To determine whether this reaction process is inter- or intra-molecular, the cross reaction between deutero-aniline and deutero-N,N-dimethylaniline was carried out. The results are shown in Fig. 7 and 8. The decrease in the signal intensity of $NH_2$ was accompanied by increase in the signal intensity of the *ortho*- and *para*-protons of deutero-aniline and deutero-N,N-dimethylaniline.

In this case the signal of *meta*-proton is converted to multiplets due to increase of protons at the *ortho*- and *para*-positions. These results indicate that the mechanism of the H-D-exchange reaction is intermolecular.

This results consistent with the conclusion that this reaction is $H^+$ catalysed reaction.

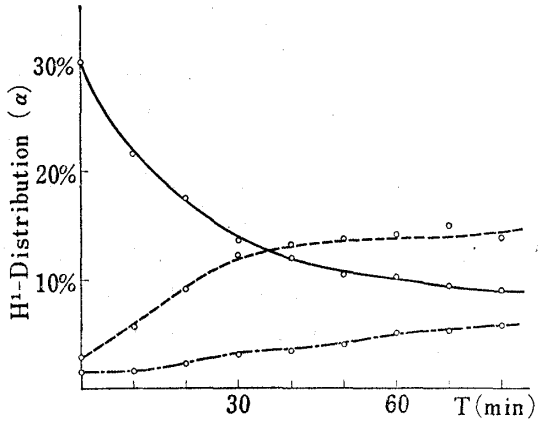


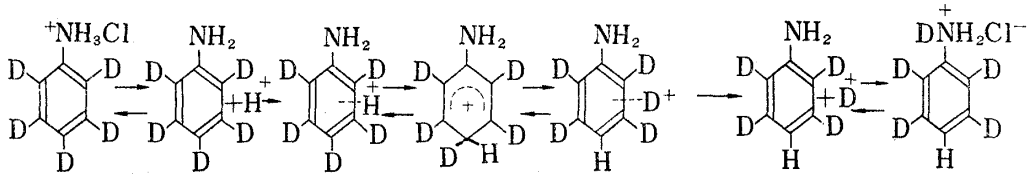

Fig. 8. Time-dependence of α-Values in a Mixture of Deutero-aniline and Deutero-N,N-dimethylaniline

———: $NH_2$/aniline
----------: *ortho* and *para*/N,N-dimethylaniline and *para*/aniline
———: *ortho*/aniline

## Conclusion

The H-D-exchange reaction of deutero-aniline between the amino group and ring deuterium proceeds by addition of a small amount of aliphatic halides. This reaction was confirmed to be intermolecular mechanism by the cross reaction of deutero-aniline and deutero-N,N-dimethylaniline. And this reaction was showen to be initiated by $H^+$ produced from deutero-aniline and aliphatic halides (*e.g.* reaction (1)).

Results suggest the following scheme.



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# The Ring Contraction of Pyridazinones to Pyrazoles. VII[1]

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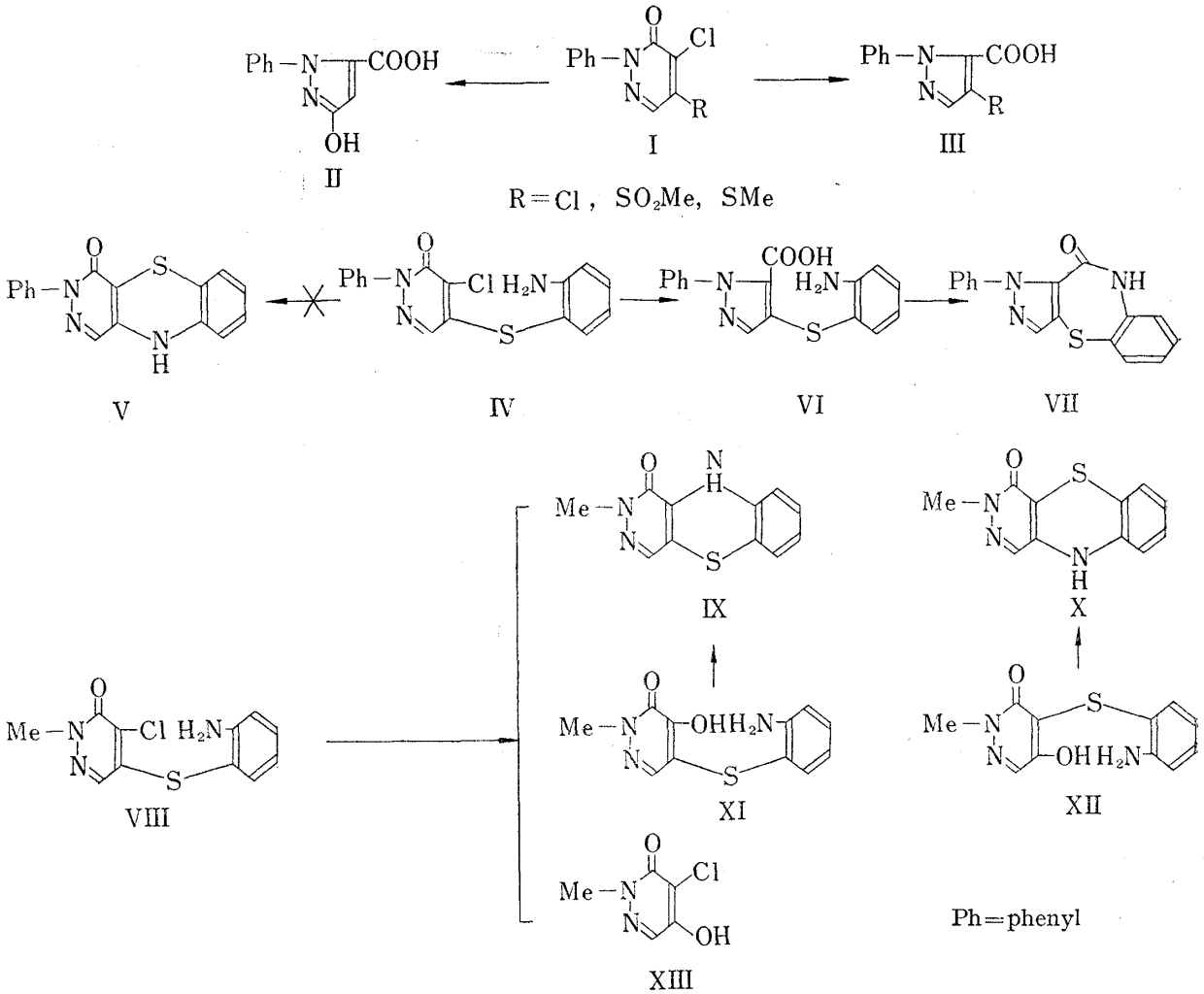
Recent investigation in this laboratory has shown an unusual ring contraction of 4,5-dichloro-3(2*H*)-pyridazinone (I: R=Cl) leading to 1-phenyl-3-hydroxypyrazole-5-carboxylic acid (II) by alkaline treatment.[3] It has also noted that 2-phenyl-4-chloro-5-methylsulfonyl

1) Part VI: Y. Maki and M. Takaya, *Chem. Pharm. Bull.* (Tokyo), **20**, 747 (1972).
2) Location: *Mitahora, Gifu.*
3) Y. Maki, G.P. Beardsley, and M. Takaya, *Tetrahedron Letters*, **1971**, 1507.

or methylthio-3(2*H*)-pyridazinones (I: R=$MeSO_2$, MeS) undergo smooth conversions into 2-phenyl-4-methylsulfonyl or methylthiopyrazole-5-carboxylic acids (III: R=$MeSO_2$, MeS) under identical conditions.[4]

The present study was undertaken to extend previous results to a synthetic approach to the new type of heterocycles. We describe here that the alkaline treatment followed by dehydration of 2-phenyl-4-chloro-5(*o*-aminophenylthio)-3(2*H*)-pyridazinone (IV) can be converted into 1-phenylpyrazolo(3,4-*b*)(1,5)benzothiazepin-10(9*H*)-one (VII) which is a new condensed heterocycle.[5] The reaction of 2-methyl-4-chloro-5(*o*-aminophenylthio)-3(2*H*)-pyridazinone (VIII) with alkali resulted in the formation of 3-methyl-10*H*-benzo(*b*)pyridazino-(4,5-*e*)(1,4)thiazine-3(4*H*)-one (IX), 2-methyl-10*H*-benzo(*b*)pyridazino(4,5-*e*)(1,4)thiazine-1(2*H*)-one (X), 2-methyl-4-hydroxy-5(*o*-aminophenylthio)-3(2*H*)-pyridazinone (XI), 2-methyl-4-(*o*-aminophenylthio)-5-hydroxy-3(2*H*)-pyridazinone (XII) and 4-chloro-5-hydroxy-3(2*H*)-pyridazinone (XIII) without isolation of any ring contracted products. This observation clearly demonstrates a significant efficacy of the $N_2$-phenyl grouping for this type of ring contraction.




Chart

4) Y. Maki and M. Takaya, *Chem. Pharm. Bull.* (Tokyo), **19**, 1635 (1971).
5) Recently, isomeric pyrazolo(3,4-*c*)(1,5) benzothiazepine system has been synthesized from the viewpoint of psychotropic interest. (*cf.* I. Ito, T. Ueda, and N. Oda, *Chem. Pharm. Bull.* (Tokyo), **18**, 2058 (1970); I. Ito and T. Ueda, *Yakugaku Zasshi*, **93**, 207 (1973)).

When a suspension of IV in 10% sodium hydroxide was heated at 150° for several hr and acidified, 1-phenyl-4(*o*-aminophenylthio)-pyrazole-5-carboxylic acid (VI), mp 179—180°, was obtained in 70% yield. The presence of a carboxyl group in VI was confirmed by its infrared (IR) spectrum (2400—2600 $cm^{-1}$) and its conversion to methyl ester, mp 155°. Treatment of VI with thionyl chloride in boiling chloroform for 1 hr led to the cyclization to benzothiazepine VII, mp 227—228°, in 75% yield. Microanalytical and mass spectral data on VII established its molecular formula $C_{10}H_{11}ON_3S$. The IR spectrum of VII showed bands at 3130 and 1660 $cm^{-1}$ due to an amide function (-NHCO-). The nuclear magnetic resonance (NMR) spectrum of VII exhibited signals (2.36 $\tau$, 1H, singlet and 1.45 $\tau$, 1H, deuterium exchangeable) ascribed to an azomethine proton and an amide proton respectively, in addition to phenyl proton signals (2.2—3.1 $\tau$, 9H, multiplet). Thus the thiazepine structure of VII was unambiguously established.

The sequence of above reactions provides a novel synthetic route to the pyrazolo(3,4-*b*)-(1,5)thiazepine system. Previously, it has been demonstrated that alkaline treatment of acetate of IV takes place the formation of 3-phenyl-10*H*-benzo(*b*)pyridazino(4,5-*e*)(1,4)thiazine (V) *via* the Smiles rearrangement.[6] The present result is in a sharp contrast to that.

The reaction of VIII with 10% sodium hydroxide under the conditions similar to the case of IV recovered the starting material almost quantitatively.

By employment of more drastic conditions (heating at 150° for 50 hr), however, VIII gave IX(40%), X(20%), XI(15%), XII(5%), and XIII(4%). IX, X, and XIII were identical with specimens[7,8] previously prepared in every respect. XII underwent easily the thermal cyclization to X, suggesting that X resulted from the intermediary XII initially formed *via* an unusual displacement.[4,7,9] Cyclization of XI to IX was effected only in a poor yield.

It is worthwhile noting that the reaction of VIII with aqueous sodium hydroxide did not give any ring-contracted products. This fact is compatible with the previous finding, *i.e.*, the presence of the $N_2$-phenyl grouping is requisite for the ring contraction of 4,5- or 4,6-dichloro-3(2*H*)-pyridazinones.[8]

## Experimental[10]

**Reaction of 2-Phenyl-4-chloro-5(*o*-aminophenylthio)-3(2*H*)-pyridazinone (IV) with 10% Sodium Hydroxide**——1.0 g of IV was heated in 10 ml of 10% NaOH at 150° for 10 hr. After cooling, insoluble substance was collected and recrystallized from MeOH to give 0.3 g of unchanged IV. The mother liquor was acidified with 10% HCl and the resulting precipitate was collected by filtration and recrystallized from MeOH to give 0.6 g of 1-phenyl-3(*o*-aminophenylthio)-pyrazole-5-carboxylic acid (VI) as colorless prisms, mp 179—180°. IR (nujol) $cm^{-1}$: 3450, 3350, 2400—2600, 1715, 1620. NMR (DMSO-$d_6$) $\tau$: 4.90 (2H, broad, $NH_2$), 3.6—2.6 (4H, m, aromatic proton),s 2.97 (1H, s; $C_3$-H), 2.55 (5H, s, $C_6H_5$). *Anal.* Calcd. for $C_{16}H_{13}O_2N_3S$: C, 61.71; H, 4.21; N, 13.49. Found: C, 61.46; H, 4.28; N, 13.36.

VI was further characterized by its conversion to methyl ester, mp 155°, colorless plates (MeOH). IR (nujol) $cm^{-1}$: 3440, 3330, 1720, 1630. NMR (DMSO-$d_6$) $\tau$: 6.23 (3H, s, $COOCH_3$), 4.54 (2H, s, $NH_2$), 3.6—2.6 (4H, m, aromatic protons), 2.93 (1H, s, $C_3$-H), 2.53 (5H, s, $C_6H_5$). *Anal.* Calcd. for $C_{17}H_{15}O_2N_3S$: C, 62.74; H, 4.65; N, 12.91. Found: C, 62.53; H, 4.75; N, 13.02.

**1-Phenylpyrazolo(4,3-*b*)(1,5)benzothiazepin-10(9*H*)-one (VII)**——To a solution of 0.3 g of VI in 30 ml of $CHCl_3$ was added 0.5 ml of $SOCl_2$ at room temperature. The reaction mixture was refluxed for 1 hr and concentrated under reduced pressure. The oily residue was poured into $H_2O$, neutralized with 5% $Na_2CO_3$ and extracted with $CHCl_3$. After evaporation of the solvent, the residue was recrystallized from MeOH

6) Y. Maki, M. Suzuki, O. Toyota, and M. Takaya, *Chem. Pharm. Bull.* (Tokyo), **21**, 241 (1973).
7) Y. Maki and M. Suzuki, *Yakugaku Zasshi*, **93**, 171 (1973).
8) Y. Maki, M. Takaya, and M. Suzuki, *Yakugaku Zasshi*, **86**, 487 (1966).
9) This observation indicates that the formation of X is not *via* the Smiles rearrangement in agreement with the fact observed in the reaction of IV with sodium ethoxide.[7]
10) All melting points are uncorrected. NMR spectra were measured with a Hitachi Model R-20B instrument at 60 Mc and tetramethylsilane was used as internal standard. Signal multiplicities were represented by s (singlet) and m (multiplet).

to give 0.22 g of VII as colorless needles, mp 227—228°. IR (nujol) $cm^{-1}$: 3130, 1660. NMR ($CDCl_3$) $\tau$: 3.1—2.2 (4H, m, aromatic protons), 2.58 (5H, s, $C_6\underline{H}_5$), 2.36 (1H, s, $C_3$-H), 1.45 (1H, broad, N<u>H</u>). *Anal.* Calcd. for $C_{16}H_{11}ON_3S$: C, 65.50; H, 3.78; N, 14.32. Found: C, 65.04; H, 3.97; N, 14.17.

**Reaction of 2-Methyl-4-chloro-5(*o*-aninophenylthio)-3(2*H*)-pyridazinone (VIII) with 10% Sodium Hydroxide**——1.0 g of VIII was heated in 20 ml of 10% NaOH at 150° for 50 hr. After cooling, the orange crystals precipitated were collected by filtration, washed well with $H_2O$ and taken up with $CHCl_3$.

The insoluble substance was recrystallized from DMF to give 0.2 g of 2-methyl-10*H*-benzo(*b*)pyridazino-(4,5-*e*)(1,4)thiazine-1(2*H*)-one (X) as orange needles, mp 300° (decomp.), identical in IR and NMR spectra with an authentic sample.[7] The soluble part in $CHCl_3$ was concentrated and the residue was recrystallized from EtOH to give 0.4 g of 3-methyl-10*H*-benzo(*b*)pyridazino(4,5-*e*)(1,4)thiazine-3(4*H*)-one (IX) as orange needles, mp 216—217°, identical in IR and NMR spectra with an authentic sample.[7]

The alkaline mother liquor was acidified with dil. HCl. The precipitated solid was collected and recrystallized from MeOH to give 0.15 g of 2-methyl-4-hydroxy-5(*o*-aminophenylthio)-3(2*H*)-pyridazinone (XI) as colorless needles, mp 186°. IR (nujol) $cm^{-1}$: 3460, 3360, 1620. NMR (DMSO-$d_6$) $\tau$: 3.30 (1H, s, $C_3$-H). *Anal.* Calcd. for $C_{11}H_{11}O_2N_3S$: C, 53.01; H, 4.45; N, 16.86. Found: C, 53.14; H, 4.71; N, 16.98.

After removal of XI, the acidic solution was extracted with $CHCl_3$. The $CHCl_3$ extract was concentrated to give 0.05 g of 2-methyl-4(*o*-aminophenylthio)-5-hydroxy-3(2*H*)-pyridazinone (XII) as colorless prisms, mp 167—169°. IR (nujol) $cm^{-1}$: 3350, 3250, 1620. NMR (DMSO-$d_6$) $\tau$: 2.30 (1H, s, $C_3$-H). *Anal.* Calcd. for $C_{11}H_{11}O_2N_3S$: C, 53.01; H, 4.45; N, 16.86. Found: C, 53.07; H, 4.82; N, 16.50.

The aqueous solution was concentrated to dryness under reduced pressure and the residue was recrystallized from $CHCl_3$ to give 0.04 g of 4-chloro-5-hydroxy-3(2*H*)-pyridazinone (XIII) as colorless needles, mp 243—244°, identical in IR and NMR spectra with an authentic sample.[8]

**Thermal Cyclization of XI and XII to IX and X**——a) 10 mg of XI was heated at 250° for 5 min without solvent. After cooling, the reaction mixture was recrystallized from MeOH to give 1 mg of IX as orange needles, mp 216°, identical in IR spectrum with the specimen obtained above.

b) 10 mg of XII was heated at 250° for 3 min without solvent. After cooling, the reaction mixture was recrystallized from MeOH to give X as orange needles, mp 300° (decomp.), identical in IR spectrum with the specimen obtained above.

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*UDC 615.011.3.04*

# Influence of Operational Variables on Vibro-milling of Silica Sands

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(Received June 5, 1973)

Vibro-milling is much more effective than ball-milling for production of fine powders and practically used in the industrial field. But the detailed mechanism of vibro-milling has not been clarified yet.

In this paper, influence of operational variables on the rate of an increase of the surface area of silica sands by vibro-milling was investigated.

## Experimental

The material used was silica sands (Type 3) purchased from Kokusan Kagaku Co., whose true density was 2.65 g/cm³.

The balls used were ceramic balls of true density of 2.35 g/cm³ and of diameter between 1.4 cm and 3.0 cm, ceramic balls of true density of 3.65 g/cm³ and of diameter between 1.0 cm and 4.0 cm, stainless steel balls of true density of 8.29 g/cm³ and of diameter of 0.5 cm and stainless steel balls of true density of 7.50

1) Location: *1-5-8, Hatanodai, Shinagawa-ku, Tokyo.*