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159. Hiroshi Kugita, Mikio Takeda, Toyonari Oine, and Ko Higaki : Alkylsulfonyltoluene Derivatives (Diuretics. I.).

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Since the derivatives of *m*-benzenedisulfonamide attracted attention as orally active diuretics, a great number of compounds of this series with various substituents on the benzene ring have hitherto been synthesized.[1] According to a general survey of the literatures in this field compounds of the aminobenzenedisulfonamide series appeared to be currently of interest. Correlation between substituents on the benzene ring and diuretic activity was studied; for example, introduction of a chlorine, bromine, or trifluoromethyl group into the 5-position, *ortho* to the second sulfamyl group, of aminobenzenedisulfonamide improves activity. Further extensive studies resulted in the synthesis of the heterocyclic compounds, 2*H*-1,2,4-benzothiadiazine 1,1-dioxides and their hydrogenated derivatives from which many compounds of practical value have stemmed.[2] Studies on diuretics which started from benzenedisulfonamides thus seem to have been directed toward the heterocyclic compounds. The heterocycles, 2*H*-1,2,4-benzothiadiazine 1,1-dioxides and their hydrogenated derivatives were primarily developed from simple aminobenzenedisulfonamide derivatives in which two sulfamoyl groups on the benzene ring were regarded essential for diuretic activity. In the heterocycles two sulfamoyl groups, one of which is intact and the other forms part of the heterocyclic ring, are also significant. Any type of substituent on one of the two sulfamoyl groups of the *m*-benzenedisulfonamide series is reported to decrease the activity.[1c,2g]

It was interesting to us to see whether the substitution of one of the two sulfamoyl groups in the *m*-benzenedisulfonamide series by an alkylsulfonyl group would produce diuretic properties. The replacement of the sulfamoyl group of 4-amino-6-chloro-*m*-benzenedisulfonamide by an alkylsulfonyl group appeared in the literatures.[1d,2g] It is reported that introduction of a methylsulfonyl group in place of one of the sulfamoyl groups decreased diuretic activity.

The compounds which we synthesized include those in which one of the two sul-

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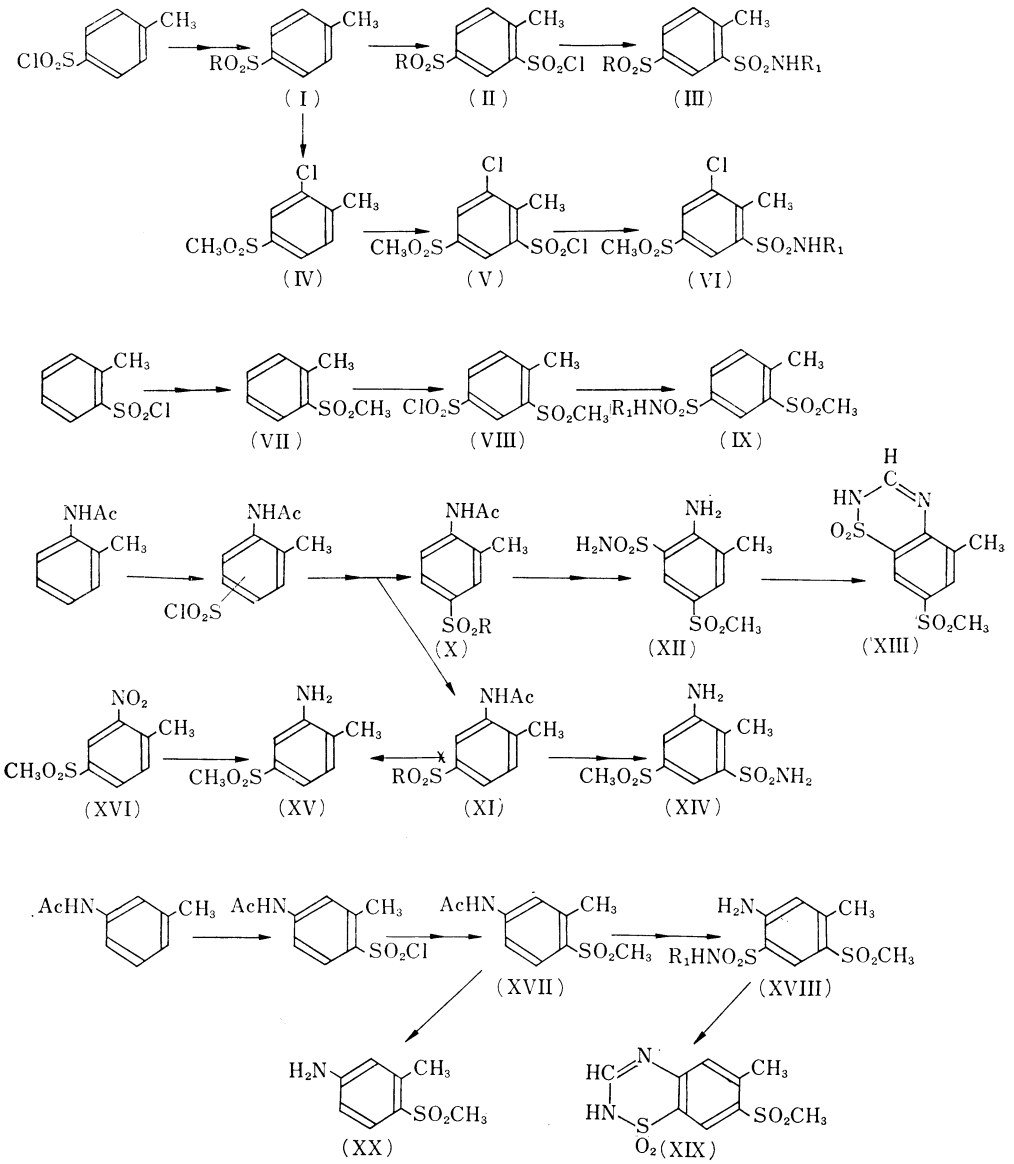
1) *a*) F.C. Novello, J.M. Sprague; J. Am. Chem., Soc., **79**, 2028 (1957). *b*) B.G. Boggiano, S. Condon, M.T. Davis, G.B. Jackman, B.G. Overell, V. Petrow, O. Stephenson, A.M. Wild : J. Pharm. and Pharmacol., **12**, 419 (1960). *c*) B.G. Boggiano, V. Petrow, O. Stephenson. A.M. Wild : *Ibid.*, **12**, 497 (1960). *d*) F.C. Novello, S.C. Bell, E.L.A. Abrams, C. Ziegler, J.M. Sprague : J. Org. Chem., **25**, 965 (1960).

2) *a*) F.C. Novello, J.M. Sprague : J. Am. Chem. Soc., **79**, 2028 (1957). *b*) C.T. Holdrege, R.B. Babel, L.C. Chency : *Ibid.*, **81**, 4807 (1959). *c*) W.J. Close, L.R. Swett, L.E. Brady, J.H. Short, M. Vernsten : *Ibid.*, **82**, 1132 (1960), *d*) J.H. Short, U. Biermacher : *Ibid.*, **82**, 1135 (1960). *e*) L.H. Warner, A. Haramandaris, S. Ricca, Jr., L. Porfman, G. DE Stevens : *Ibid.*, **82**, 1161 (1960). *f*) H.L. Yale, K. Losee, J. Bernsten : *Ibid.*, **82**, 2042 (1960). *g*) F.C. Novello, S.C. Bell, E.L.A. Abrams, C. Ziegler, J.M. Sprague : J. Org. Chem., **25**, 970 (1960).

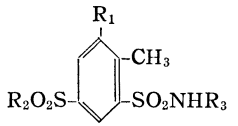
famoyl groups of toluene-2,4-disulfonamide was replaced by an alkylsulfonyl group, their N-substituted compounds and the related derivatives with a chlorine or an amino group on the benzene ring.

4-Alkylsulfonyltoluenes (I) R=CH_3, C_2H_5, and C_3H_7)[3] were heated with chlorosulfonic acid at 120~130° for 2~3 hours to give the sulfonyl chlorides (II). Conversion of the sulfonyl chlorides (II) to the sulfonamides (III), in cases where R_1=H, CH_3, and C_2H_5, was carried out by adding the sulfonyl chlorides (II) to a large excess of an aqueous solution of ammonia or appropriate aliphatic amines and stirring at room temperature for 1~2 hours. The reactions with propyl, arylalkyl and arylamines were conducted by heating the sulfonyl chlorides with two equivalents or more appropriate amines in acetone solu-



3) P. Oxley, M.W. Partridge, T.D. Robson, W.F. Short: J. Chem. Soc., **1946**, 763.

TABLE I.



No.	R_1	R_2	R_3	m.p. (°C)	Recryst. Solvent	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Diuretic activity
1	H	CH_3	H	200～202	A	$C_8H_{11}NO_4S_2$	38.56	4.45	5.62	38.56	4.45	5.34	++
2	〃	〃	CH_3	123～124	〃	$C_9H_{13}NO_4S_2$	41.07	4.98	5.32	40.73	4.65	5.31	−
3	〃	〃	C_2H_5	108～110	B	$C_{10}H_{15}NO_4S_2$	43.31	5.44	5.04	43.32	5.11	4.73	−
4	〃	〃	n-C_3H_7	114～115.5	A	$C_{11}H_{17}NO_4S_2$	45.2	5.86	4.79	45.02	5.98	5.38	++
5	〃	〃	$CH_2C_6H_5$	152～154	〃	$C_{15}H_{17}NO_4S_2$	53.1	5.05	4.13	53.05	5.14	3.94	−
6	〃	〃	C_6H_5	165～166	〃	$C_{14}H_{15}NO_4S_2$	51.69	4.64	4.31	51.62	4.65	4.35	+
7	〃	〃	m-ClC_6H_4	198～201	C	$C_{14}H_{14}NO_4S_2$	46.73	3.92	3.89	47.69	3.94	4.05	++
8	〃	C_2H_5	H	124～126	A	$C_9H_{13}NO_4S_2$	41.07	4.98	5.32	41.04	5.1	5.14	−
9	〃	〃	CH_3	80～82	〃	$C_{10}H_{15}NO_4S_2$	43.31	5.44	5.04	42.57	5.0	4.74	−
10	〃	〃	C_2H_5	91～96	〃	$C_{11}H_{17}NO_4S_2$	45.34	5.87	4.8	44.53	5.68	4.65	−
11	〃	〃	C_6H_5	126～128	〃	$C_{15}H_{17}NO_4S_2$	53.1	5.05	4.13	53.01	5.03	4.24	+
12	〃	〃	o-ClC_6H_4	167～170	C	$C_{15}H_{16}ClNO_4S_2$	48.18	4.3	3.74	47.52	4.17	4.11	−
13	〃	〃	m-ClC_6H_4	83～85	B*	$C_{15}H_{16}ClNO_4S_2$	48.18	4.3	3.74	49.42	4.9	3.96	−
14	〃	〃	p-ClC_6H_4	202～203	C	$C_{15}H_{16}ClNO_4S_2$	48.18	4.3	3.74	46.96	3.87	3.96	−
15	〃	C_3H_7	H	163～165	A	$C_{10}H_{15}NO_4S_2$	43.31	5.44	5.04	43.88	5.47	4.91	−
16	〃	〃	CH_3	104～106	〃	$C_{11}H_{17}NO_4S_2$	45.34	5.87	4.8	45.0	5.62	4.79	++
17	〃	〃	C_6H_5	175～176.5	C	$C_{16}H_{19}NO_4S_2$	54.37	5.41	3.96	54.29	5.35	3.97	+
18	〃	〃	o-ClC_6H_4	103～106	A	$C_{16}H_{18}ClNO_4S_2$	49.53	4.66	3.61	49.55	4.81	3.88	−
19	〃	〃	m-ClC_6H_4	155～157	B*	$C_{16}H_{18}ClNO_4S_2$	49.53	4.66	3.61	50.31	4.9	3.76	++
20	Cl	CH_3	H	200～202	C	$C_8H_{10}ClNO_4S_2$	33.86	3.55	4.93	33.69	3.49	4.88	++
21	〃	〃	CH_3	170～171.5	A	$C_9H_{12}ClNO_4S_2$	36.31	4.06	4.7	36.32	4.29	4.74	++
22	〃	〃	iso-C_3H_7	142～143	〃	$C_{11}H_{16}ClNO_4S_2$	40.56	4.95	4.3	39.59	4.66	4.16	++
23	〃	〃	C_6H_5	175～176	C	$C_{14}H_{14}ClNO_4S_2$	46.73	3.92	3.89	46.89	4.0	4.05	++

A : MeOH-H_2O B : AcOEt-Ligroin C : MeOH D : 80% AcOH E : 10% AcOH

* Aqueous methanol sepprated an oil which formed semi-solid on standing for several days. Recrystallization from AcOEt-Ligroin gave colorless rectangles from with a slight odour or *m*-chloroaniline.

tion for 2~4 hours at the boiling point. 2-Methylsulfonyltoluene (VII) was likewise converted to 3-methylsulfonyl-*p*-toluenesulfonamides (IX) by the same sequence of reactions *via* the sulfonyl chloride (VIII).

4-Methylsulfonyltoluene (I) (R=CH_3) was chlorinated in the presence of antimony trichloride in the molten state[4] to afford 4-methylsulfonyl-6-chlorotoluene (IV). (IV) was converted to the sulfonyl chloride (V) by reaction with chlorosulfonic acid and then to the sulfonamides (VI) with appropriate amines. Alkylsulfonyltoluenesulfonamides and chlorinated analogues thus prepared are listed in Table I.

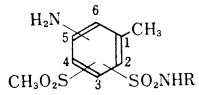
The authors next turned to the synthesis of the amino analogues of alkylsulfonyltoluenesulfonamides. *o*-Acetotoluidide was converted to the sulfonyl chloride by the procedure used in the monochlorosulfonation of acetanilide.[5] The crude semi-solid sulfonyl chloride was reduced with sodium sulfite followed by the reaction with methyl iodide, ethyl bromide and propyl bromide, thus yielding methyl, ethyl, and propylsulfonyltoluene derivatives, respectively. Recrystallization of each of the alkylsulfonyl compounds finally afforded two isomers which were both identified as a mono alkylsulfonyl compound by elemental analysis. Chlorosulfonation of *o*-acetotoluidide was reported to yield 3-acetamido-*p*-toluenesulfonyl chloride in a yield of 51 per cent.[6] Of the two isomers one which has a lower-melting point and was always predominant in yield, was tentatively formulated as 5'-alkylsulfonyl-*o*-acetotoluidide (XI) (R=CH_3, C_2H_5, and C_3H_7). (XI) (R=CH_3) was then hydrolyzed to give the corresponding amino derivative, which was proved to be identical with 5-methylsulfonyl-*o*-toluidide (XV) derived from the known 4-methylsulfonyl-6-nitrotoluene (XVI)[7] by comparison of melting points and infrared spectra. Infrared spectra of the other isomer of a higher-melting point in the case of the methyl, ethyl and propylsulfonyl derivatives showed NH bands at 2.93~2.96 μ and CO bands at 5.9~5.94 μ. On the other hand the isomer (XI) (R=CH_3, C_2H_5, C_3H_7) exhibited absorption bands at 3.05~3.08 μ and 6.02~6.04 μ. When these isomers are compared with aceto-*o*-toluidine which shows the bands at 3.12 μ and 6.05 μ, it seems probable that the shift of NH and CO bands in both isomers to lower wave lengths is caused by the presence of a strong electronegative RSO_2 group on the benzene ring. The greater shift of the bands displayed by the higher-melting isomer might be due to the RSO_2 group at the *ortho*- or *para*-position to the acetamido group, which may be considered to reduce the ionic state $\overset{+}{\underset{H}{N}}=\overset{O^-}{C}-R$ more remarkably than the RSO_2 group at the *meta*-position. The alkylsulfonyl group in the higher melting isomer (X) (R=CH_3, C_2H_5, C_3H_7) was later found to be located at the 3-position by formation of the heterocyclic compound (XIII). Alkylsulfonyl-*o*-acetotoluidides thus obtained are listed in Table III.

Methylsulfonyl compounds (X, XI) (R=CH_3) were converted *via* the sulfonyl chlorides to the sulfonamides (XII) and (XIV), respectively (XII) afforded the heterocyclic compound, 2*H*-1,2,4-benzothiadiazine 1,1-dioxide (XIII) by heating with formic acid.

m-Acetotoluidide was likewise submitted to chlorosulfonation followed by reduction with sodium sulfite and methylation to afford 4'-methylsulfonyl-*m*-acetotoluidide (XVII). The position of the newly introduced group in (XVII) was well confirmed by comparison of the melting point of the hydrolyzed amino derivative (XX) with that reported in the

4) W. Davies: J. Chem. Soc., **1921**, 853.
5) Org. Syntheses, Vol., 5, p. 3 (1925).
6) L. N. Goldyrev, I. Ya. Postorskii: J. Applied Chem., (U. S. S. R.), **11**, 316 (1938); C. A., 32, 5801 (1938).
7) L. Katz, L. S. Karger, W. Schroeder, M. S. Cohen: J. Org. Chem., **18**, 1380 (1953).

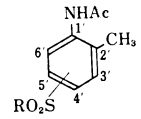
TABLE II.



No.	NH_2	CH_3SO_2	SO_2NHR	m.p. (°C)	Recryst. Solvent	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Diuretic activity
24	6	4	2 R=H	262~263	D	$C_8H_{12}N_2O_4S_2$	36.37	4.58	10.6	36.28	4.58	10.38	±
25	6	3	5 R=H	118~119	C	〃	36.37	4.58	10.6	36.27	4.19	10.6	++
26	5	2	4 R=H	233~235	E	〃	36.37	4.58	10.6	36.15	4.47	10.79	−
27	5	2	4 R=CH_3	150~151	A	$C_9H_{14}N_2O_4S_2$	38.85	5.07	10.07	37.04	5.12	9.93	−

A : MeOH-H_2O B : ACOH-Ligroin C : MeOH D : 80% AcOH E : 10% AcOH

TABLE III.



RSO_2	m.p. (°C)	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
5′ R=CH_3	141~143	$C_{10}H_{13}NO_3S$	52.86	5.77	6.17	52.8	5.66	6.13
4′ R=CH_3	220~222	〃	52.86	5.77	6.17	52.8	5.7	6.07
5′ R=C_2H_5	115~116	$C_{11}H_{15}NO_3S$	54.76	6.27	5.81	54.85	6.22	5.74
4′ R=C_2H_5	166~168	〃	54.76	6.27	5.81	54.31	6.29	5.67
5′ R=C_3H_7	108~110	$C_{12}H_{17}NO_3S$	56.46	6.71	5.49	56.76	6.68	5.4
5′ R=C_3H_7	120~121	〃	56.46	6.71	5.49	57.49	6.74	5.39

literature.[8] (XVII) was converted to the sulfonamides (XVIII) (R_1=H, CH_3) in the usual way. (XVIII) (R_1=H) produced the heterocyclic compound (XIX) by heating with formic acid. The amino analogues of alkylsulfonyltoluenesulfonamides are given in Table II.

Compounds reported herein were screened for diuretic activity by the diuretic bioassay using mice.[9] Each compound was administered orally at a dose of 0.5 mg./10 g. in the form of 0.5% suspension in carboxymethylcellulose (CMC). Hydrochlorothiazide (6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide) was used as a criterion at the same dose level. Diuretic activites shown in the tables with the marks ++, +, ±, and − were determined by comparison of excreted urine volumes; ++ represents nearly the same activity as that of hydrochlorothiazide at the given dose level, and − shows inactivity. Intermediate values + and ± represent moderate activity and slight activity as compared with that of hydrochlorothiazide. Diuretic activity appeared to reside generally in 5-alkylsulfonyl-*o*-toluenesulfonamide derivatives (Table I) except for 4-ethylsulfonyl analogs, while 3-methylsulfonyl-*p*-toluenesulfonamides (IX) exhibited no activity. Introduction of a chlorine atom into the benzene ring increased activity.

Experimental*2

5-Alkylsulfonyl-*o*-toluenesulfonyl chloride (II)——R=CH_3 : 4-Methylsulfonyltoluene[3] (50 g.) was added to $ClSO_3H$ (250 cc.) under stirring at room temperature. The mixture was heated slowly to 120~130°, and stirring was continued for 2 hr. The mixture was poured onto cracked ice and the white precipi-tate was filtered, washed with water and dried in a desiccator to give the crude sulfonyl chloride (II) (75 g.).

*2 All melting points are uncorrected.

8) P. Pfeifer, H. Jager : Ber., **75B**, 1885 (1942).
9) G. Hayashi, K. Higaki, S. Nakagami, Y. Kowa : Yakugaku-Kenkyu, **31**, 706 (1959).

The analytical sample was recrystallized from a mixture of Me_2CO and benzene; colorless needles, m.p. 143~144°. *Anal.* Calcd. for $C_8H_9O_4ClS_2$: C, 35.75; H, 3.37. Found : C, 35.82; H, 3.22. This crude material was used in the next step without purification.

R=C_2H_5 : Colorless needles (from Me_2CO), m.p. 121~122°. *Anal.* Calcd. for $C_9H_{11}O_4ClS_2$: C, 38.23; H, 3.91. Found : C, 38.03; H, 3.93.

R=C_3H_7 : Colorless rectangles (from benzene-ligroin), m.p. 73~75°. *Anal.* Calcd. for $C_{10}H_{13}O_4ClS_2$: C, 40.47; H, 4.41. C, 41.18; H, 4.45.

5-Alkylsulfonyl-*o*-toluenesulfonamides (III) (Table I, No. 1~19)——General procedure. R_1=H: The sulfonyl chloride (II) (5.0 g.) was added to 30% NH_4OH (20 cc.) and stirred for 1~2 hr. at room temperature. NH_3 was removed under reduced pressure in a water bath. The crude sulfonamide that separated out was filtered and dissolved in 5% NaOH. The alkaline solution was filtered and acidified with 10% HCl. Recrystallization from appropriate solvents gave the pure sulfonamide (III : R_1=H).

R_1=CH_3, C_2H_5 : To an aqueous solution (30%, 20 cc.) of $MeNH_2$ ($EtNH_2$) was added the sulfonyl chloride (5 g.) and the mixture worked up in the same way as in R_1=H.

R_1=C_3H_7, C_6H_5 and $C_6H_5CH_2$: A mixture of the sulfonyl chloride (II) and 2.5 moles. equiv. of an appropriate amine was heated in Me_2CO for 2~4 hr. after which Me_2CO was distilled. The residue was dissolved in 5% NaOH and shaken with Et_2O to remove the amine. The aqueous layer was acidified with 10% HCl and filtered to give the crude sulfonamide, which was purified by recrystallization. The general procedure mentioned above was also applicable to the syntheses of compounds (VI), (IX), (XII), (XIV), and (XVIII).

4-Methylsulfonyl-6-chlorotoluene (IV)——To a melted mixture of 4-methylsulfonyltoluene (30 g.) and $SbCl_3$ (0.8 g.) was introduced Cl_2 at such a rate as to maintain the temperature of the content at 85~90° until the increase in its weight reached 7 g. (ca. 3 hr.). The reaction mixture, which solidified on cooling, was dissolved in benzene, washed with water, 5% NaOH, and again with water. The dried solution was evaporated to give a crystalline residue which was crystallized from 80% MeOH, m.p. 92~94° (30 g.). The analytical sample was recrystallized from Et_2O to form colorless plates, m.p. 95~96°. *Anal.* Calcd. for $C_8H_9O_2ClS$: C, 46.95; H, 4.43. Found : C, 46.95; H, 4.24.

3-Chloro-5-methylsulfonyl-*o*-toluenesulfonyl chloride (V)——(IV) (15 g.) was added under stirring to $ClSO_3H$ (75 cc.) and the mixture heated at 115~125° for 3 hr. The crude wet sulfonyl chloride was dissolved in warm benzene and the separated aqueous layer was discarded. Evaporation of benzene gave the sulfonyl chloride (V) (16.5 g.), m.p. 184~186°. Analytical sample; colorless needles, m.p. 186~187° (from Me_2CO). *Anal.* Calcd. for $C_8H_8O_4Cl_2S_2$: C, 31.69; H, 2.65. Found : C, 31.69; H, 2.83.

3-Chloro-5-methylsulfonyl-*o*-toluenesulfonamides (VI) (Table I, No. 20~23)——The synthesis of sulfonamides (VI) from (V) was carried out by the general procedure described in the synthesis of (III).

3-Methylsulfonyl-*p*-toluenesulfonamides (IX) (R_1=H, Ph)——*o*-Toluenesulfonyl chloride (45 g.) was reduced with a mixture of $Na_2SO_3 \cdot 7H_2O$ (120 g.), $NaHCO_3$ (40 g.), and water (250 cc.) in the same way as the *p*-isomer.[3] The filtered aqueous solution was concentrated to a half of its volume, treated with EtOH (120 cc.) and MeI (30 cc.), and the solution heated to reflux for 11 hr. in a water bath. The reaction mixture was concentrated to a half of its volume and extracted thrice with Et_2O. The ethereal extracts were evaporated and distilled at 157~159° (6 mm.) to yield 15 g. of 2-methylsulfonyltoluene (VII) which was chlorosulfonated with 75 cc. of $ClSO_3H$ in the usual way. One half of the crude sulfonyl chloride (VIII) was treated with 200 cc. of NH_4OH according to the general procedure. The sulfonamide (IX) (R_1=H) was obtained from EtOH in colorless plates, m.p. 159~161°; yield 7 g. *Anal.* Calcd. for $C_8H_{11}O_4NS_2$: C, 38.56; H, 4.45; N, 5.62. Found : C, 38.72; H, 4.51; N, 5.48.

The other half of the crude sulfonyl chloride was heated with aniline (15 g.) in Me_2CO and worked up as usual. Recrystallization from aq. MeOH gave (IX) (R_1=Ph) as colorless rectangles, m.p. 170~172°; yield 8.2 g. *Anal.* Calcd. for $C_{14}H_{15}O_4NS_2$: C, 51.69; H, 4.65; N, 4.31. Found : C, 51.68; H, 4.54; N, 4.31.

Chlorosulfonation of *o*-Acetotoluidide——*o*-Acetotoluidide (74.5 g.) was added under stirring to $ClSO_3H$ (250 g.) during 40 min. at 10~15°. The mixture was stirred at the same temperature for an additional 20 min., then at 55~60° for 2 hr. The reaction mixture was poured onto cracked ice, and the semi-solid sulfonyl chloride was washed with water and filtered.

Reduction of Acetoamidotoluenesulfonyl chloride——The crude sulfonyl chloride, $Na_2SO_3 \cdot 7H_2O$ (250 g.) and water (500 cc.) were stirred for 3 hr. during which period 50% NaOH was added at intervals to maintain the solution slightly alkaline. The filtered solution was concentrated to a small volume under reduced pressure. A mixture of the sodium sulfinate and inorganic material was collected and used in the next step.

4'-Alkylsulfonyl-*o*-acetotoluidides (X) and 5'-Alkylsulfonyl-*o*-acetotoluidide (XI)——R=CH_3 : A solution of one-third of the crude sodium sulfinate and MeI (20 cc.) in 50% EtOH (160 cc.) was refluxed for 10 hr. Concentration of the solution to about a half of its volume separated a mixture of the reaction product and inorganic materials. Extraction with Et_2O (3~4 times) and evaporation of the combined Et_2O extracts gave a crystalline product which was recrystallized from water to give 3.5 g. of

(XI) (R=CH_3) as colorless needles, m.p. 141~143°. IR λ_{max}^{Nujol} μ: 3.08, 6.04. To the aqueous phase water was added to re-dissolve inorganic materials and the insoluble organic crystals were filtered. Recrystallization from 50% EtOH afforded (X) (R=CH_3), m.p. 212~217°, which formed colorless prisms, m.p. 220~222°, by recrystallization from water. Yield 1.5 g. IR λ_{max}^{Nujol} μ: 2.96, 5.91. The mother liquo γ (50% EtOH) was concentrated and filtered; m.p. 110~140°. Recrystallization from water furnished an additional 3 g. of (XI) (R=CH_3), m.p. 141~143°.

R=C_2H_5: One-third of the crude sodium sulfonate, EtBr (20 cc.), EtOH (80 cc.) and water (80 cc.) were heated together for 10 hr. The solution was concentrated to a half of its volume and extracted several times with Et_2O. Evaporation of Et_2O and recrystallization of the residue from EtOH afforded a product of m.p. 112~145° which was raised to 183~186° by recrystallization from EtOH and finally to 186~188° (colorless prisms) by an additional purification from water. Yield, 1.6 g. of (X) (R=C_2H_5). IR λ_{max}^{Nujol} μ: 2.95, 5.90. The combined filtrates were evaporated to dryness and the residue was recrystallized twice from water to give (XI) (R=C_2H_5) as colorless needles, m.p. 115~116°; yield, 4.7 g. IR λ_{max}^{Nujol} μ: 3.06, 6.02.

R=C_3H_7: The last one-third of the crude sodium sulfinate was likewise alkylated with PrBr (20 cc.) in aq. EtOH. After concentration of the reaction mixture to about a half of its volume water was added to re-dissolve the separated inorganic materials and the insoluble crystals were filtered. Recrystallizations from aq. EtOH (3:1) and then from EtOH afforded (X) (R=n-C_3H_7) as colorless plates, m.p. 120~121° (2.0 g.). IR λ_{max}^{Nujol} μ: 2.93, 5.93. The combined mother liquors were concentrated and filtered. Recrystallization from aq. EtOH gave (XI) (R=n-C_3H_7) as colorless needles, m.p. 108~111° (5.2 g.). IR λ_{max}^{Nujol} μ: 3.05, 6.02.

2-Amino-5-methylsufonyl-*m*-toluenesulfonamide (XII) (Table II, No. 25)——(X) (R=CH_3) (1.0 g.) was chlorosulfonated with 5 cc. of $ClSO_3H$ in the usual way. The sulfonyl chloride was treated with NH_4OH (10 cc.) by the general precedure to give (XII).

5-Methyl-7-methylsulfonyl-2*H*-1, 2, 4-benzothiadiazine 1, 1-dioxide (XIII)——(XII) (0.1 g.) and 98% HCOOH were heated under gentle reflux for 2 hr. Distillation of HCOOH gave a crystalline residue which was recrystallized from aq. MeOH to give colorless needles, m.p. 325~326° (decomp.). *Anal.* Calcd. for $C_9H_{10}O_4N_2S_2$: C, 39.42; H, 3.68; N, 10.22. Found: C, 39.34; H, 3.71; N, 10.88. IR λ_{max}^{Nujol} μ: 3.12, 6.14.

5-Methylsulfonyl-*o*-toluidine (XV)——a) 5'-Methylsulfonyl-*o*-acetotoluidide (XI) (R=CH_3) (0.5 g.) and 10% HCl (10 cc.) were heated for 1 hr., and the solution was basified with 10% NaOH and filtered. Recrystallization from water gave colorless needles of (XV) (0.3 g.), m.p. 114~116°. *Anal.* Calcd. for $C_8H_{11}O_2N_2S$: C, 51.88; H, 5.99; N, 7.56. Found: C, 51.59; H, 5.87; N, 7.44.

b) 4-Methylsulfonyl-6-nitrotoluene (XVI) was prepared from 4-methylsulfonyltoluene (I) (R=CH_3) (10 g.) following the Katz's method;[7] yield, 11.2 g., m.p. 118~119°. (XVI) (2.2 g.) was heated with Sn (4 g.) and conc. HCl (25 cc.) in a steam bath. The filtered solution was treated with H_2S and filtered. The acidic solution was made alkaline with 10% NaOH and the separated amino compound was filtered. Recrystallization from water afforded (XV) (1.2 g.), m.p. 114~116°, undepressed by admixture with the sample obtained in a).

4'-Methylsulfonyl-*m*-acetotoluidide (XVII)——Chlorosulfonation of *m*-acetotoluidide (65 g.) was effected by the procedure given in the synthesis of 4-acetamido-*o*-toluenesulfonyl chloride. The semi-solid sulfonyl chloride was added to a stirred solution of $Na_2SO_3 \cdot 7H_2O$ (250 g.) in water (500 cc.), which was preheated and maintained at 60~70° during the reaction. The addition was completed in 2 hr. during which 50% NaOH was added at intervals to make the solution slightly alkaline. After concentration of the solution the sodium sulfinate, accompanied with a substantial amount of inorganic material, was filtered and methylated with MeI (50 cc.) in aq. EtOH. The solution was concentrated to dryness and extracted twice with 400 cc. of warm AcOEt. The dried extracts were evaporated to give a syrup (15 g.), which was chromatographed in $CHCl_3$ solution on Al_2O_3 and eluted with Me_2CO. Evaporation of Me_2CO gave a light yellow syrup (13 g.) which solidified on standing. Recrystallization from AcOEt-Et_2O gave colorless rectangles of (XVII) (10.3 g.), m.p. 92~94°. *Anal.* Calcd. for $C_{10}H_{13}O_3NS$: C, 52.86; H, 5.77; N, 6.17. Found: C, 52.74; H, 5.8; N, 6.29.

Neither of the possible isomers, 2'-and 6'-methylsulfonyl derivatives was obtained in this experiment.

4-Methylsulfonyl-*m*-toluidine (XX)——(XVII) (0.9 g.) was heated with 10% HCl (10 cc.) for 1.5 hr. and basified with 10% NaOH. The amino compound was filtered and recrystallized from water; m.p. 154~156° (155°).[9] *Anal.* Calcd. for $C_8H_{11}O_2N_2S$: C, 51.88; H, 5.99; N, 7.56. Found: C, 51.73; H, 5.94; N, 7.75.

2-Amino-5-methylsulfonyl-*p*-tuluenesulfonamides (XVIII) (Table II, No. 26, 27)——(XVII) (6.8 g.) was heated with $ClSO_3H$ (35 cc.) at 120~125° for 2 hr, The reaction mixture was poured into ice-water and the sulfonyl chloride was filtered, washed with water, then with 50% aq. Me_2CO and dried in a desiccator (7 g.); m.p. 179~180° (from Me_2CO-Et_2O). The sulfonyl chloride was converted to the sulfonamides (XVIII) (R_1=H and CH_3) as usual.

6-Methyl-7-methylsulfonyl-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (XIX)——(XVIII) (R_1=H) (0.2 g.) in 98% HCOOH (40 cc.) was heated under reflux for 3 hr. Distillation of the formic acid gave white crystals which were recrystallized from dimethylformamide-H_2O to form colorless needles, m.p. 308~310° (decomp.). *Anal.* Calcd. for $C_9H_{10}O_4N_2S_2$: C, 39.42; H, 3.68; N, 10.22. Found : C, 39.03; H, 3.65; N, 10.47. IR λ_{max}^{Nujol} μ : 3.11, 6.16.

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Summary

Alkylsulfonyltoluenesulfonamides and their derivatives bearing a chlorine and an amino group on the benzene rings, or a variety of substituents on the nitrogen atom were synthesized. All compounds were evaluated for diuretic activity.

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160. Hiroshi Kugita, Mikio Takeda, Toyonari Oine, and Ko Higaki : Alkylsulfonyltoluene Derivatives (Diuretics. II.).*1

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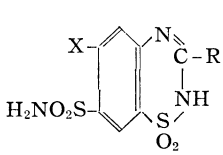
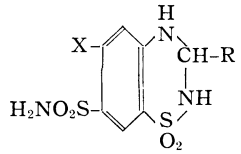
In the preceding paper,*1 the preparation and diuretic activity of alkylsulfonyltoluenesulfonamide derivatives were reported. The diuretic activity, observed generally in this series of compounds, incited us to extend our study of the compounds. The enhanced activity was reported to be observed on conversion of amino-*m*-benzenedisulfonamides to the heterocyclic compounds, 2*H*-1,2,4-benzothiadiazine 1,1-dioxides (A) and their hydrogenated derivatives (B)[1] which could be, considered in a sense as sulfonamide derivatives with a nitrogen-containing substituent, being a part of the unique ring structure, on the sulfamoyl group. It can be also seen in the course of studies on sulfanilamide series that an introduction of the various type of nitrogen-containing substituents on the sulfamoyl group resulted in an increase of potential activity, and in some cases, a littel change has been observed in their properties.



(A)



(B)

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