## 9. Takeo Naito, Renzo Dohmori, and Mutsuo Shimoda : Rearrangement of Sulfonamide Derivatives. III.[1] Considerations on the Reaction Mechanism.

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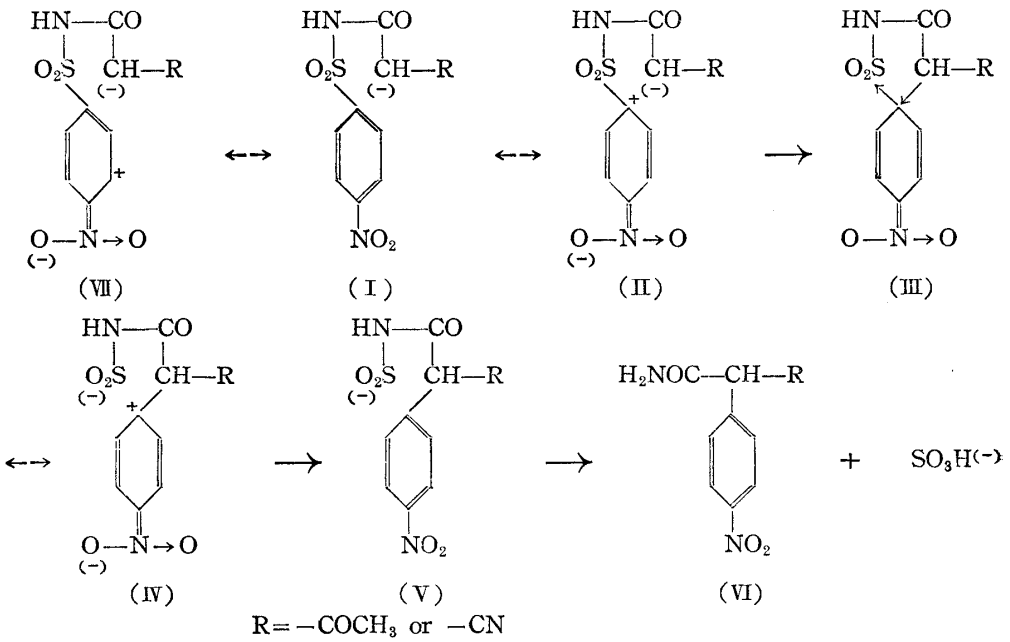
In the previous papers of this series,[1] it was shown that the compounds of (*p*- or *o*-)$NO_2$-$C_6H_4$-$SO_2NH$-$COCH_2R$ type (where R is $-COCH_3$, -CN, -COOR, or $-C_6H_5$ group) easily undergo decomposition in the presence of alkali and a rearrangement accompanied by the liberation of sulfur dioxide occurs to form *p*- or *o*-nitrophenylacetamide and its derivatives in a good yield.

In the present paper are presented some considerations on the reaction mechanism of this rearrangement. Summarizing the experimental results obtained to date, it may be concluded that the presence of a nitro group in the *para*- or *ortho*-position of the benzene ring is a prerequisite and that this reaction does not occur when such a group is in the *meta*-position. Based on the fact that the methylene group present must be active, it was assumed that the present rearrangement occurs through the following steps. For example, in N-acetoacetyl or N-cyanoacetyl-*p*-nitrobenzenesulfonamide, the active methylene in the acetoacetyl or cyanoacetyl group exists as an anion (I) in an alkaline solution by the loss of a proton, or as its resonance type (II). At this stage, the close association between the nucleophilic and electrophilic centers suggests the formation of an isothiazole-type ring (III) compounds as an intermediate. At the same time, the bond between the carbon in the benzene ring and sulfur is severed to form a new anion (IV) and its resonance type (V). Here, the liberation of sulfur dioxide occurs and this rearrangement reaction is completed. It is possible that (I) exists with its resonance type (VII) but a compound with the sulfonamide group in the *ortho*-position that might be formed by rearrangement of such a type has not been isolated and this fact may endorse the assumption that a five-membered ring is formed as an intermediate.

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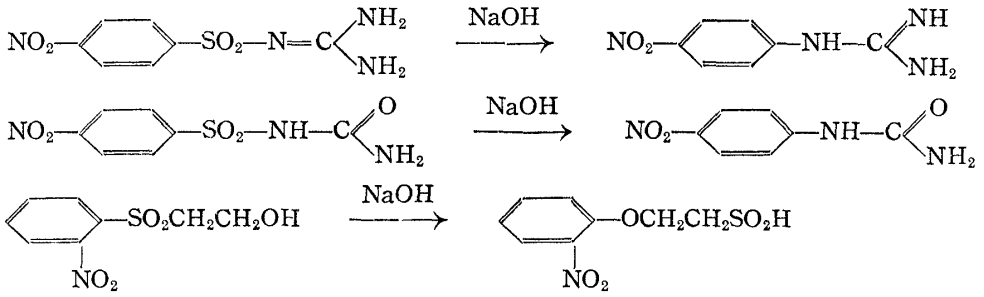
1) Part II : J. Pharm. Soc. Japan, **74**, 593; *ibid.*, 596(1954).

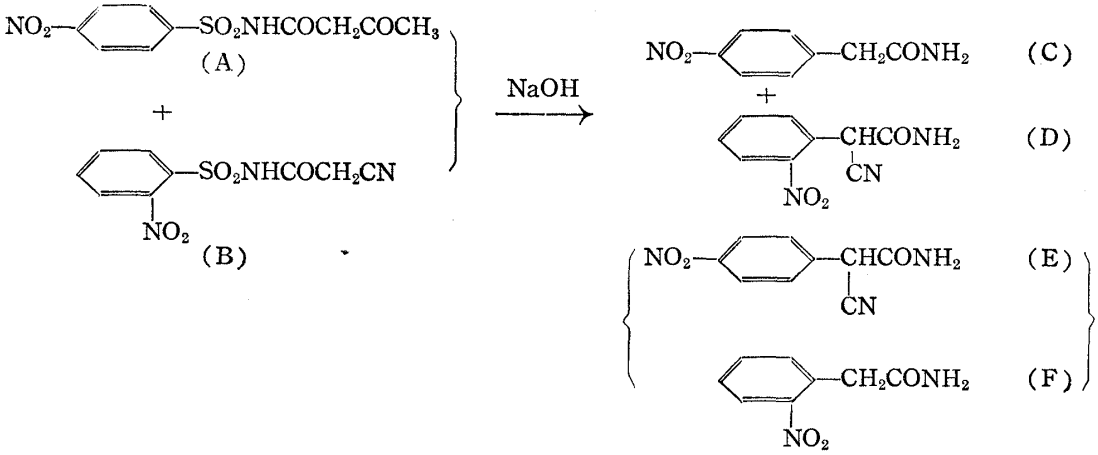
On going through published literatures, it has been found that some reports have been made on reactions similar to this rearrangement. For example, Backer and others[2] reported on the formation of *p*- and *o*-nitrophenylguanidine and -nitrophenylurea by the intramolecular rearrangement accompanied with liberation of sulfur dioxide from *p*- and *o*-nitrophenylsulfonylguanidine or -nitrophenylsulfonylurea in alkaline medium. Kent and Smiles[3] reported on the rearrangement of *o*-nitrophenyl β-hydroxyethyl sulfone to *o*-nitrophenoxyethylsulfinic acid in sodium hydroxide solution.




On comparing these rearrangement reactions with the present one, it is seen that all the compounds possess a nitro group in the *para*- or *ortho*-position of the benzene ring, there is $-CH_2$, $-NH_2$, or -OH group in the fourth position from the $SO_2$ group indicating the ease of formation of a five-membered ring, and that the rearrangement occurs after liberation of $SO_2$ group and not in any other position. Backer and others offered some explanations on the reaction mechanism of their rearrangement which are approximately identical with the present assumption.

As shown in the foregoing, the present reaction is assumed to be an intramolecular rearrangement and confirmation of this assumption was attempted by the following series of experiments.

N-Acetoacetyl-*p*-nitrobenzenesulfonamide (A) and N-cyanoacetyl-*o*-nitrobenzenesulfonamide (B), assumed to possess the same rate of reaction velocity, were each reacted in sodium hydroxide solution from which *p*-nitrophenylacetamide (C) and α-cyano-*o*-nitrophenylacetamide (D) were respectively obtained in a good yield. If this rearrangement is an intramolecular reaction, a mixture of (A) and (B) in sodium hydroxide solution, reacted under exactly the same conditions, should yield only (C) and (D), while if it were intermolecular rearrangement, α-cyano-*p*-nitrophenylacetamide (E) and *o*-nitrophenylacetamide (F) should also be formed by interchange, besides (C) and (D). In the present series of experiments, as shown in Table I, the products from a mixture of (A)



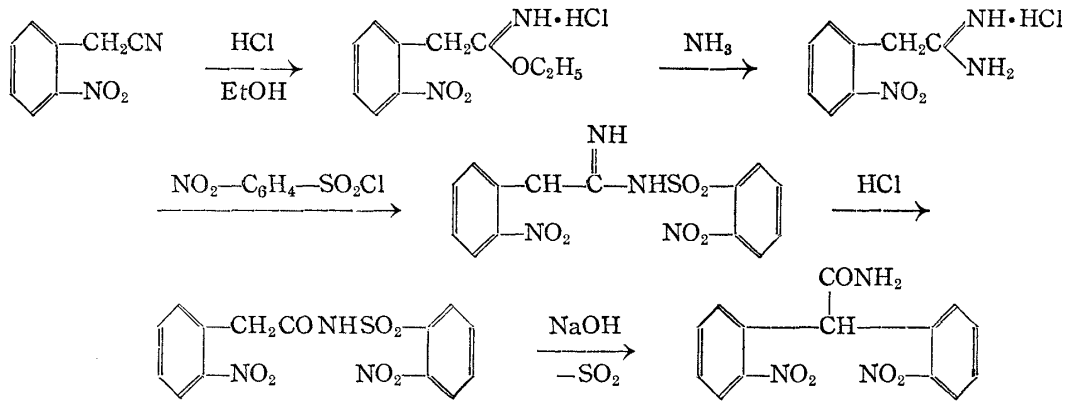

2) Backer, Moed: Rec. trav. chim., **66**, 689(1947); Backer, Groot: *Ibid.*, **69**, 1323(1950).
3) Kent, Smiles: J. Chem. Soc., **1934**, 422.

and (B) were inevitably (C) and (D), and their yield was no different from that on reacting (A) or (B) alone, compounds such as (E) and (F) not being obtained. Therefore, it may be concluded that this reaction is an intramolecular rearrangement.

Table I. Rearrangement Reaction of (A) and (B), alone or in a Mixture, in 10% NaOH Solution

| Compd. | Reaction conditions | Product | Yield(%) | Reaction conditions | Product | Yield(%) |
|---|---|---|---|---|---|---|
| A | room temp., 10 mins. | C | 96.7 | 50°, 20 mins. | C | 87.5 |
| B | 〃 | D | 71.0 | 〃 | D | 76.3 |
| A + B | 〃 | C + D | 96.7 68.0 | 〃 | C + D | 93 72.5 |

In the present rearrangement reactions, it was shown that the methylene group must be active and the following experiments confirmed this point. The reaction velocity of N-phenylacetyl-*o*-nitrobenzenesulfonamide, reported in the second paper of this series,[4] is slow compared to other N-acetoacetyl and N-cyanoacetyl compounds. Formation of an indazole ring did occur finally by a secondary reaction and this was assumed to be due to the lowering of the activity of the methylene in the phenylacetyl group. Assuming that the activation of this methylene would shorten the reaction time and also prevent occurrence of the side-reaction, N-(*o*-nitrophenylacetyl)-*o*-nitrobenzenesulfonamide, possessing a nitro group in the *ortho*-position of the phenylacetyl group, was prepared by the method described below and submitted to the present rearrangement reaction. It was thereby found that the reaction was concluded in a short time and bis(*o*-nitrophenyl)acetamide was obtained in a quantitative yield. This compound was confirmed by its elemental analytical values and absorption of six moles of hydrogen.




The writers take this opportunity to extend their deep gratitude to Dr. Junzo Shinoda, the President of this Company, and to Mr. Isamu Nakano, Director of the Yanagishima Laboratory, for their unfailing encouragement, and to Prof. E. Ochiai for the review and kind criticisms of this work. The writers are indebted to Messrs. Minoru Negishi and Kazumasa Mayeda of this Factory for elemental analyses.

## Experimental

**Rearrangement Reaction of N-Acetoacetyl-*p*-nitrobenzenesulfonamide**—On the addition of 0.5 g. of the sample in 4 cc. of 10% NaOH solution, a red solution resulted with generation of heat and yellow needle crystals began to separate out. After allowing the mixture to stand for 10 mins., the crystals were collected by filtration, washed with water, and dried by which 0.3 g. (96.7%) of *p*-nitrophenylacetamide, m.p. 190~195°, was obtained. Recrystallization from EtOH yielded pale yellow needles, m.p. 196.5~197°.

**Rearrangement Reaction of N-Cyanoacetyl-*o*-nitrobenzenesulfonamide**—A dark red solution formed by the addition of 0.5 g. of the sample into 4 cc. of 10% NaOH was allowed to stand for 10 mins. Acidification of this solution with HCl separated crystals with generation of $SO_2$. The crystals

4) J. Pharm. Soc. Japan, **74**, 596(1954).

were collected by filtration, washed with water, and dried at low temperatures to 0.27 g.(71%) of α-cyano-*o*-nitrophenylacetamide, m.p. 171~172°. Recrystallization from benzene furnished colorless needles, m.p. 171~172°.

**Rearrangement Reaction of a Mixture of N-Acetoacetyl-*p*-nitrobenzenesulfonamide and N-Cyanoacetyl-*o*-nitrobenzenesulfonamide**—A thorough mixture of 0.5 g. each of the two compounds was added to 8 cc. of 10% NaOH and the resulting dark red solution began to separate out crystals. After standing for 10 mins., the crystals were collected by filtration, washed with a small amount of water, and dried. Yield, 0.3 g. Recrystallization from EtOH yielded *p*-nitrophenylacetamide (96.7%) as pale yellow needles, m.p. 196.5~197°. A combined filtrate and washings was acidified with HCl, the crystals that separated out with evolution of $SO_2$ were collected by filtration, washed with water, and dried at low temperatures. Yield, 0.26 g. Recrystallization from benzene yielded α-cyano-*o*-nitrophenylacetamide (68%) as colorless needles, m.p. 171~172°.

**N-(*o*-Nitrophenylacetimino)-*o*-nitrobenzenesulfonamide**—i) *o*-Nitrophenylacetimidoether Hydrochloride: To a solution of 32.5 g. of *o*-nitrobenzyl cyanide dissolved in 70 cc. of dehyd. EtOH, dry HCl gas was bubbled in under chilling until saturation. After 2~3 hrs., the cyanide dissolved completely and crystals began to separate out after 5 hrs. After allowing the mixture to stand for 24 hrs., 70 cc. of ether was added, and the crystals that separated out were collected by filtration. On washing with ether and drying in a desiccator, 41 g. of white powder was obtained. Yield, 88%.

ii) A mixture of 41 g. of the foregoing white powder and 300 cc. of dehyd. EtOH containing 13% of $NH_3$ was allowed to stand, by which the powder dissolved in 2~3 hrs. and crystals began to separate out gradually. The mixture was allowed to stand over night, the solvent was concentrated under a reduced pressure, and the crystals that separated out were collected by filtration and dried to 30 g. (78%) of colorless prisms, m.p. 213~214°.

iii) To a solution of 2.1 g. of the foregoing amidine hydrochloride and 0.8 g. of NaOH dissolved in 3 cc. of water, 4 cc. of acetone was added, and a solution of 2.2 g. of *o*-nitrobenzenesulfochloride dissolved in 10 cc. of acetone was added dropwise, while maintaining the temperature at 10~15°, by which the solution gradually colored slightly yellowish. After allowing the solution to stand over night, the reaction mixture was concentrated, the crystals that separated out were collected by filtration, and washed with water. Recrystallization from EtOH yielded 2.4 g. (66%) of colorless needles, m.p. 151~152°(decomp.). *Anal.* Calcd. for $C_{14}H_{12}O_6N_4S$: C, 46.15; H, 3.32; N, 15.38. Found: C, 46.54; H, 3.48; N, 15.20.

**N-(*o*-Nitrophenylacetyl)-*o*-nitrobenzenesulfonamide**—A mixture of 730 mg. of N-(*o*-nitrophenylacetimino)-*o*-nitrobenzenesulfonamide and 10 cc. of 15% HCl was heated on a water bath for 1 hr. at 90~95° by which the crystals underwent change. The newly formed crystals were collected by filtration, dissolved in $NaHCO_3$ solution, insoluble matter removed by filtration, and the filtrate was acidified with HCl. The crystals thereby formed were collected by filtration, washed with a small amount of MeOH, and dried to 670 mg. (91.6%) of a product. Recrystallization from EtOH yielded colorless prisms, m.p. 178~179°. *Anal.* Calcd. for $C_{14}H_{11}O_7N_3S$: C, 46.03; H, 3.03. Found: C, 45.81; H, 2.63.

**Rearrangement Reaction of N-(*o*-Nitrophenylacetyl)-*o*-nitrobenzenesulfonamide (Formation of Bis(*o*-nitrophenyl)acetamide)**—A solution of 730 mg. of the sample dissolved in 8 cc. of 5% NaOH was heated at 70~80° for 5 mins. by which the color of the solution turned red and crystals separated out. After being cooled, the crystals were collected by filtration, washed with a small amount of ether, and dried. Yield, 580 mg. (97.5%). Recrystallization from MeOH yielded pale yellow plates, m.p. 232~233°(decomp.). *Anal.* Calcd. for $C_{14}H_{11}O_5N_3$: N, 13.95. Found: N, 13.96.

## Summary

Considerations were made on the reaction mechanism of a rearrangement reaction whereby compounds of *p*- or *o*-$NO_2$-$C_6H_4$-$SO_2NH$-$COCH_2R$ type (where R is $-COCH_3$, $-CN$, $-COOR$, or $-C_6H_5$ group) easily undergo decomposition in the presence of alkali, with liberation of sulfur dioxide to form *p*- or *o*-nitrophenylacetamide or its derivatives. It was shown that this reaction is an intramolecular rearrangement and that the methylene group present must be active in order that this rearrangement reaction proceeds, which was explained by the fact that N-(*o*-nitrophenylacetyl)-*o*-nitrobenzenesulfonamide is more reactive than N-phenylacetyl-*o*-nitrobenzenesulfonamide.

(Received November 20, 1954)