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.

The authors express their thanks to Mrs. F. Hisamichi and Mr. T. Kono for microanalyses and to Dr. K. Kotera for infrared spectra determinations.

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.

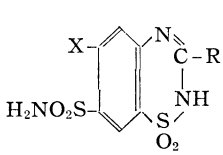
(Received June 8, 1961)

UDC 615.761

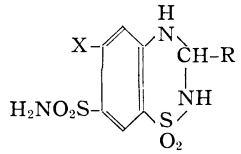
160. Hiroshi Kugita, Mikio Takeda, Toyonari Oine, and Ko Higaki : Alkylsulfonyltoluene Derivatives (Diuretics. II.).*1

(*Osaka Research Laboratory, Tanabe Seiyaku Co., Ltd.**2)

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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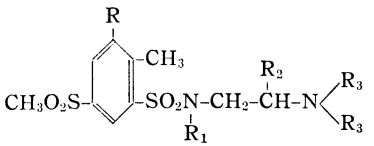
*1 Part I : This Bulletin, **10**, 1001 (1962).

*2 Kajima-cho, Higashiyodogawaku, Osaka (釘田博至, 武田幹男, 大稲豊生, 檜垣 鴻).

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

TABLE I.

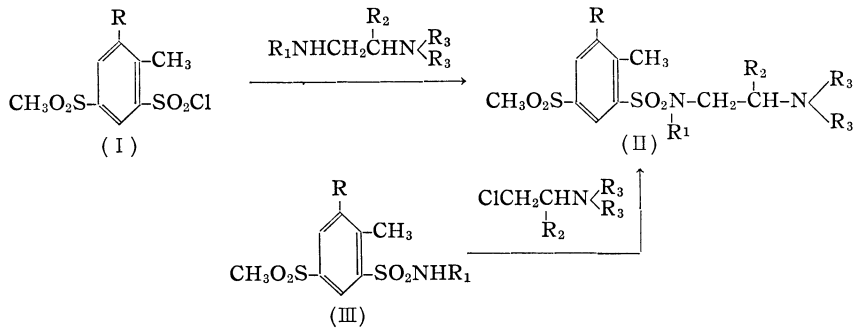


No.	R	R_1	R_2	$N\langle^{R_3}_{R_3}$	m.p. (°C)	Yield (%)	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1	H	H	H	$N(CH_3)_2$	hydrochloride, 250～251 a	28.5 A	$C_{12}H_{21}ClN_2O_4S_2$	40.38	5.93	7.85	40.54	5.53	7.69
2	〃	C_6H_5	〃	〃	hydrochloride, 249～250 a	81 〃	$C_{18}H_{25}ClN_2O_4S_2$	49.93	5.82	6.47	50.3	6.01	6.35
3	〃	CH_3	〃	〃	picrate, 161～162.5 b	36 〃	$C_{19}H_{25}N_5O_{11}S_2$	40.49	4.47	12.43	40.22	4.37	12.52
4	〃	H	〃	Piperidino	114.5～115.5 c	17 〃	$C_{15}H_{24}NnO_4S_2$	49.99	6.71	7.77	50.0	6.75	7.86
5	〃	C_6H_5	〃	$N(C_2H_5)_2$	hydrochloride, 171～172 d	12 C	$C_{20}H_{29}ClN_2O_4S_2$	52.1	6.34	6.07	52.34	6.4	6.27
6	〃	〃	CH_3	〃	Picrate, 156～159 b	44 B	$C_{29}H_{33}N_5O_{11}S_2$	48.87	4.97	10.48	48.87	4.74	10.44
7	〃	〃	H	Piperidino	115.5～117 e	90 A	$C_{21}H_{28}N_2O_4S_2$	57.79	6.47	6.42	57.98	6.5	6.49
8	〃	〃	〃	Morpholino	95～96 f	18 〃	$C_{20}H_{26}N_2O_5S_2$	54.79	5.98	6.39	54.78	5.97	6.43
9	〃	〃	CH_3	〃	hydrobromide, 183～186 g	18 B	$C_{21}H_{29}BrN_2O_5S_2$	47.28	5.47	5.25	47.48	5.37	5.58
10	〃		$-SO_2N\langle\rangle N-Ph$		162～163 b	62 〃	$C_{18}H_{22}N_2O_4S_2$	54.82	5.63	7.1	54.65	5.92	7.22
11	〃	*m*-ClC_6H_4	H	$N(CH_3)_2$	hydrochloride, 240～241.5 a	71 A	$C_{18}H_{24}Cl_2N_2O_4S_2$	46.25	5.17	5.99	46.68	4.99	5.89
12	〃	〃	〃	Piperidino	hydrochloride, 227～228 h	80 〃	$C_{21}H_{28}Cl_2N_2O_4S_2$	49.7	5.55	5.51	50.15	5.65	5.83
13	Cl	H	〃	$N(CH_3)_2$	hydrochloride, 259～261 a	38 〃	$C_{12}H_{20}Cl_2N_2O_4S_2$	36.83	5.15	7.16	36.89	5.36	7.16
14	〃	C_6H_5	〃	〃	105～106 e	20 〃	$C_{18}H_{23}ClN_2O_4S_2$	50.46	5.38	6.5	50.73	5.43	6.34
15	〃	〃	CH_3	$N(C_2H_5)_2$	hydrochloride, 181～183 g	16 B	$C_{21}H_{30}Cl_2N_2O_4S_2$	49.5	5.93	5.49	49.2	5.96	5.53

A : Method A B : Method B C : Method C.
Solvent for Recrystallization : a. 90% EtOH b. EtOH c. Benzene d. EtOH+AcOEt e. MeOH+H_2O
f. Et_2O g. H_2O h. 50% EtOH

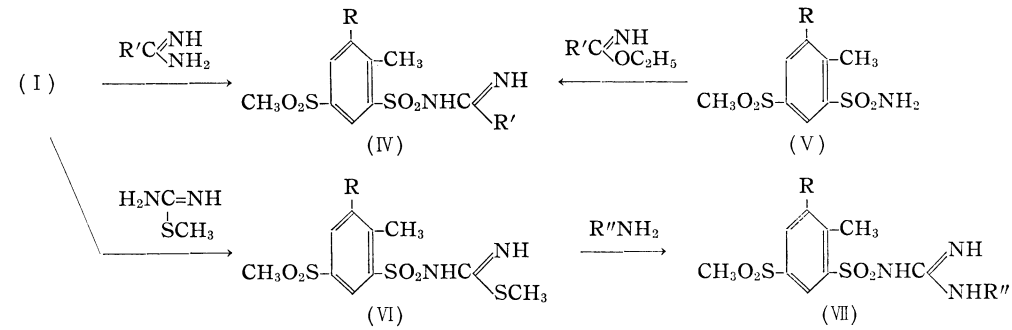
The report deals with the synthesis and biological activities of the compounds derived from alkylsulfonyltoluenesulfonamides by an introduction of nitrogen-containing alkyl groups into the sulfamoyl group as shown below.

5-Methylsulfonyl-*o*-toluenesulfonamides and their chlorinated analogs were employed in the present study as parent compounds. A condensation of sulfonyl chlorides (I)



(R=H, Cl) with substituted ethylenediamines afforded N-(2-dialkylaminoethyl)sulfonamide derivatives (II). A reaction of sodium derivatives of sulfonamides (III) (R=H, Cl, R_1=H, CH_3, C_6H_5) with N,N-dialkyl-2-chloroethylamine was an alternative route predominantly employed in the present study. Optimal conditions of both reactions have not been investigated. Dialkylaminoethyl derivatives (II) thus prepared are shown in Table I.

The alkyl groups with a nitrogen-containing group or two at the α-position were also introduced to the sulfamoyl group. Sulfonyl chloride (I) (R=H, Cl) were converted

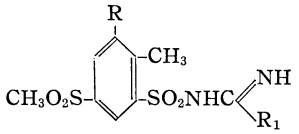


to sulfonamidines (IV) by the reaction with various amidines. Reaction of sulfonamides (V) (R=H, Cl) with ethyl iminoacetate and benzoate illustrated an alternate course to (IV). Sulfonyl chloride (I) were also converted to N-sulfonyl-*S*-methylisothiourea (VI). Displacement of the methylthio group of (IV) to (VII) by aliphatic amines proceeded in ethanol solution at 70~80°. Reaction time depended on the case in which the amines were participated, being increased with an increase of number of carbons. The reaction with aniline, though it was failed to proceed under usual conditions, gave the reaction product, in poor yield, if (VI) was heated with a drop of conc. hydrochloric acid[2] in aniline solution. Compounds (IV), (VI), and (VII) are listed in Table II.

Pharmacology : Compounds listed in Table I and II were tested for diuretic activity.*1 Of the N-(2-*tert*-aminoalkyl)sulfonamide derivatives listed in Table I, Nos, 5, and 13

2) cf. E.C. Tayler, R.J. Knopf, R.F. Meyer, A. Molems, M.L. Hoefle : J. Am. Chem. Soc., **82**, 5712 (1960).

Table II.



No.	R	R_1	m.p. (°C)	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
16	H	CH_3	159~160	$C_{10}H_{14}N_2O_4S_2$	41.38	4.86	9.65	41.06	4.8	9.61
17	〃	C_2H_5	114~115	$C_{11}H_{16}N_2O_4S_2$	43.32	5.3	9.21	43.43	5.38	9.16
18	〃	C_4H_9	148~150	$C_{13}H_{20}N_2O_4S_2$	46.98	6.07	8.43	46.99	6.22	8.45
19	〃	C_6H_5	177~178.5	$C_{15}H_{16}N_2O_4S_2$	51.14	4.58	7.95	50.46	4.76	8.05
20	Cl	CH_3	173~175	$C_{10}H_{13}ClN_2O_4S_2$	36.99	4.04	8.63	37.18	4.0	8.63
21	〃	C_6H_5	212~214	$C_{15}H_{15}ClN_2O_4S_2$	46.58	3.91	7.24	46.68	3.99	7.31
22	H	SCH_3	149~150	$C_{10}H_{14}N_2O_4S_2$	37.44	4.48	8.95	37.3	4.24	8.66
23	Cl	〃	179~180	$C_{10}H_{13}ClN_2O_4S_2$	33.66	3.67	7.87	34.2	3.68	7.26
24	H	$NH \cdot NH_2$	218.5~220	$C_9H_{14}N_4O_4S_2$	35.28	4.61	18.29	34.61	4.36	17.19
25	〃	CH_3NH	195~177	$C_{10}H_{15}N_3O_4S_2$	39.35	5.23	14.53	39.29	5.04	14.24
26	〃	C_2H_5NH	179~180	$C_{11}H_{17}N_3O_4S_2$	41.36	5.37	13.16	41.4	5.56	12.51
27	〃	C_4H_9NH	177~179	$C_{13}H_{21}N_3O_4S_2$	44.94	6.09	12.1	44.56	5.98	12.01
28	〃	C_6H_5NH	221~223	$C_{15}H_{17}N_3O_4S_2$	49.05	4.67	11.44	48.82	4.76	11.62

appeared to be most active, nearly the same as hydrochlorothiazide at the dose levels of 50 mg./kg., 25 mg./kg., and 5 mg./kg. administered orally to mice Nos. 7 and 12 produced a sedative effect at 50 mg./kg. dose. Most of the compounds listed in Table II showed any diuretic activity. Further pharmacological studies will be reported elsewhere.

Experimental*3

N-(2-*tert*-Aminoethyl)-5-methylsulfonyl-*o*-toluenesulfonamides (II)——General procedures illustrated below were alternatively engaged in the syntheses of the compounds listed in Table I.

Method A. (From 5-Methylsulfonyl-*o*-toluenesulfonamides III)——To the solution prepared from Na (2.76 g.) and MeOH (300 cc.) was added 36 g. of 5-methylsulfonyl-*o*-toluenesulfonanilide (III) (R=H, $R_1=C_6H_5$). MeOH was distilled off under reduced pressure on a steam bath and Na salt of the sulfonamide was heated in an oil bath with 300 cc. of toluene and N,N-dimethyl-2-chloroethylamine hydrochloride (prepared from 24 g. of hydrochloride) for 10 hr. The solution was washed with water and evaporated under reduced pressure. The residue was treated with 10% HCl (40 cc.) to separate in a crystalline hydrochloride. Recrystallization from 90% EtOH afforded colorless needles, m.p. 248~249° (No. 2), yield 38.5 g.

Method B. (From 5-Methylsulfonyl-*o*-toluenesulfonyl Chloride I)——A solution of 2.7 g. of 5-methylsulfonyl-*o*-toluenesulfonyl chloride (I) (R=H), 2.1 g. of N-(2-diethylaminopropyl)aniline[3] and 0.8 g. of pyridine in Me_2CO (20 cc.) was refluxed for 4 hr. Me_2CO was removed by distillation and water was added to the residue. The filterate was made alkaline with Na_2CO_3 and extracted with Et_2O. An evaporation of the solvent and distillation of the residue at 220~224° (3 mm.) gave a light yellow oil (1.9 g.) which was characterized as a picrate, yellow square plates, m.p. 156~159° (from EtOH). (No. 6).

Method C. (From 4-Methylsulfonyltoluenesulfonamide. Ethanol Solvent)——To a solution of Na (0.3 g.) in EtOH (20 cc.) was added 2 g. of the sulfonamide (III) (R=H, $R_1=C_6H_5$) and then 1.1 g. of N,N-diethyl-2-chloroethylamine hydrochloride. After 9 hr. reflux of the mixture the solvent was removed by distillation and water was added to the residue. The reaction product was taken into Et_2O, washed with water, dried and evaporated. The residue was dissolved in Et_2O (10 cc.), treated with 30% HCl-MeOH and cooled in a refrigerator. The hydrochloride (0.5 g.), colorless needles, m.p. 171~172°, were crystallized (No. 5).

5-Methylsulfonyl-*o*-toluenesulfamidines (IV)——Following experiment illustrates the general procedure employed in the compounds, Nos. 16~21 (Table II). To a solution of Na (0.51 g.) in EtOH (10 cc.) was added 2 g. of acetamidine hydrochloride followed by an addition of sulfonyl chloride

*3 All melting points were uncorrected.

3) Amines used in the condensation of (I) were supplied by Mr. M. Shigematsu of this laboratory.

(I) (R=H) (2.7 g.) in Me_2CO (30 cc.). The reaction mixture after standing overnight, was heated on a water bath for 1 hr. Separated from NaCl and evaporated. The crystalline residue was washed with water, filtered and recrystallized from water to (IV) (R=H, $R_1=CH_3$), colorless prisms, m.p. 159~160°, yield 1.5 g. (No, 16).

Reaction of 5-Methylsulfonyl-*o*-toluenesulfonamides (V) with Iminoesters. (Alternative Route to IV)——(IV) (R=H, $R_1=CH_3$): (V) (R=H) (2.5 g.) and ethyl iminoacetate hydrochloride (1.9 g.) were added to a solution of Na (0.46 g.) in EtOH (30 cc.) and heated under reflux for 2.5 hr. An evaporeation of the filterate afforded a crystalline residue which was washed with water and recrystallized from MeOH, m.p. 159~160°, yield 0.9 g.

***S*-Methyl-1-(5-methylsulfonyl-*o*-tolylsulfonyl)isothiourea (VI)**——R=H: The synthesis of *S*-methyl-1-(4-acetaminophenylsulfonyl)isothiourea followed to the Birtwell's method.[4] To a suspension of the chloride (I) (R=H) (8.1 g.) and *S*-methylisothiourea sulfate (4.2 g.) in Me_2CO (60 cc.) and water (60 cc.) aq. NaOH (NaOH 2.4 g., H_2O 18 cc.) was added dropwise at 3~5°. After an additional stirring for 2 hr. at the same temperature, the crystalline product was filtered and washed with water. Recrystallization from MeOH afforded (VI) (R=H), colorless plates, m.p. 149~150°, yielding 5.5 g. (No. 22).

(VI) (R=Cl): From 1.5 g. of (I) (R=Cl), 0.7 g. of *S*-methylisothiourea sulfate was obtained likeweise (VI) (R=Cl), colorless plates, m.p. 179~181° (from EtOH), yield 0.85 g. (No. 23).

N-Amidino-5-methylsulfonyl-*o*-toluenesulfonamide (VII)——$R_1=CH_3$: (VI) (R=H) (0.5 g.), 30% aq. $MeNH_2$ (1.5 cc.) and EtOH (20 cc.) were heated together for 3.5 hr. at 70~80°. On cooling, a crystalline product was separated, which was filtered and recrystallized from water, colorless needles, m.p. 195~197°; yield 0.5 g. (No. 25).

$R_1=C_2H_5$: (VI) (R=H) (1 g.), 70% aq. $EtNH_2$ and EtOH were heated for 8 hr. at 70~80°. Yield 0.6 g., colorless square plates, m.p. 179~180° (from EtOH-AcOEt) (No. 26).

$R_1=C_4H_9$: (VI) (R=H) (1 g.) and butylamine (1 g.) in EtOH (30 cc.) were heated at 70~80° for 12 hr. Yield 0.7 g., colorless needles, m.p. 177~179° (from EtOH) (No. 27).

$R_1=C_6H_5$: (VI) (R=H) (1 g.) and aniline (2 g.) were heated with a drop of conc. HCl at 150~160° for 6 hr. After distillation of aniline the dark brown residue was washed with water, aq. MeOH, then with Et_2O and filtered. Recrystallization from MeOH gave (VII) ($R_1=C_6H_5$), colorless plates, m.p. 221~223°, yield 0.12 g. (No. 28).

$R_1=NH_2$: (VI) (R=H) (1 g.), 80% $NH_2 \cdot NH_2 \cdot H_2O$ (0.5 cc.) and EtOH (20 cc.) were refluxed for 3 hr. The crystals separated were filtered and recrystallized from water to give (VII) ($R_1=NH_2$) (0.8 g.), colorless needles, m.p. 218.5~220° (No. 24).

The authors express their gratitude to Mrs. F. Hisamichi and Mr. T. Kono for microanalyses.

Summary

The alkyl groups with a tertiary amino group at the β-carbon atom or an imino group at the α-carbon atom were introduced into the sulfamoyl or N-substituted sulfamoyl group of 4-methylsulfonyl-*o*-toluenesulfonamides to investigate possible alteration of the biological activity of the parent sulfonamides.

(Received June 8, 1961)

4) S. Birtwell, E. Haworth, J. Chem. Soc., **1946**, 491.