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84. **Renzo Dohmori**: Rearrangement of Sulfonamide Derivatives. VI.[*1] Rearrangement Reaction of N-Acetoacetyl-*p*-methylsulfonylbenzenesulfonamide with Alkali.

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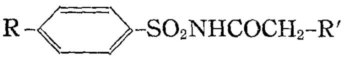
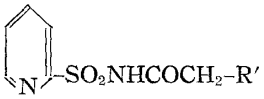
In the previous paper[1,2] of this series, we reported that the compounds of (*p*- or *o*-) NO_2-C_6H_4-SO_2NH-$COCH_2$-R type (where R is -$COCH_3$, -CN, -COOR, or -C_6H_5 group) underwent a new rearrangement reaction accompanied with the liberation of sulfur dioxide in alkaline solution and gave *p*- or *o*-phenylacetamide and their derivatives. Previously, on this rearrangement reaction, it was presumed that the presence of a nitro group in the *para*- or *ortho*-position of the benzene ring and also the active methylene group in the side chain were necessary prerequisite.

In the present paper, this rearrangement reaction are extended to N-substituted benzenesulfonamide derivatives, which in the *para*-position possessed an electron attracting group, *i.e.* cyano, acetyl and methylsulfonyl group, besides a nitro group.

The following compounds as shown in Table I were synthesized for this study.

Table I. N-Substituted Sulfonamide Derivatives

Compd. No.	Substituents		m.p. (°C)	Appearance	Crystn. solvent.	Formula	Analysis (%)					
							Calcd.			Found		
	R	R′					C	H	N	C	H	N
 R-, -$SO_2NHCOCH_2$-R′												
I	-CN	-$COCH_3$	118~119	colorless needles	EtOH	$C_{11}H_{10}O_4N_2S$	49.61	3.78	10.52	49.78	3.30	10.40
II	〃	-CN	241~242 (decomp.)	colorless prisms	〃	$C_{10}H_7O_3N_3S$	48.18	2.83	16.86	47.94	2.58	16.89
III	-$COCH_3$	-C_6H_5	166~167	colorless needles	〃	$C_{16}H_{15}O_4NS$	60.55	4.76	4.41	60.30	4.86	4.50
IV	-SO_2CH_3	-CN	208~210 (decomp.)	colorless leaflets	EtOH+ Me_2CO	$C_{10}H_{10}O_5N_2S$	39.72	3.33		39.38	3.16	
V	-SO_2CH_3	-C_6H_5	209~210	colorless needles	Me_2CO	$C_{15}H_{15}O_5N_2S$	50.98	4.28	3.96	51.24	4.36	3.60
VI	-SO_2CH_3	-$COCH_3$	162~165 (decomp.)	colorless leaflets	EtOH	$C_{11}H_{13}O_6NS$	41.37	4.10	4.39	41.44	3.76	4.76
 N, -$SO_2NHCOCH_2$-R′												
VII		-$COCH_3$	143	colorless plates	EtOH	$C_9H_{10}O_4N_2S$	44.72	4.16	11.56	44.62	4.03	11.25
VIII		-C_6H_5	218 (decomp.)	colorless leaflets	Me_2CO	$C_{13}H_{12}O_3N_2S$	56.50	4.37	10.14	56.66	4.15	9.66

p-Acetylbenzenesulfonamide (XII), m.p. 178~179°, was prepared in the following procedure. *p*-Sulfamoylbenzoic acid chloride (X) and ethyl ethoxymagnesiummalonate was reacted in benzene solution to form XI, which was hydrolyzed and decarboxylated to XII.

[*1] Part V. T. Naito, R. Dohmori, T. Kotake: This Bulletin, **12**, 588 (1964).

[*2] Minamifunabori-cho, Edogawa-ku, Tokyo (堂森廉三).

1) T. Naito, R. Dohmori, O. Nagase: Yakugaku Zasshi, **74**, 593 (1954).

2) T. Naito, R. Dohmori, M. Sano: *Ibid.*, **74**, 596 (1954).

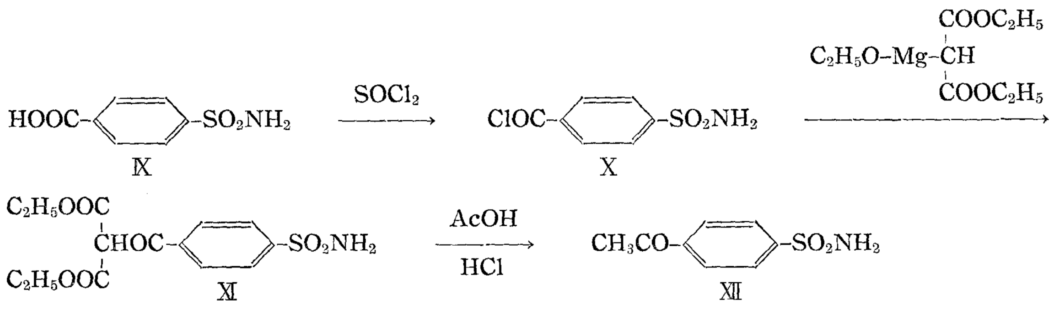


Chart 1.

N-Acetoacetylsulfonamide derivatives (I, Ⅵ, Ⅶ) were synthesized by the reaction of the corresponding sulfonamide derivatives with ketene dimer in acetone solution, and N-phenylacetylsulfonamide derivatives (Ⅲ, V, Ⅷ) were obtained by heating of the corresponding sulfonamide derivatives with phenylacetyl chloride. From the reaction of monochloroacetyl chloride and the sulfonamide derivatives were obtained the corresponding N-chloroacetyl derivatives, which were derived to N-cyanoacetyl derivatives (Ⅱ, Ⅳ) with sodium cyanide.

These N-substituted sulfonamide derivatives were treated with 10% sodium hydroxide. The reactions were observed as follows.

The reactions of I and Ⅱ gave *p*-sulfamoylbenzoic acid (Ⅸ), and Ⅲ, Ⅳ, and V were converted into *p*-substituted benzenesulfonamide (Ⅻ and XⅢ) respectively. Ⅶ was hydrolyzed to N-acetyl-2-pyridinesulfonamide (XIV) and 2-pyridinesulfonamide (XV), and Ⅷ was converted into XV.

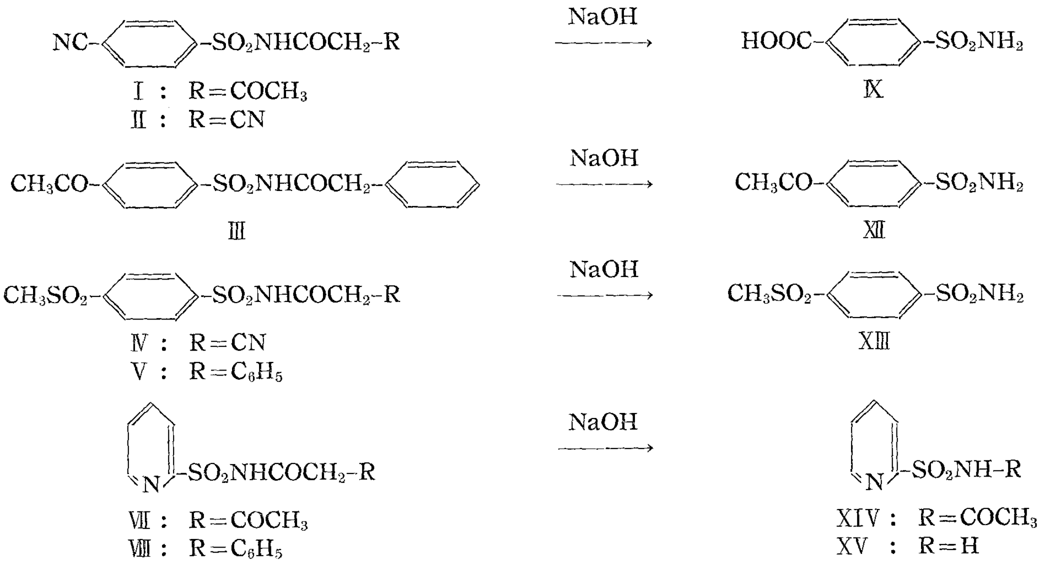


Chart 2.

However, N-acetoacetyl-*p*-methylsulfonylbenzenesulfonamide (Ⅵ) evolved ammonia with 10% sodium hydroxide at 90~95° and the reaction mixture generated a strong odor of sulfur dioxide by acidification with hydrochloric acid. This fact suggested the occurrence of the rearrangement reaction. The colorless crystals, m.p. 137~138° were obtained from the acidic solution and proved to be identical with *p*-methylsulfonylphenylacetic acid (XⅧ).[3]

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[3] H. S. Forrest, A. T. Fuller, J. Walker: J. Chem. Soc., **1948**, 1504.

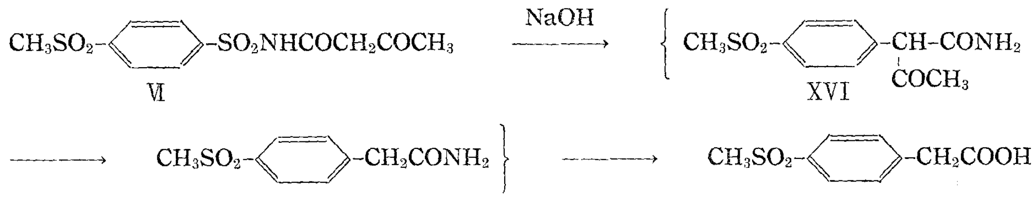

Chart 3.

N-Acetoacetyl-*p*-nitrobenzenesulfonamide gave the acid amide by the rearrangement reaction,[1] but in the case of *p*-methylsulfonyl derivative, it was assumed that the corresponding acid amide was hydrolyzed to XVIII by heating. In addition, N-phenylacetyl derivatives of nitrobenzenesulfonamide underwent rearrangement in alkaline solution,[2] but for the same methylsulfonylbenzenesulfonamide derivative (V) the rearrangement did not occur. These facts showed that the electron attracting effect of methylsulfonyl group is smaller than that of nitro group.

Experimental[*3]

General Procedure of N-Substituted Sulfonamide Derivatives. i) N-Acetoacetyl Derivatives——A solution of ketene dimer in Me_2CO was added dropwise to a solution of the corresponding sulfonamide derivative in 10% NaOH with stirring at below 5°. The reaction mixturen was allowed to stand overnight at a room temperature and acidified with 10% HCl. The precipitate was filtered off.

ii) N-Phenylacetyl Derivatives——A mixture of phenylacetyl chloride and the corresponding sulfonamide derivative was fused on an oil bath (150°) for 1 hr. After cooling the reaction mixture was treated with H_2O and the material was taken by suction and recrystallized.

iii) N-Chloroacetyl Derivatives——To a solution of the corresponding sulfonamide derivative in 10% NaOH was added monochloroacetyl chloride dropwise under stirring at 5°. After allowing to stand for 1 hr., the reaction mixture was adjusted to pH 5.0 with 10% AcOH and the crystalline material was filtered off. The filtrate was acidified with 10% HCl and the resulting precipitate was collected and recrystallized.

N-Chloroacetyl-*p*-cyanobenzenesulfonamide was recrystallized from benzene to give colorless needles, m.p. 153~154°. *Anal.* Calcd. for $C_9H_7O_3N_2SCl$: N, 10.83. Found : N, 11.04.

N-Chloroacetyl-*p*-methylsulfonylbenzenesulfonamide was also obtained from EtOH as colorless leaflets, m.p. 168~170°. *Anal.* Calcd. for $C_9H_{10}O_5NS_2Cl$: C, 34.67; H, 3.23. Found : C, 34.46; H, 3.61.

iv) N-Cyanoacetyl Derivatives——A mixture of N-chloroacetyl derivatives in 10% NaOH and NaCN auas allowed to stand overnight at a room temperature. The reaction mixture was acidified with HCl and the separated crystals were recrystallized.

***p*-Acetylbenzenesulfonamide (*p*-Sulfamoylacetophenone) (XII)**——*p*-Sulfamoylbenzoic acid (10 g.) was converted into the chloride by treatment on a steam bath for about 5 hr. with a mixture of $SOCl_2$ (10.7 g.) and benzene (80 ml.) containing a few drops of pyridine. The solvent and excess $SOCl_2$ were removed *in vacuo*. Benzene solution (60 ml.) of the chloride was added dropwise to a solution of ethyl ethoxymagnesiummalonate[*4] in warm benzene (70 ml.). A yellow gelatinous mass separated and the mixture was warmed on a steam bath for 1 hr., and treated with 10% H_2SO_4 after cooling. The benzene layer was dried and evaporated *in vacuo*. The brown syrupy residue was refluxed for 2 hr. with a mixture of conc. HCl (40 ml.), AcOH (40 ml.) and H_2O (20 ml.). The mixture was diluted with H_2O (100 ml.) and cooled. The precipitate was recrystallized from MeOH to form colorless needles, m.p. 177~179°. Yield, 6.0 g. (63.8%). *Anal.* Calcd. for $C_8H_9O_3NS$: C, 48.22; H, 4.55; N, 7.03. Found : C, 48.12; H, 4.44; N, 7.14.

N-Acetyl-2-pyridinesulfonamide (XIV)——To a mixture of 2-pyridinesulfonamide (320 mg.) in Ac_2O (2 ml.) was added one drop of H_2SO_4. The reaction mixture was heated on a steam bath for 30 min. and evaporated to dryness *in vacuo*. The residue was poured into ice H_2O. The crystals were recrystallized from MeOH to give colorless prisms, m.p. 220~221° (decomp.). Yield, almost quantitatively. *Anal.* Calcd. for $C_7H_8O_3N_2S$: C, 42.03; H. 4.02; N, 13.99. Found : C, 42.25; H, 3.93; N, 13.88.

[*3] All melting points are uncorrected.

[*4] This compound was prepared from Mg (1.52 g.), ethyl malonate (10 g.) in abs. EtOH (8 ml.) and five drops of CCl_4 as described by H. Lund.[4]

4) H. Lund : Ber., **67**, 937 (1934).

Reaction of N-Substituted Sulfonamide Derivatives. i) N-Acetoacetyl-*p*-cyanobenzenesulfonamide (I)——I (1.33 g.) in 10% NaOH (8 ml.) was heated at 70～80° for 2 hr. Acidification of the reaction mixture with 10% HCl gave colorless crystals, which showed m.p. 282° (decomp.) after recrystallization from H_2O. It was identical with *p*-sulfamoylbenzoic acid (Ⅸ) by the mixed melting point test and the comparison of IR spectra with an authentic sample.

ii) N-Cyanoacetyl-*p*-cyanobenzenesulfonamide (II)——When Ⅱ was treated with 10% NaOH at a room temperature for 15 hr. or at 90～95° for 20 min., Ⅱ also gave Ⅸ quantitatively.

iii) N-Phenylacetyl-*p*-acetylbenzenesulfonamide (III)——A mixture of Ⅲ (5 g.) in 10% NaOH (45 ml.) was heated on a steam bath (90°) for 3 hr. After cooling the reaction mixture, the colorless material was crystallized. The material was suspended in H_2O and treated with 10% HCl. The resulting precipitate (2.8 g. or 88%) was recrystallized from MeOH to form colorless prisms, m.p. 178～179°, which were identical with *p*-sulfamoylacetophenone by the mixed melting point test.

iv) N-Cyanoacetyl-*p*-methylsulfonylbenzenesulfonamide (IV)——By heating of a mixture of Ⅳ (900 mg.) and 10% NaOH (6 ml.) at 90～95° for 2 hr. was produced colorless crystals (540 mg. or 76.8%), m.p. 238～239°, which were identical with *p*-methylsulfonylbenzenesulfonamide (ⅩⅢ) by mixed melting point test.

v) N-Phenylacetyl-*p*-methylsulfonylbenzenesulfonamide (V)——When Ⅴ was treated with 10% NaOH as described above, Ⅴ also gave ⅩⅢ.

vi) N-Acetoacetyl-2-pyridinesulfonamide (VII)——a) Reaction at 20～25°: After standing a solution of Ⅶ (500 mg.) in 10% NaOH (4 ml.) for 20 hr. at 20～25°, the reaction mixture was acidified with HCl and colorless precipitate (350 mg.) was collected by filtration. The precipitate was separated into two fractions by Me_2CO. The easily soluble material gave colorless plates, m.p. 143° from MeOH, which were undepressed on admixture with an authentic Ⅶ. The Me_2CO insoluble material was recrystallized from MeOH to give colorless prisms, m.p. 221° (decomp.), which were identical with N-acetyl-2-pyridinesulfonamide (XIV) synthesized by the other procedure.
b) Reaction at 90～95°: By heating of a mixture of Ⅶ (500 mg.) and 10% NaOH (4 ml.) were obtained colorless plates, m.p. 143～145°. Yield, 220 mg. (69.6%). The mixture of this compound and Ⅶ (m.p. 143°) melted at 110～120°, but the melting point of this compound was not depressed by admixture with 2-pyridinesulfonamide (XV) (m.p. 143～145°).

vii) N-Phenylacetyl-2-pyridinesulfonamide (VIII)——When Ⅷ was treated with 10% NaOH at 90～95° for 4 hr., Ⅷ was hydrolized to XV.

Rearrangement Reaction of N-Acetoacetyl-*p*-methylsulfonylbenzenesulfonamide (VI): Formation of XVIII——A mixture of Ⅵ (320 mg.) and 10% NaOH (2 ml.) was heated on a steam bath (90～95°) for 40 min. and acidified with HCl. Recrystallization of the product from EtOH gave colorless needles, m.p. 137～138°. Yield, 150 mg. (70%). *Anal.* Calcd. for $C_9H_{10}O_4S$: C, 50.45; H, 4.70. Found: C, 50.37; H, 4.58.

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Summary

N-Substituted benzenesulfonamide derivatives, which possessed electron attracting group in *para*-position, treated with 10% NaOH. N-Acetoacetyl-*p*-methylsulfonylbenzenesulfonamide underwent the rearrangement reaction to form *p*-methylsulfonylphenylacetic acid. The other compounds were all hydrolyzed.

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