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

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In order to explore the scope of the ring contraction of pyridazinone to pyrazole, 2-phenyl-3(2H)-pyridazinones (IIIa—f) and (IVa—e) having 4 and 5 substituents other than chlorine were prepared and examined their behavior against sodium hydroxide. Among them, (IIIa, b) and (IVa, b, e) undergo the ring contraction to afford the corresponding pyrazole carboxylic acid, (V), (VII), and (VIII). From available data, substituent effects and mechanisms for these ring contractions were discussed.

In the course of this study, an unusual displacement reaction was observed in the reaction of 2-phenyl-4-chloro-5-methylthio-3(2H)-pyridazinone (IIIa) with sodium hydroxide and sodium ethoxide.

Previous papers[1] have described the ring contraction of 4,5- and 4,6-dichloro-2-phenyl-3(2H)-pyridazinone.

On the basis of deuterium labelling experiments,[3] we have proposed mechanisms for these ring contractions. In particular, we suggested that the unusual conversion of 2-phenyl-4,5-

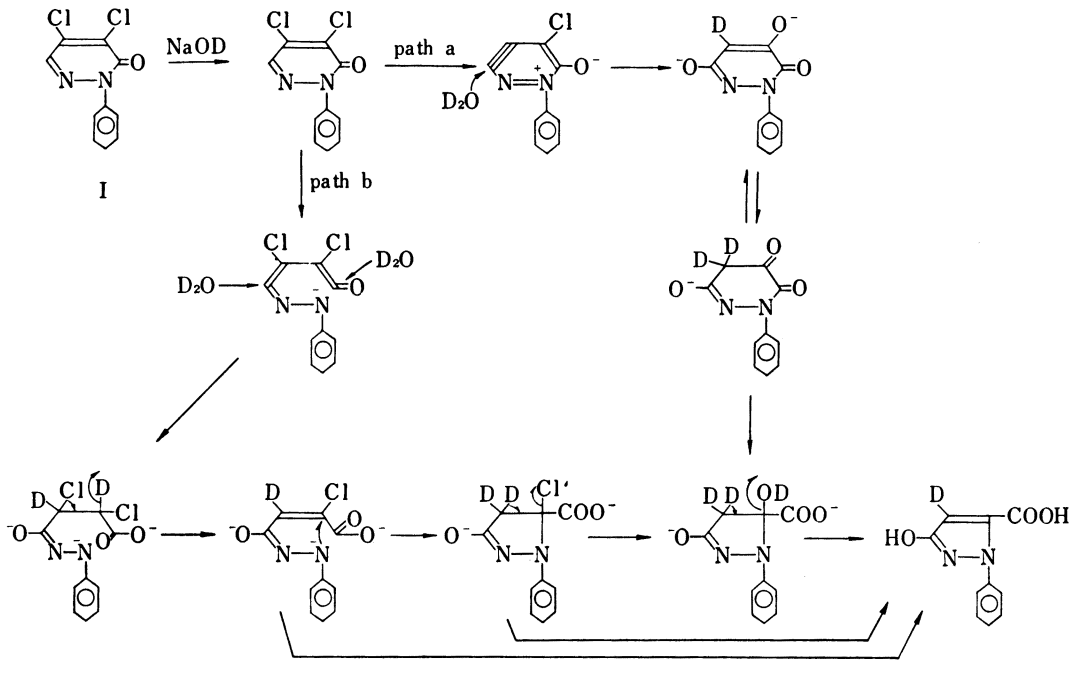


Chart 1

1) Part IV: Y. Maki, M. Takaya and M. Suzuki, *Yakugaku Zasshi*, **86**, 487 (1966); Part III: Y. Maki and K. Obata, *Chem. Pharm. Bull.* (Tokyo), **12**, 176 (1964).
2) Location: *a) Sakanoshita, Mitahora, Gifu; b) Yasu, Shiga.*
3) Y. Maki, G.P. Beardsley and M. Takaya, *Tetrahedron Letters*, **1969**, 1507.

dichloro-3(2H)-pyridazinone (I) to 1-phenyl-3-hydroxypyrazole-5-carboxylic acid (II) involves C_6-carbanion formation followed by either the elimination–addition (hetaryn) mechanism (path a) or the ring opening mechanism (path b) as outlined in Chart 1.

The present work was undertaken to explore the scope of this reaction. We wondered whether 2-phenyl-3(2H)-pyridazinones having 4 and 5 substituents other than chlorine would undergo the ring contraction. The compounds (III a—f and IVa—e) were prepared and their chemical behavior was examined. In the course of this study an unusual displacement reaction was observed in the case of the 4-chloro-5-methylthio derivative (IIIa).

When IIIa[4] was heated in 10% NaOH at 135° for 6 hr followed by acidification, 2-phenyl-4-methylthiopyrazole-3-carboxylic acid (V) (mp 191—192°, yield 40%) was isolated together with IVa (mp 204—205°, yield 2%), IIIc (mp 273°, yield 3%) and 2-phenyl-4-methylthio-5-hydroxy-3(2H)-pyridazinone (VI) (mp 188°, yield 5%). When, however, the duration of heating was prolonged to 10 hr, the by-product IVa was not present.

4-Chloro-5-methylsulfonyl derivative (IIIb)[4] was obtained from IIIa by oxidation with hydrogen peroxide. Upon treatment with 5% NaOH, IIIb rearranged to the corresponding pyrazole carboxylic acid (VII) (mp 167—168°, yield 55%; methyl ester mp 123—124°) under milder conditions (100° for 20 min) than required for IIIa. The acid was accompanied by a small amount of (IVb) (mp 220°). VII was also obtained from V by hydrogen peroxide oxidation. The conversion of the by-product IVb into VII required more severe conditions (10% NaOH, 120° for 2 hr) than those employed in the case of IIIb.

Upon the same conditions as employed for IIIb, 2-phenyl-4-hydroxy-5-nitro-3(2H)-pyridazinone (IVe) was transformed into the pyrazole carboxylic acid (VIII).[5]

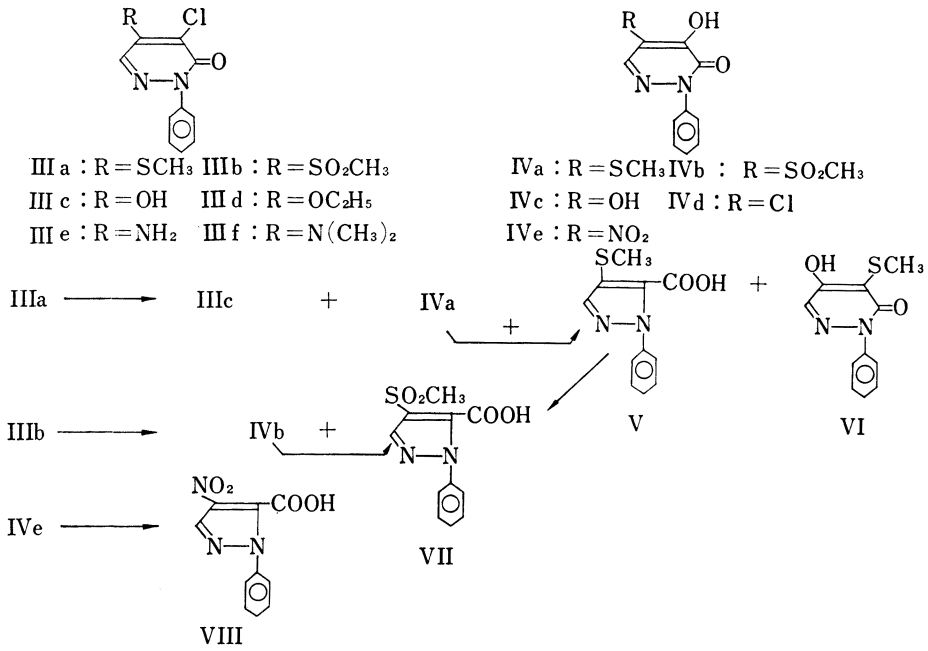


Chart 2

4) T. Takahashi. M. Takaya and Y. Maki, *Yakugaku Zasshi*, **89**, 1516 (1969).
5) This conversion has been previously reported without detailed description. K. Dudy, *Angew. Chem.*, **77**, 282 (1965).

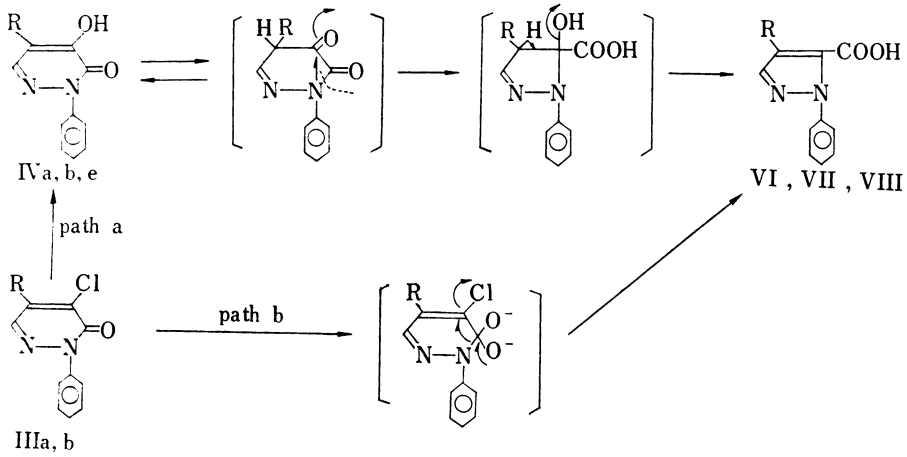
In the contrast to the above, even severe treatment of IIId—f[5-7] did not afford any ring contracted products, but resulted in the formation of IIIc[6] in 75—85% yield.

Subjection of IVc,d[5,6] to the ring contraction conditions resulted only in the recovery of starting materials.

From the available data the following reasonable conclusions may be drawn:

1) The ring contraction was observed in IVa, b, and IVe, but not in IVc, d. This sharp contrast can be ascribed to the electronic effects of the C_5-substituents. Presumably the C_5-substituent affects the keto-enol equilibrium of the C_4-hydroxy function and also the ease of elimination of water (*cf.* Chart 3). As a result, only the compounds IVb and IVe bearing strong electron attracting groups (NO_2, SO_2CH_3) at C_5-position rearrange with ease. It is also interesting that in IVa the ring contraction occurred, but required considerably stronger conditions, indicating the indifferent electron withdrawing capability of the methylthio group.

2) More drastic conditions were required for the ring contraction of IVb in comparison with that of IIIb. This indicates that IVa, b may be not intermediates in the ring contraction of IIIa, b. It seems that the direct ring contraction *via* path b occurs in competition with the formation of IVa, b *via* path a (*cf.* Chart 3).



R=SO_2CH_3, SCH_3, NO_2

Chart 3

3) Contrary to our expectation, the unusual ring contraction observed in I did not take place in IIIb. This may be explained in terms of that the C_5-methylsulfonyl group much more strongly activates the C_4-chlorine than the C_5-chlorine. Thus the reaction proceeds *via* the course as discussed in 2) (path a and b in Chart 3) to give the product VII rather than the expected II.[8]

In the reaction of IIIa with 10% NaOH described previously, the unexpected product VI was isolated. The structure of VI was elucidated as follows:

When IIIa was refluxed with NaOEt for 0.5 hr, 2-phenyl-4-methylthio-5-ethoxy-3(2H-pyridazinone (IX) (mp 123—124°, yield 40%) was isolated. IX was converted easily into VI by heating with 45% hydrobromic acid. IX was identical with a specimen prepared by

6) Y. Maki and K. Obata, *Chem. Pharm. Bull.* (Tokyo), **12**, 176 (1964).
7) F. Reiheneder, K. Zuri and A. Fischer, Japan patent, 36-15950 (1961).
8) When IIIb was treated with 10% NaOD-D_2O at 120° for 20 min, the product VII deuterated both at position 5 and at methyl group was isolated. The above result indicates that IIIb also may form the C_6-carbanion in analogy to I under the conditions employed.

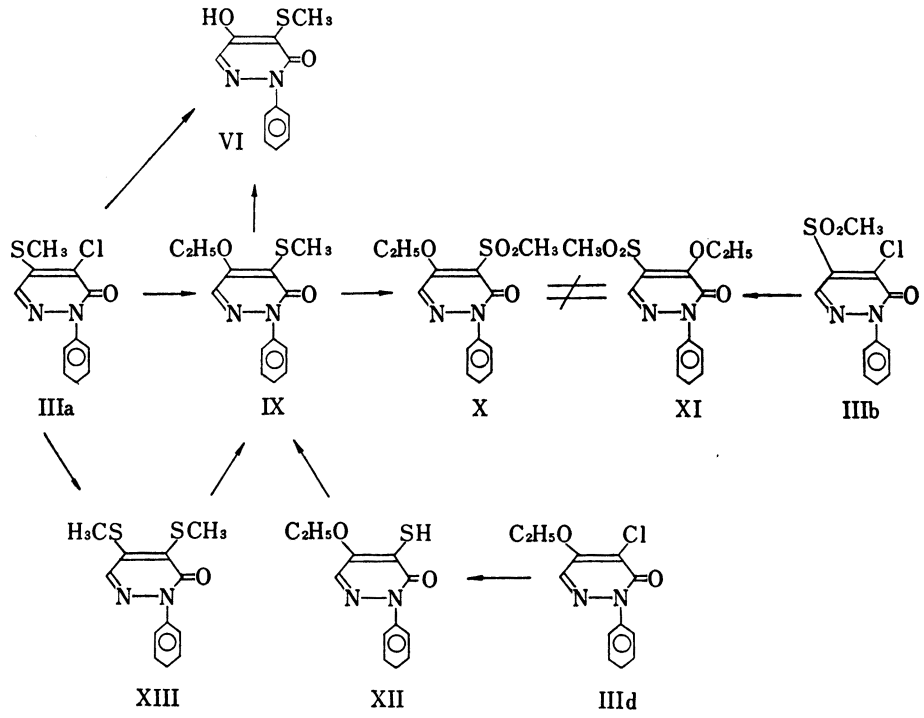


Chart 4

the reaction of IIId with sodium hydrosulfide followed by methylation with methyl iodide.[9] Oxidation of IX to the corresponding sulfone (X) (mp 142°, yield 80%) was accomplished by treatment with hydrogen peroxide at 60°. X was different in every respect from the position isomer (XI) (mp 134°, yield 25%), prepared by treatment of IIIb with sodium ethoxide at 100° for 5 min.

The unusual nucleophilic displacements in IIIa seem to be similar to those which have been observed in 2-chloro-4-(*p*-chlorophenyl)thio quinazoline and 2-methylthio-4-chloropyrimidine systems[10,11] *i.e.*, the methylthio anion, liberated by the normal displacement of methylthio group in IIIa with hydroxy or ethoxy anion, attacks position 4 of the remaining IIIa to give the 4,5-dimethylthio derivative (XIII). The active methylthio group at position 5 of XIII is displaced normally with hydroxy or ethoxy groups to afford VI or IX, respectively.

In fact, the 4,5-dimethylthio compound (XIII) synthesized from IIIa gave easily VI and IX upon treatment with sodium hydroxide or sodium ethoxide. When IIIa was treated with an equivalent amount of sodium ethoxide at room temperature, XIII was isolated in 15% yield. The present displacement involves the neighboring *ortho*-positions in the 3(2H)-pyridazinone system, and differs from those observed in the quinoxaline and pyrimidine systems which involve the *meta*-positions. Accordingly, the present displacement may occur to some extent *via* the intramolecular migration of the methylthio group from C_5 to C_4.

Experimental

Reaction of 2-Phenyl-4-chloro-5-methylthio or Methylsulfonyl-3(2H)-pyridazinone (IIIa,b) with 10% Sodium Hydroxide——III (1 g) was heated with 5 ml of 10% NaOH at 135° for 6 hr. After cooling, a small

9) *cf.* R.N. Castle and K. Kaji, *J. Hetero. Chem.*, **2**, 463 (1965).
10) F.H. Curd, E. Hoggarth, J.K. Landoquist and F.L. Rose, *J. Chem. Soc.*, **1948**, 1766.
11) R.S. Shadbolt and J.L.V. Ulbricht, *Chem. Ind.* (London), **1966**, 459.

amount of insoluble substance was removed by filtration. The reaction mixture was acidified with 10% HCl and the resulting precipitate was collected, washed with H_2O and dried. This material was then extracted with boiling benzene (30 ml). The insoluble residue was recrystallized from MeOH to give 28 mg of IIIc[6] as colorless prisms, mp 273—274° (decomp.).

The benzene extract was concentrated to half-volume and allowed to stand overnight. The crystals separated were recrystallized from isopropyl ether to give 390 mg of V as colorless needles, mp 191—192°. UV λ_{max}^{EtOH} mμ (log ε): 205 (4.27), 303 (3.84). IR (nujol) cm^{-1}: 1710 (COOH). NMR ($CDCl_3$) τ: 2.39 (1H, singlet, C_5-H), 2.60 (5H, singlet, C_6H_5), 7.48 (3H, singlet, SCH_3). *Anal.* Calcd. for $C_{11}H_{10}O_2N_2S$: C, 56.41; H, 4.27; N, 12.00. Found: C, 56.08; H, 4.25; N, 11.74.

The mother liquor was concentrated to dryness under reduced pressure and the residue was fractionated by crystallization from isopropyl ether to give 15 mg of IVa (less soluble) as colorless needles, mp 204—205° and 50 mg of VI (more soluble) as colorless plates, mp 188°. IVa: UV λ_{max}^{EtOH} mμ (log ε): 217 (4.27), 303 (3.78). IR (nujol) cm^{-1}: 1610 (C=O). NMR ($CDCl_3$) τ:2.14 (1H, singlet, C_6-H), 2.50 (5H, multiplet, C_6H_5), 7.55 (3H, singlet, SCH_3). *Anal.* Calcd. for $C_{11}H_{10}O_2N_2S$: C, 56.41; H, 4.27; N, 12.00. Found: C, 55.97; H, 3.86; N, 12.02. VI: UV λ_{max}^{EtOH} mμ (log ε): 214 (4.23), 320 (3.83). IR (nujol) cm^{-1}: 1620 (C=O). NMR ($CDCl_3$) τ: 2.16 (1H, singlet, C_5-H), 2.52 (5H, multiplet, C_6H_5), 7.56 (3H, singlet, SCH_3). *Anal.* Calcd. for $C_{11}H_{10}O_2N_2S$: C, 56.41; H, 4.27; N, 12.00. Found: C, 56.51; H, 4.27; N, 11.85.

b) IIIb (500 mg) was heated with 5 ml of 10% NaOH at 100° for 10 min. After cooling, the reaction mixture was acidified with 10% HCl, and then cooled to 10°. The crystals which separated were extreacted with boiling isopropyl ether. The insoluble residue was recrystallized from MeOH to afford 28 mg of IVb as colorless powder, mp 219—220°. IR (nujol) cm^{-1}: 3300 (OH), 1650 (C=O), 1140 ($-SO_2-$). NMR (DMSO-d_6)τ:1.97 (1H, singlet, C_6-H), 2.47 (5H, singlet, C_6H_5), 4.00 (1H, singlet, OH), 6.72 (3H, singlet, SO_2CH_3). *Anal.* Calcd. for $C_{11}H_{10}O_4N_2S$: C, 49.63; H, 3.76; N, 10.53. Found: C, 49.82; H, 3.81; N, 10.52.

The isopropyl ether extract was concentrated and the crystals which separated were recrystallized from the same solvent to give 280 mg of VII, mp 166—167°. UV λ_{max}^{EtOH} mμ (log ε): 204 (4.30), 243 (4.10). IR nujol) cm^{-1}: 1720 (COOH), 1142 ($-SO_2-$). NMR (DMSO-d_6) τ: 1.83 (1H, singlet, C_5-H), 2.45 (5H, singlet, C_6H_5), 6.65 (3H, singlet, SO_2CH_3). *Anal.* Calcd. for $C_{11}H_{10}O_4N_2S$: C, 49.63; H, 3.76; N, 10.53. Found: C, 50.17; H, 4.05; N, 10.56. VII was also obtained from V in the same manner as previously discribed for IIIb.[4] Yield 80%. The methyl ester of VII was prepared by adding 600 mg of $(CH_3)_2SO_4$ to a solution of 240 mg of VII in 2 ml of 10% NaOH. The mixture was heated at 145° for 5 hr, cooled, diluted with 5 ml of H_2O, and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, and dried over anhydrous Na_2SO_4. After evaporation of solvent, the residue was recrystallized from isopropyl ether to give 50 mg of colorless prisms, mp 122—123°. UV λ_{max}^{EtOH} mμ (log ε): 203 (4.10), 245 (3.89). IR (nujol) cm^{-1}: 1730 ($COOCH_3$), 1140 ($-SO_2-$). NMR ($CDCl_3$) τ: 1.91 (1H, singlet, C_5-H), 2.55 (5H, singlet, C_6H_5), 6.18 (3H, singlet, $COOCH_3$), 6.68 (3H, singlet, SO_2CH_3). *Anal.* Calcd. for $C_{12}H_{12}O_4N_2S$: C, 51.41; H, 4.31; N, 9.99. Found: C, 51.25; H, 4.47; N, 9.96.

2-Phenyl-4-methylthio-5-ethoxy-3(2H)-pyridazinone (IX)——a) To a solution of 110 mg of Na metal in 15 ml of EtOH was added 1 g of IIIa. The reaction mixture was refluxed for 0.5 hr and evaporated under reduced pressure to dryness. After washing with H_2O, the insoluble residue was recrystallized from isopropyl ether to give 400 mg of IX as colorless plates,mp 123—124°. UV λ_{max}^{EtOH} mμ (log ε): 209 (4.29), 242 (sh), 330 (3.84). IR (nujol) cm^{-1}: 1630 (C=O). NMR ($CDCl_3$) τ: 2.20 (1H, singlet, C_6-H), 2.53 (5H, multiplet, C_6H_5), 5.70 (2H, quartet, OCH_2CH_3), 7.40 (3H, singlt, SCH_3), 8.50 (3H, triplet, OCH_2CH_3). *Anal.* Calcd. for $C_{13}H_{14}O_2N_2S$: C, 59.51; H, 5.38; N, 10.68. Found: C, 59.57; H, 5.24; N, 10.52.

The presence of small amounts of other products, presumably IIIc, XIII, 2-phenyl-4-ethoxy-5-methylthio-3(2H)-pyridazinone, *etc.*, was detected by thin layer chromatographic analysis of the reaction mixture.

When IX was heated with 47% HBr at 155 ° for 5 hr, VI was obtained in 60% yield. The product was identical in every respect with a specimen obtained from the reaction of IIIa with 10% NaOH.

b) To a solution of 100 mg of Na in 25 ml of EtOH was added 1 g of IIIa. The reaction mixture was stirred at room temperature for 4 hr and then allowed to stand overnight. The crystals which separated were collected by filtration, washed with H_2O and dried. Recrystallization from EtOH gave 200 mg of XIII as colorless needles, mp 122—123°. UV λ_{max}^{EtOH} mμ (log ε): 209 (4.14), 235 (4.09), 252 (4.11), 317 (4.01). IR (nujol) cm^{-1}: 1650 (C=O). NMR ($CDCl_3$)τ: 2.27 (1H, singlet, C_6-H), 2.51 (5H, multiplet, C_6H_5), 7.33 (3H, singlet, C_5-SCH_3), 7.43 (3H, singlt, C_5-SCH_3). *Anal.* Calcd. for $C_{12}H_{12}ON_2S_2$: C, 54.54; H, 4.54; N, 10.60. Found: C, 54.50; H, 4.55; N, 10.31. XIII was identical in every respect with a specimen prepared by the reaction of 2-phenyl-4,5-dimercapto-3(2H)-pyridazinone[12] with CH_3I.

XIII (400 mg) was refluxed in a solution prepared from 44 mg of Na in 6 ml of EtOH for 0.5 hr. The reaction mixture was concentrated and diluted with H_2O. The resulting precipitate was collected and recrystallized from isopropyl ether–EtOH (2:1) to give 150 mg of IX, identified by mixed mp determination and IR comparison with a specimen obtained in a).

12) A. Pollak and M.Tisler, *Tetrahedron*, **21**, 1323 (1965).

c) XII, mp 107—109°. IR (nujol) cm^{-1}: 2550 (sh), 1680 (C=O). *Anal.* Calcd. for $C_{12}H_{12}O_2N_2S$: C, 58.05; H, 4.87; N, 11.28. Found: C, 57.94; H, 4.89; N, 11.28, was prepared from IIIa in a manner similar to the synthesis of 2-phenyl-4-mercapto-5-methoxy-3(2H)-pyridazinone.[9]

To a solution of XII (350 mg) in 5 ml of MeOH (containing 43 mg of Na) was added 300 mg of CH_3I. The reaction mixture was allowed to stand at room temperature for 24 hr. The crystals which separated were recrystallized from isopropyl ether to give 300 mg of IX, identical in every respect with specimens obtained in a) and b).

2-Phenyl-4-methylsulfonyl-5-ethoxy-3(2H)-pyridazinone (X)——To a solution of 350 mg of IX in 5 ml of AcOH was added 1.2 g of 30% H_2O_2. The reaction mixture was stirred at 60° for 8 hr, and evaporated under reduced pressure. The oily residue crystallized immediately upon adding H_2O. Recrystallization of the crude product from MeOH gave 320 mg of X as colorless needles, mp 142°. UV λ_{max}^{EtOH} mμ (log ε): 212 (4.37), 272 (3.85), 324 (3.76). IR (nujol) cm^{-1}: 1670 (C=O), 1140 (-SO_2-). NMR ($CDCl_3$) τ: 1.98 (1H, singlet, C_6-H), 2.50 (5H, multiplet, C_6H_5), 5.52 (2H, quarter, OCH_2CH_3), 6.61 (3H, singlt, SO_2CH_3), 8.43 (3H, triplet, OCH_2CH_3). *Anal.* Calcd. for $C_{13}H_{14}O_4N_2S$: C, 53.05; H, 4.79; N, 9.52. Found: C, 52.88; H, 5.02; N, 9.55.

2-Phenyl-4-ethoxy-5-methylsulfonyl-3(2H)-pyridazinone (XI)——To a solution of 61 mg of Na in 5 ml of EtOH was added 500 mg of IIIb. The reaction mixture was refluxed for 10 min and concentrated under reduced pressure. After extraction with H_2O, the oily residue crystallized. Recrystallization of the crude product from MeOH gave 300 mg of XI as colorless needles, mp 134°. UV λ_{max}^{EtOH} mμ (log ε): 213 (4.21), 266 (3.60), 321 (3.81). IR (nujol) cm^{-1}: 1670 (C=O), 1140 (SO_2CH_3). NMR ($CDCl_3$) τ: 1.77 (1H, singlet, C_6-H), 2.50 (5H, multiplet, C_6H_5), 5.05 (2H, quartet, OCH_2CH_3), 6.74 (3H, singlet, SO_2CH_3), 8.51 (3H, triplet, OCH_2CH_3). *Anal.* Calcd. for $C_{13}H_{14}O_4N_2S$: C, 53.03; H, 4.79; N, 9.52. Found: C, 53.00; H, 4.75; N, 9.35.

The alkaline extract was acidified with 10% HCl. The resulting precipitate was recrystallized from MeOH to give 0.1 g of IVb, identical in every respect with a specimen obtained from the reaction of IIIb with 10% NaOH.