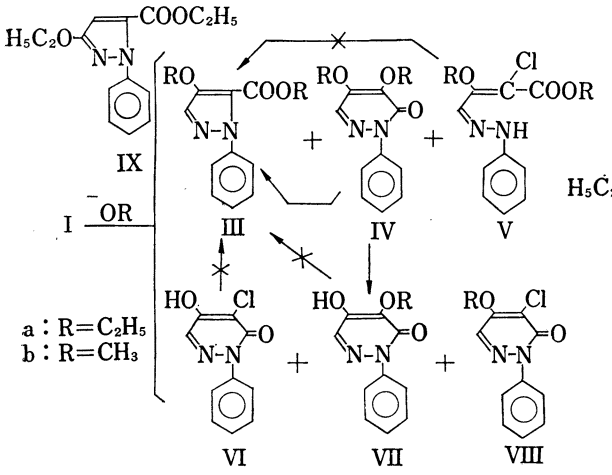


Chart 2

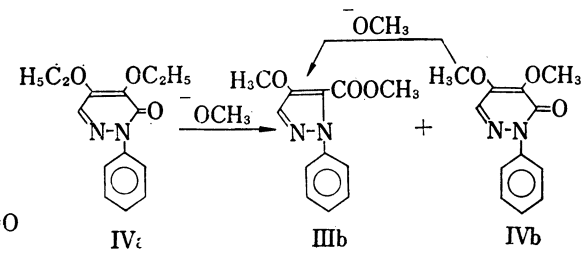


Chart 3

IVa was converted to VIIa by the action of aqueous sodium hydroxide. The assignment of structure, VIIa, is based on the following observations: 1) Its IR spectrum shows a lactam carbonyl band (1615 cm^{-1}) and an enolic hydroxy band (3175 cm^{-1}); 2) The compound gives a possitive ferric chloride test; 3) Its NMR spectrum shows a signal (δ 7.82) due to the C_6-proton adjacent to a ring nitrogen; and 4) In the 2-phenyl-3(2H)-pyridazinones nucleophilic attack at the C_5-position is favored over attack at the C_4-position.[3]

(IVa),[5] (VI),[3] and (VIIIa)[3] were identical in every respect with authentic samlpes.

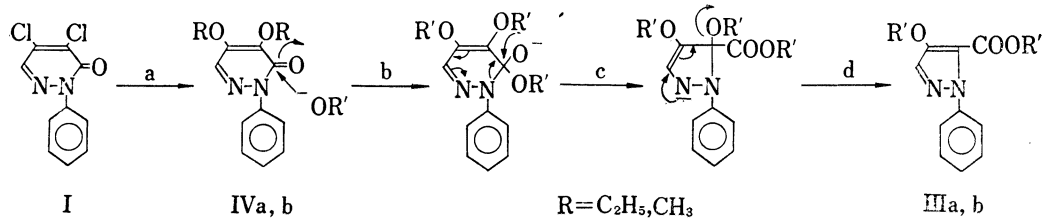
Similar treatment of I with sodium methoxide resulted in the formation of (IIIb), (IVb), (Vb), (VI), (VIIb), and (VIIIb).

When Va, VI, and VIIa were allowed to react with sodium ethoxide under the same conditions as the previous cases, no formation of the ring contraction product, IIIa, was observed. However, IVa was converted to IIIa in 60% yield by analogous treatment. These observations readily accommodate IVa as an intermediate in the ring contraction of I to IIIa.

Treatment of IVa (1 mole) with boiling methanol containing sodium methoxide (1.5 moles) for 0.5 hr led to the formation of 1-phenyl-4-methoxy-5-methoxycarbonylpyrazole (IIIb) (60%) and 2-phenyl-4,5-dimethoxy-3(2H)-pyridazinone (IVb) (25%). IVb also gave the ring contraction product, IIIb, by prolonged treatment with sodium methoxide (reflux for 8 hr).

These experimental results clearly indicate that the ring contraction of IVa to IIIb involves an alkoxide exchange reaction[6] and again support the intermediary of IVa and IVb in the ring contraction.

For an explanation of this interesting ring contraction, we propose the mechanism outlined as shown in Chart 4. This mechanism consists of formation of the key intermediate, IV, (step a), attack of an alkoxide ion at position 3[7] (step b), the ring contraction process (step c)[7] and elimination of alcohol (step d). The electron attracting effect of a ring nitrogen (N_1) may play an important role for the ring contraction (step c).



I IVa, b R=C_2H_5,CH_3 IIIa, b

Chart 4

A noteworthy observation in the present work is that no 3-alkoxypyrazoles (*cf.* IX) but rather III formed in the reaction of I with sodium alkoxide. Thus the present reaction dose not involve the anomalous substitution realized in the reaction of I with aqueous sodium hydroxide (I→II).

The following considerations may account for the above difference. The latter reaction (I→II) takes place in a highly polar medium. Under these conditions initial proton abstraction to form a C_6-carboanion may be favored. The anion may then loss chloride ion to generate the pyridazine intermediate, as suggested previously. Contrary to this, the present reaction (I→III) occurs in a less polar medium. Displacement of the C_5-chlorine of I by alkoxide ion (a better nucleophile than hydroxide ion) occurs to give 2-phenyl-4-chloro-5-alkoxy-3(2H)-pyridazinones (VIIIa,b) and then the key intermediates, IVa,b. The formation of IVa,b precludes the initial C_6-carboanion formation and subsequent reactions. In fact, when IVa was treated with boiling C_2H_5ONa–C_2H_5OD for 10 hr, the resulting IIIa dose not contain deuterium at position 3. The differences in reaction course may also be related to the fact that conversion (I→II) is carried out as a heterogeneous suspension whereas the present reaction (I→III) takes place in a homogeneous solution.

In any event the occurence of the unusual conversion (I→II) depends strongly upon the nature of the C_5-substituent in the pyridazinone and also upon reaction conditions employed.

Experimental

Reaction of 2-Phenyl-4,5-dichloro-3(2H)-pyridazinone (I) with Sodium Alkoxides——I (10 g) was refluxed in a solution of 4.1 g of metallic Na dissolved in 140 ml of EtOH for 7 hr. After cooling, the insoluble substance was collected by filtration, and recrystallized from EtOH to give 0.7 g of VIIIa[3] as colorless needles, mp 136—137°. The filtrate was concentrated and diluted with water. The resulting precipitate was collected by filtration and recrystallized from a mixture of water and EtOH (1:1) to give 1.9 g of IVa[5] as colorless needles, mp 80°. VIIIa and IVa were identical in every respect with authentic samples.[3,5] The alkaline filtrate was extracted with 150 ml of chloroform. After the chloroform was removed by evaporation, the residue was recrystallized from isopropyl ether to give 2.9 g of IIIa as colorless needles, mp 101°. UV λ_{max}^{EtOH} mμ (ε): 248 (16700), 320 (4900). IR ν_{max}^{Nujol} cm^{-1}: 1735 ($COOC_2H_5$). NMR

6) Alkoxide exchange reactions in pyridazines have been reported. (See, for example, P. Coad, R.A. Coad and J. Hyepock, *J. Org. Chem.*, **29**, 1751 (1964).) Upon treatment of IIIa with sodium methoxide, exchange of the C_4-ethoxy group in the pyrazole ring by methoxide anion did not occur.

7) In the previous paper (reference 1), we suggested that the ring contraction of 2-phenyl-4-chloro-5-methylsulfonyl (or methylthio)-3(2H)-pyridazinone to 1-phenyl-4-methylsulfonyl (or methylthio) pyrazole-5-carboxylic acid may involve similar process.

($CDCl_3$) δ: 7.28 (1H, singlet, C_3-H), 4.55 (2H, quartet, $O\underline{CH_2}CH_3$), 4.33 (2H, quartet, $COO\underline{CH_2}CH_3$), 1.45 (3H, triplet, $OCH_2\underline{CH_3}$), 1.38 (3H, triplet. $COOCH_2\underline{CH_3}$). Mass Spectrum *m/e*: 260 (M^+), 245 (M^+-CH_3), 231 (M^+-C_2H_5). *Anal.* Calcd. for $C_{14}H_{16}O_3N_2$: C, 64.60; H, 6.20; N, 10.78. Found: C, 64.55; H, 6.23; N, 10.50.

The mother liquor was neutralized with 10% HCl and cooled to 10°. The precipitate thus formed was recrystallized from MeOH to give 1.5 g of Va as colorless needles, mp 159—160°. UV λ_{max}^{EtOH} mμ (ε): 214.5 (12700), 275 (13100). IR ν_{max}^{Nujol} cm^{-1}: 3250—3300 (NH), 1730 ($COOC_2H_5$). NMR (DMSO-d_6) δ: 10.59 (1H, broad singlet, NH), 5.00 (1H, singlet, C_3-H). Mass Spectrum *m/e* 296 (M^+), 261 (M^+-Cl). *Anal.* Calcd. for $C_{14}H_{17}O_3N_2Cl$: C, 56.55; H, 5.73; N, 9.44. Found: C, 57.17; H, 5.78; N, 8.90.

The neutral solution was acidified with 10% HCl and the resulting precipitate was collected, washed with H_2O and dried. Recrystallization from MeOH gave 0.5 g of VIa as colorless prisms, mp 273—274° (decomp). The acidic filtrate was extracted with chloroform (50 ml) and the chloroform extract was evaporated to dryness under reduced pressure. The residue was recrystallized from MeOH to give 0.7 g of VII$_a$ as colorless needles, mp 167—168°. IR ν_{max}^{Nujol} cm^{-1}: 3150 (OH), 1610 (C=O). NMR ($CDCl_3$) δ: 7.82 (1H, singlet, C_6-H), 5.57 (1H, singlet, OH), 4.44 (2H, quartet, $O\underline{CH_2}CH_3$), 1.42 (3H, triplet, $OCH_2\underline{CH_3}$). *Anal.* Calcd. for $C_{12}H_{12}O_3N_2$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.17; H, 5.46; N, 12.07.

IIIb, IVb,[5] Vb, VI,[3] VIIb and VIIIb[3] were obtained when I was treated with ethanolic sodium methoxide as described above. IIIb, mp 144—146°, colorless needles, UV λ_{max}^{EtOH} mμ (ε): 247 (19700), 320 (6100). IR ν_{max}^{Nujol} cm^{-1}: 1742 ($COOCH_3$). NMR ($CDCl_3$) δ: 7.28 (1H, singlet, C_3-H), 4.19 (3H, singlet, $O\underline{CH_3}$), 4.01 (3H, singlet, $COO\underline{CH_3}$). *Anal.* Calcd. for $C_{12}H_{12}O_3N_2$: C, 62.06; H, 5.21, 6, 12.06. Found: C, 62.09; H, 5.22; N, 11.99. Vb, mp 186—187°, colorless needles. UV λ_{max}^{EtOH} mμ (ε): 209 (15000), 276 (15200). IR ν_{max}^{Nujol} cm^{-1}: 3200—3250 (NH), 1737 ($COOCH_3$). NMR ($CDCl_3$) δ: 4.44 (1H, singlet, C_3-H), 3.55 (3H, singlet, CH_3), 3.53 (3H, singlet, CH_3). *Anal.* Calcd. for $C_{12}H_{13}O_3N_2Cl$: C, 56.63; H, 4.84; N, 10.42. Found: C, 53.58; H, 4.85; N, 10.10. VIIb, mp 182—184°, colorless needles, IR ν_{max}^{Nujol} cm^{-1}: 3150 (OH), 1630 (C=O). *Anal.* Calcd. for $C_{11}H_{10}O_3N_2$: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.63; H, 4.60; N, 12.88.

IVb, VI ond VIIIb were identical in every respect with authentic samples.[3,5]

Reaction of 2-Phenyl-4-chloro-5-ethoxy-3(2H)-pyridazinones (VIIIa) with Sodium Methoxide——VIIIa (1 mole) was heated with sodium methoxide (2.5 moles as Na) at 100° for 5 hr. Further treatment as described above resulted in the formation of IIIb (35%), IVb (20%), Vb (15%), VI (5%) and VIIb (5%). These products were identical in every respect with the sample prepared by reaction of I with sodium methoxide.

Reaction of 2-Phenyl-4,5-diethoxy-3(2H)-pyridazinone (IVa) with Sodium Methoxide——A mixture of 0.07 g of Na in 6 ml of MeOH and 0.5 g of IVa was heated at reflux for 0.5 hr. IIIb (60%) and IVb (25%) were isolated. When refluxing was continued for 8 hr, IIIb was obtained in 70% yield. IIIb and IVb were identical in every respect with samples prepared from I and sodium methoxide.