dide. By fractional recrystallization from Me_2CO-MeOH, 180 mg.(17.8%) (m.p. 208~210°(decomp.)) and 250 mg. (24.9%) (m.p. 174~176°(decomp.)) of crystals were obtained. The former (IR ν_{max}^{KBr} cm^{-1}: 3360 (OH), 1737 (C=O), 1049 (C-O)) on further recrystallization gave colorless prisms, m.p. 214~215° (decomp.), undepressed with ethyl 3α-hydroxy-8-nortropaneacetate methiodide (m.p. 214~215°(decomp.)). *Anal.* Calcd. for $C_{12}H_{22}O_3NI$: C, 40.54; H, 6.24; N, 3.94. Found: C, 41.07; H, 5.87; N, 4.16.

The latter (IR ν_{max}^{KBr}: 1737 cm^{-1}(C=O in ester and ketone)) on further purification furnished colorless feathers, m.p. 189~190°(decomp.), identical with the starting material on mixed fusion. *Anal.* Calcd. for $C_{12}H_{20}O_3NI$: N, 3.96. Found: N, 4.09.

The authors express their deep gratitude to Dr. Junzo Shinoda, President of this Company, and to Dr. Takeo Ishiguro, Director of this Laboratory, for their kind encouragement. The authors are indebted to Mr. S. Okada for technical assistance and to Mr. K. Abe for elemental analyses.

Summary

High-pressure catalytic hydrogenation of N-substituted 3-nortropanones reported in Part I of this series and also of their methiodides was examined. In the case of tertiary amines, only the corresponding 3α-ols were obtained as the main product and the influence of N-substituents was not observed. Before the reduction of methiodides, the necessary infrared spectra were measured in order to establish the purity of the products and recovered materials. In reduction of methiodides, the more bulky the N-substituent became, the smaller did the amounts of 3α-ol methiodides. The possibility of a steric hindrance by fixed N_a (piperidine side) substituents in the reduction was discussed.

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35. Tadakazu Tsuji, Taka Nakata, and Takeo Ueda: Synthesis and Antimicrobial Activity of 1-Acyl-2-sulfanilylhydrazine and 1-Acyl-2-(4-amino-1-naphthylsulfonyl)hydrazine.

(*Pharmaceutical Institute, Keio-Gijuku University*[*1])

In a previous report,[1] it was shown that N-(4-acetamido-1-naphthylsulfonyl)dodecanamide was potentiated as to its effect on the Nakayama strain of Japanese B encephalitis virus by the addition of an acid hydrazide such as anthranilic acid hydrazide or aspartic acid hydrazide. This finding suggested the introduction of a hydrazino group into the basic structure of N-acyl-4-acylamino-1-naphthalenesulfonamide.

Thus, 1-acyl-2-sulfanilylhydrazine, 1-acyl-2-(4-amino-1-naphthylsulfonyl)hydrazine and their acyl derivatives were synthesized and their effect on several pathogenic microbes was examined. This paper describes the synthesis and antimicrobial activity of 1-acyl-2-sulfanilylhydrazine and 1-acyl-2-(4-amino-1-naphthylsulfonyl)hydrazine.

Synthesis of 1-(N-Acetylsulfanilyl)-2-acylhydrazine

Among the compounds of 1-(N-acetylsulfanilyl)-2-acylhydrazine series, Curtius, *et al.*[2] synthesized N^1-amino-N^4-acetylsulfanilamide by reacting N-acetylsulfanilyl chloride with

*1 Shinano-machi, Shinjuku-ku, Tokyo (辻 忠和, 中田多嘉, 上田武雄).

1) T. Ueda, S. Toyoshima, T. Wachi: This Bulletin, **1**, 379 (1953).

2) Th. Curtius, W. Stoll: J. prakt. Chem., 2, **112**, 217 (1925).

hydrazine and Niemiec[3] obtained benzoyl derivative by condensation of N^1-amino-N^4-acetylsulfanilamide with benzoyl chloride. However, acyl derivative having a higher acyl chain has not been reported up to now. Regarding the synthesis of 1-(N-acetylsulfanilyl)-2-acylhydrazine, McFayden, *et al.*[4] synthesized 1-acetyl-2-phenylsulfonylhydrazine by reacting benzenesulfonic acid hydrazide with acetyl chloride, as in the case of benzenesulfonyl chloride with acetohydrazide.

Taking the work of McFayden and others into consideration, compounds of 1-(N-acetylsulfanilyl)-2-acylhydrazine were synthesized by the reaction of (i) N-acetylsulfanilic acid hydrazide with acylation reagents and (ii) of N-acetylsulfanilyl chloride with acylhydrazine. The two synthetic process are shown in Chart 1.

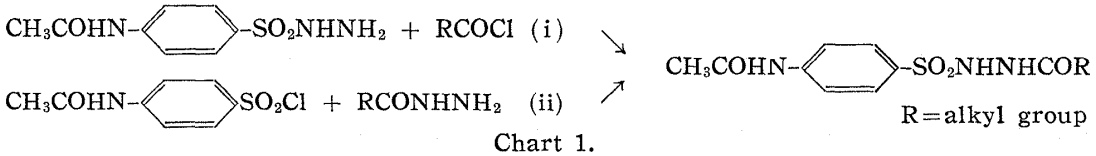


Chart 1.

Since all of the products were ascertained not to react with benzaldehyde, their N-acetylsulfanilyl residue and acyl group should be in 1 and 2 separately. Eleven compounds of 1-(N-acetylsulfanilyl)-2-acylhydrazine so obtained are listed in Table I.

Table I. $CH_3COHN-C_6H_4-SO_2NHNHR$

R	m.p. (°C)	Yield (%)	Formula	N (%) Calcd.	N (%) Found	Method
H	183~184 (decomp.)	—	$C_8H_{11}O_3N_3S$	18.31	—	—
CH_3CO	206~207	73.9	$C_{10}H_{13}O_4N_3S$	15.49	15.18	b
C_2H_5CO	207~208	84.2	$C_{11}H_{15}O_4N_3S$	14.70	15.27	b
C_3H_7CO	200~201	57.0	$C_{12}H_{17}O_4N_3S$	14.00	14.02	a, b
$C_5H_{11}CO$	197.5~198.5	61.1	$C_{14}H_{21}O_4N_3S$	12.84	13.36	a
$C_7H_{15}CO$	172~174	45.1	$C_{16}H_{25}O_4N_3S$	11.82	11.97	a
$C_9H_{19}CO$	172~174	54.8	$C_{18}H_{29}O_4N_3S$	10.97	10.96	b
$C_{11}H_{23}CO$	147~148	68.1	$C_{20}H_{33}O_4N_3S$	10.22	10.45	b
$C_{13}H_{27}CO$	137.5~139.5	47.8	$C_{22}H_{37}O_4N_3S$	9.57	9.17	b
$C_{15}H_{31}CO$	115~117	47.1	$C_{24}H_{41}O_4N_3S$	9.00	8.89	b
$C_{17}H_{35}CO$	109~110	42.5	$C_{26}H_{45}O_4N_3S$	8.49	8.90	b

All compounds are colorless needles.

Synthesis of 1-Acyl-2-sulfanilylhydrazine

Curtius[2] obtained sulfanilic acid hydrazide by hydrolysis of N-acetylsulfanilic acid hydrazide with a small amount of conc. hydrochloric acid. According to this method, compounds of 1-(N-acetylsulfanilyl)-2-acylhydrazine were treated with conc. hydrochloric acid, but the anticipated product, 1-acyl-2-sulfanilylhydrazine, was not obtained. This seemed to be due to the cleavage of their hydrazino group which might occur before deacetylation.

Referring to the method for synthesis of sulfanilamide, compounds of 1-acyl-2-sulfanilylhydrazine were synthesized by refluxing 1-(N-acetylsulfanilyl)-2-acylhydrazine with a mixture of sodium hydroxide solution and ethanol. This hydrolytic process is shown in Chart 2 and the compounds thereby synthesized are listed in Table II.

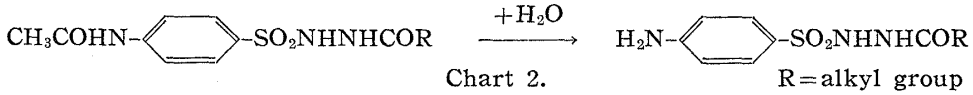


Chart 2.

3) E. Niemiec : J. Am. Chem. Soc., **70**, 1067 (1948).
4) J.S. McFayden, T.S. Stevens : J. Chem. Soc., **1936**, 584.

Table II. H_2N-C$_6$H$_4$-SO_2NHNHR

R	m.p. (°C)	Appearance	Yield (%)	Formula	N (%) Calcd.	N (%) Found
H	130~131	Colorless prisms	58.8	$C_6H_9O_2N_3S$	24.46	24.79
CH_3CO	158~159	〃	34.9	$C_8H_{11}O_3N_3S$	18.34	18.45
C_2H_5CO	159~160	〃	49.4	$C_9H_{13}O_3N_3S$	17.28	16.49
C_3H_7CO	162~163	〃	81.8	$C_{10}H_{15}O_3N_3S$	16.34	16.14
$C_5H_{11}CO$	145~146	〃	73.6	$C_{12}H_{19}O_3N_3S$	14.74	14.18
$C_7H_{15}CO$	141~142	Colorless needles	57.4	$C_{14}H_{23}O_3N_3S$	13.41	13.50
$C_9H_{19}CO$	143~144	〃	58.5	$C_{16}H_{27}O_3N_3S$	12.31	12.16
$C_{11}H_{23}CO$	144~145.5	〃	38.0	$C_{18}H_{31}O_3N_3S$	11.38	11.08
$C_{13}H_{27}CO$	141~142.5	〃	37.8	$C_{20}H_{35}O_3N_3S$	10.58	10.24
$C_{15}H_{31}CO$	133~134	〃	37.6	$C_{22}H_{39}O_3N_3S$	9.88	9.59
$C_{17}H_{35}CO$	137~138	〃	37.5	$C_{24}H_{43}O_3N_3S$	9.27	9.00

Synthesis of 1-Acyl-2-(N-dodecanoylsulfanilyl)hydrazine

1-Acyl-2-(N-dodecanoylsulfanilyl)hydrazine was taken up to obtain antiviral compounds by introduction of dodecanoyl, considered to be a group essential for antiviral effect, into 1-acyl-2-sulfanilylhydrazine. These compounds were synthesized by the condensation of 1-acyl-2-sulfanilylhydrazine with dodecanoyl chloride as shown in Chart 3 and the compounds synthesized are listed in Table III.

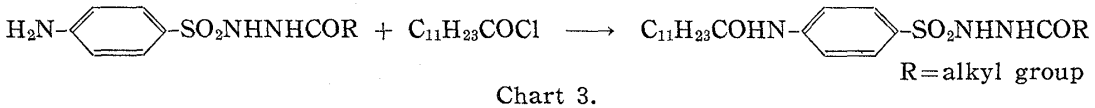


Chart 3.

Table III. $C_{11}H_{23}COHN$-C$_6$H$_4$-SO_2NHNHR

R	m.p. (°C)	Appearance	Yield (%)	Formula	N (%) Calcd.	N (%) Found
CH_3CO	182~183	Colorless feathers	22.6	$C_{20}H_{33}O_4N_3S$	10.55	10.39
C_2H_5CO	172~174	Colorless needles	11.8	$C_{21}H_{35}O_4N_3S$	9.88	10.03
C_3H_7CO	166~167	〃	16.0	$C_{22}H_{37}O_4N_3S$	9.57	9.24
$C_5H_{11}CO$	172~174	〃	21.4	$C_{24}H_{41}O_4N_3S$	8.99	8.90
$C_7H_{15}CO$	163~164	〃	16.2	$C_{26}H_{45}O_4N_3S$	8.48	8.18
$C_9H_{19}CO$	176~177.5	〃	11.5	$C_{28}H_{49}O_4N_3S$	8.03	8.26
$C_{11}H_{23}CO$	173~174.5	〃	14.5	$C_{30}H_{53}O_4N_3S$	7.62	7.43

Synthesis of 1-(4-Acetamido-1-naphthylsulfonyl)-2-acylhydrazine

2-Naphthalenesulfonic acid hydrazide is the only known compound having a naphthalene ring and sulfonylhydrazino (-SO_2NHNH-) structure, compounds of 1-acyl-2-(4-amino-1-naphthylsulfonyl)hydrazine and its acyl substitute have not been reported in literature. The objective compounds were obtained by applying the method for synthesis of 1-acyl-2-sulfanilylhydrazine and its acyl substitute.

For the synthesis, condensation of (i) 4-acetamido-1-naphthalenesulfonyl chloride with acylhydrazine, and (ii) of 4-acetamido-1-naphthalenesulfonic acid hydrazide with acyl chloride was considered. According to the former method, compounds of 1-(4-acetamido-1-naphthylsulfonyl)-2-acylhydrazine were successfully synthesized, as illustrated in Chart 4 and the compounds thereby synthesized are listed in Table IV.

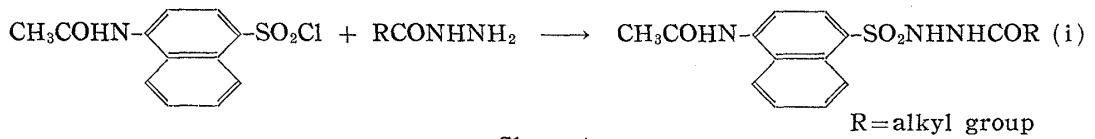
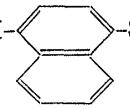


Chart 4.

Table IV. CH_3CONH-  -SO_2NHNHR

R	m.p. (°C)	Appearance	Yield (%)	Formula	N (%) Calcd.	N (%) Found
H	162 (decomp.)	Colorless needles	50.2	$C_{12}H_{13}O_3N_3S$	15.05	15.15
CH_3CO	248~250 (decomp.)	Colorless prisms	49.8	$C_{14}H_{15}O_4N_3S$	13.10	12.99
C_2H_5CO	243 (decomp.)	〃	53.8	$C_{15}H_{17}O_4N_3S$	12.51	12.45
C_3H_7CO	233~234 (decomp.)	〃	48.7	$C_{16}H_{19}O_4N_3S$	12.01	12.25
$C_5H_{11}CO$	214~215	〃	55.7	$C_{18}H_{23}O_4N_3S$	11.12	11.21
$C_7H_{15}CO$	190~192	Colorless needles	71.6	$C_{20}H_{27}O_4N_3S$	10.35	10.14
$C_9H_{19}CO$	191~192	〃	48.5	$C_{22}H_{31}O_4N_3S$	9.70	9.87
$C_{11}H_{23}CO$	148~149	〃	43.4	$C_{24}H_{35}O_4N_3S$	9.10	8.18
$C_{13}H_{27}CO$	146~147	〃	40.9	$C_{26}H_{39}O_4N_3S$	8.59	8.65
$C_{15}H_{31}CO$	147.5~148.5	〃	54.1	$C_{28}H_{43}O_3N_3S$	8.12	8.53
$C_{17}H_{35}CO$	143~144.5	〃	42.2	$C_{30}H_{47}O_4N_3S$	7.71	7.99

By the latter method, however, the reaction product was not the objective compound, but 2-diacyl derivative, as shown in Chart 5.

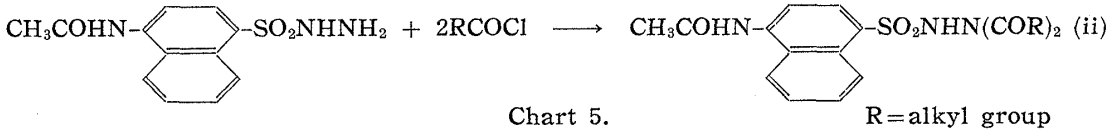
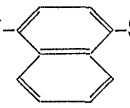


Chart 5. R=alkyl group

Synthesis of 1-Acyl-2-(4-amino-1-naphthylsulfonyl)hydrazine

Refrerring to the method for synthesis of 1-acyl-2-sulfanilylhydrazine, 1-(4-acetamido-1-naphthylsulfonyl)-2-acylhydrazine were treated with a mixture of sodium hydroxide solution and ethanol. None of the objective compounds was obtained, and either the original reactants or their decomposition products were recovered. This fact suggests that sodium hydroxide might have caused the cleavage of sulfonylhydrazino group before the acetamido group.

Consequently, 1-acyl-2-(4-ethoxycarbonylamino-1-naphthylsulfonyl)hydrazine was selected as the starting material for the synthesis of 1-acyl-2-(4-amino-1-naphthylsul-

Table V. H_2N-  -SO_2NHNHR

R	m.p. (°C)	Appearance	Yield (%)	Formula	N (%) Calcd.	N (%) Found
H	188~189 (decomp.)	Colorless prisms	67.5	$C_{10}H_{11}O_2N_3S$	17.72	16.89
CH_3CO	246~247 (decomp.)	〃	64.4	$C_{12}H_{13}O_3N_3S$	15.05	14.18
C_2H_5CO	222.5~223.5 (decomp.)	〃	61.4	$C_{13}H_{15}O_3N_3S$	14.34	14.70
C_3H_2CO	196~197	Colorless needles	52.1	$C_{14}H_{17}O_3N_3S$	13.68	13.00
$C_5H_{11}CO$	194.5~195.5	〃	59.8	$C_{16}H_{21}O_3N_3S$	12.53	12.13
$C_7H_{15}CO$	144~146	〃	77.1	$C_{18}H_{25}O_3N_3S$	11.57	11.15
$C_9H_{19}CO$	149~150	〃	71.5	$C_{20}H_{29}O_3N_3S$	10.74	10.69
$C_{11}H_{23}CO$	145~146	〃	69.1	$C_{22}H_{33}O_3N_3S$	10.01	9.59
$C_{13}H_{27}CO$	134~135	〃	51.0	$C_{24}H_{37}O_3N_3S$	9.39	9.55
$C_{15}H_{31}CO$	135~137	〃	54.7	$C_{26}H_{41}O_3N_3S$	8.84	9.23
$C_{17}H_{35}CO$	135~137	〃	49.7	$C_{28}H_{45}O_3N_3S$	8.35	8.48

fonyl)hydrazine, since ethoxycarbonylamino group was considered more easily hydrolyzed than acetamido group. Compounds of 1-acyl-2-(4-amino-1-naphthylsulfonyl)hydrazine were finally obtained by heating 1-acyl-2-(4-ethoxycarbonylamino-1-naphthylsulfonyl)-hydrazine with a mixture of sodium hydroxide solution and ethanol at 80°, as shown in Chart 6, and are listed in Table V.

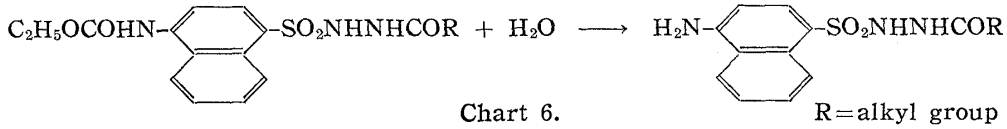


Chart 6. R=alkyl group

1-Acyl-2-(4-ethoxycarbonylamino-1-naphthylsulfonyl)hydrazine was synthesized by reaction of sodium 4-amino-1-naphthalenesulfonate with ethyl chlorocarbonate, chlorination of the resulting ethoxycarbonyl compound with phosphorus pentachloride, and condensation of the resulting sulfonyl chloride with acylhydrazine, as shown in Chart 7. The compounds thereby obtained are listed in Table VI.

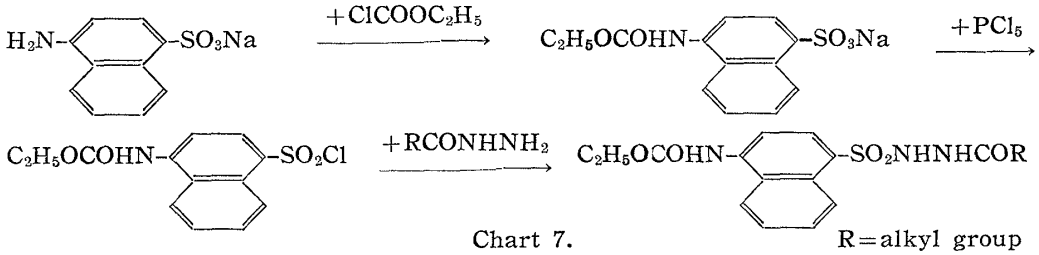


Chart 7. R=alkyl group

Table VI. C_2H_5OCONH-(naphthalene)-SO_2NHNHR

R	m.p. (°C)	Appearance	Yield (%)	Formula	N (%) Calcd.	N (%) Found
H	168~169 (decomp.)	Colorless prisms	87.4	$C_{13}H_{15}O_4N_3S$	13.59	14.16
CH_3CO	207~208.5	Colorless needles	79.8	$C_{15}H_{17}O_5N_3S$	11.97	11.57
C_2H_5CO	185~186	〃	71.2	$C_{16}H_{19}O_5N_3S$	11.51	11.45
C_3H_7CO	188~189	〃	66.0	$C_{17}H_{21}O_5N_3S$	11.08	11.07
$C_5H_{11}CO$	163~165	〃	73.8	$C_{19}H_{25}O_5N_3S$	10.32	9.93
$C_7H_{15}CO$	154~156	〃	71.3	$C_{21}H_{29}O_5N_3S$	9.65	9.91
$C_9H_{19}CO$	149~150	〃	64.9	$C_{23}H_{33}O_5N_3S$	9.07	9.10
$C_{11}H_{23}CO$	133~135	〃	77.3	$C_{25}H_{37}O_5N_3S$	8.55	8.54
$C_{13}H_{27}CO$	134.5~136	〃	42.4	$C_{27}H_{41}O_5N_3S$	8.09	8.53
$C_{15}H_{31}CO$	134~135	〃	40.2	$C_{29}H_{45}O_5N_3S$	7.68	7.65
$C_{17}H_{35}CO$	130~131	〃	40.0	$C_{31}H_{49}O_5N_3S$	7.30	7.12

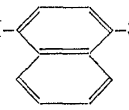
Synthesis of 1-Acyl-2-(4-acylamino-1-naphthylsulfonyl)hydrazine

1-(4-Acylamino-1-naphthylsulfonyl)-2-dodecanoylhydrazine and 1-acyl-2-(4-dodecanamido-1-naphthylsulfonyl)hydrazine were synthesized by the condensation of 1-acyl-2-

Table VII. RHN-(naphthalene)-$SO_2NHNHCOC_{11}H_{23}$

R	m.p. (°C)	Yield (%)	Formula	N (%) Calcd.	N (%) Found
C_2H_5CO	140~141.5	12.6	$C_{25}H_{37}O_4N_3S$	8.84	8.71
C_3H_7CO	133~135	14.3	$C_{26}H_{39}O_4N_3S$	8.59	8.97
$C_5H_{11}CO$	133~135	9.7	$C_{28}H_{43}O_4N_3S$	8.12	8.05
$C_7H_{15}CO$	132~133	14.7	$C_{30}H_{47}O_4N_3S$	7.71	7.85
$C_9H_{19}CO$	141~142	10.5	$C_{32}H_{51}O_4N_3S$	7.33	7.16

All the compounds are colorless needles.

Table VII. $C_{11}H_{23}CONH$-  -SO_2NHNHR

R	m.p. (°C)	Yield (%)	Formula	N (%) Calcd.	N (%) Found
CH_3CO	160~161.5	23.8	$C_{24}H_{35}O_4N_3S$	9.11	8.78
C_2H_5CO	159~161	19.0	$C_{25}H_{37}O_4N_3S$	8.84	8.52
C_3H_7CO	152~154	8.2	$C_{26}H_{39}O_4N_3S$	8.59	8.51
$C_5H_{11}CO$	138~140	13.5	$C_{28}H_{43}O_4N_3S$	8.12	7.96
$C_7H_{15}CO$	137~139	9.2	$C_{30}H_{47}O_4N_3S$	7.71	8.01
$C_9H_{19}CO$	139~141	20.9	$C_{32}H_{51}O_4N_3S$	7.33	7.24
$C_{11}H_{23}CO$	130~132	13.3	$C_{34}H_{55}O_4N_3S$	6.99	6.83

All the compounds are colorless needles.

(4-amino-1-naphthylsulfonyl)hydrazine with acyl chloride in pyridine solution and the compounds thus obtained are shown in Tables VII and VIII.

Screening Tests on Pathogenic Microbes

Antimicrobial activity of these compounds was examined with *Escherichia coli communi* or *Staphylococcus aureus*, *Mycobacterium tuberculosis* var. *hominis* H37Rv, and the Nakayama strain of Japanese B encephalitis virus as described in the preceding papers.[1,5]

Screening Tests of 1-Acyl-2-sulfanilylhydrazine and its Acyl Derivatives: All of the compounds of this series were inactive on *Escherichia coli* and *Staphylococcus aureus*. The result obtained with H37Rv strain is shown in Table IX, in which ineffective compounds have been omitted. Butanoyl, hexanoyl, octanoyl, decanoyl, and dodecanoyl derivatives of 1-acyl-2-sulfanilylhydrazine, and 1-decanoyl-2-(N-dodecanoylsulfanilyl)-hydrazine were found to be active in a concentration of $10^{-4}M$, against H37Rv strain of tubercle bacilli. None of the compounds showed any antiviral activity against Nakayama strain.

Table IX. *In Vitro* Effect of 1-Acyl-2-(N-acylsulfanilyl)hydrazine against Tubercle Bacilli H37Rv Strain

RHN-  -SO_2NHNHR'

Compound R	Compound R'	Treated Compd. Concn. (mole) 10^{-3}	10^{-4}	10^{-5}	10^{-6}	10^{-7}	10^{-8}	Untreated
H	C_3H_7CO	−	−	+	++	++	+++	+++
H	$C_5H_{11}CO$	−	−	+	++	+++	+++	+++
H	$C_7H_{15}CO$	−	−	+	+	+++	+++	+++
H	$C_9H_{19}CO$	−	−	++	++	++	+++	+++
H	$C_{11}H_{23}CO$	−	−	++	+++	+++	+++	+++
$C_{11}H_{23}CO$	$C_9H_{19}CO$	−	−	++	++	+++	+++	+++
INAH		−	−	−	−	+	+	+++
Dihydrostreptomycin		−	−	−	−	+	++	+++

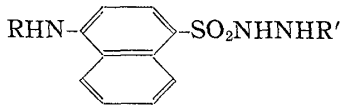
Screening Tests of 1-Acyl-2-(4-amino-1-naphthylsulfonyl)hydrazine and its Acyl Derivatives: Since 1-acyl-2-(4-amino-1-naphthylsulfonyl)hydrazine possessed both hydrazino group for antituberculous activity and a structure related to antiviral N-(4-acetamido-1-naphthylsulfonyl)dodecanamide for antiviral activity, it was of interest to test the compounds of this series.

None of the compounds showed any *in vitro* effect against *Escherichia coli communi* or *Staphylococcus aureus*. Effect of these compounds against H37Rv strain is shown in

5) F. Ueda, T. Ueda, S. Toyoshima: Yakugaku Zasshi, **79**, 925 (1959).

Table X, in which ineffective compounds have been omitted. As can be seen from this Table, 18 compounds showed *in vitro* activity in a concentration of $10^{-4}M$, 1-(4-dodecanamido-1-naphthylsulfonyl)-2-dodecanoylhydrazine in a concentration of $10^{-5}M$, and 1-(4-dodecanamido-1-naphthylsulfonyl)-2-hexanoylhydrazine in a concentration of $10^{-6}M$.

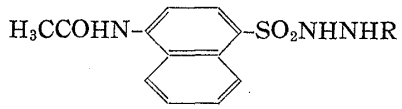
Table X. *In Vitro* Effect of 1-Acyl-2-(4-acylamino-1-naphthylsulfonyl)-hydrazine against Tubercle Bacilli H37Rv Strain



Compound		Treated Compd. Concn. (mole)						Untreated
R	R'	10^{-3}	10^{-4}	10^{-5}	10^{-6}	10^{-7}	10^{-8}	
CH_3CO	CH_3CO	−	−	##	##	##	##	##
CH_3CO	C_3H_7CO	−	−	##	##	##	##	##
CH_3CO	$C_{11}H_{23}CO$	−	−	#	##	##	##	##
CH_3CO	$C_{13}H_{27}CO$	−	−	##	##	##	##	##
CH_3CO	$C_{15}H_{31}CO$	−	−	##	##	##	##	##
C_2H_5OCO	$C_5H_{11}CO$	−	−	#	##	##	##	##
C_2H_5OCO	$C_7H_{15}CO$	−	−	#	##	##	##	##
C_2H_5OCO	$C_{11}H_{23}CO$	−	−	+	#	#	#	##
C_2H_5OCO	$C_{17}H_{35}CO$	−	−	#	##	##	##	##
H	$C_9H_{19}CO$	−	−	##	##	##	##	##
H	$C_{11}H_{23}CO$	−	−	##	##	##		##
H	$C_{13}H_{27}CO$	−	−	##	##	##		##
H	$C_{15}H_{31}CO$	−	−	+	#	#		##
$C_{11}H_{23}CO$	CH_3CO	−	−	±	#	##		##
$C_{11}H_{23}CO$	$C_5H_{11}CO$	−	−	−	−	##	##	##
$C_{11}H_{23}CO$	$C_9H_{19}CO$	−	−	##	##	##	##	##
$C_{11}H_{23}CO$	$C_{11}H_{23}CO$	−	−	−	##	##	##	##
C_2H_5CO	$C_{11}H_{23}CO$	−	−	#	##	##	##	##
$C_5H_{11}CO$	$C_{11}H_{23}CO$	−	−	±	#	##	##	##
$C_9H_{19}CO$	$C_{11}H_{23}CO$	−	−	#	##	##	##	##
INAH		−	−	−	−	+	+	##
Dihydrostreptomycin		−	−	−	−	+	#	##

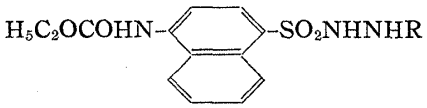
The effect of 1-(4-dodecanamido-1-naphthylsulfonyl)-2-hexanoylhydrazine was considered almost equal to that of INAH or dihydrostreptomycin employed as the control. The effect of these compounds against the Nakayama strain is given in Tables XI, XII, XIII, and XIV. It was considered from these results that 1-(4-ethoxycarbonylamino-

Table XI. Antiviral Activity against the Nakayama Strain of Japanese B Encephalitis Virus



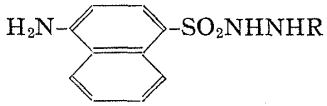
R	Dose (mg./kg.)	LD_{50} (−log)	
		Treated group	Untreated group
H	200	2.98	3.10
$COCH_3$	100	3.11	3.10
COC_2H_5	180	3.44	3.55
COC_5H_{11}	120	3.20	3.26
COC_7H_{15}	100	2.95	3.10
$COC_{11}H_{23}$	100	3.35	3.36
$COC_{13}H_{17}$	75	3.26	3.16

Table XII. Antiviral Activity against the Nakayama Strain of Japanese B Encephalitis Virus



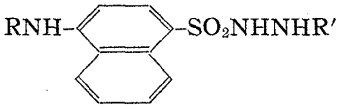
R	Dose (mg./kg.)	LD_{50} (−log)	
		Treated group	Untreated group
H	300	3.16	3.12
$COCH_3$	150	3.11	3.16
COC_3H_7	150	2.97	3.16
COC_5H_{11}	150	2.77	3.16
COC_7H_{15}	120	3.17	3.16
COC_9H_{19}	100	3.16	3.16
$COC_{11}H_{23}$	100	3.17	3.16
$COC_{13}H_{27}$	150	3.00	3.12
$COC_{17}H_{35}$	210	3.06	3.16

Table XIII. Antiviral Activity against the Nakayama Strain of Japanese B Encephalitis Virus



R	Dose (mg./kg.)	LD_{50} (−log)	
		Treated group	Untreated group
H	120	3.28	3.36
$COCH_3$	100	3.27	3.36
COC_2H_5	240	2.74	2.93
COC_3H_7	210	2.66	2.93
COC_5H_{11}	120	2.54	2.93
COC_7H_{15}	90	2.80	2.93
COC_9H_{19}	60	2.80	2.93
$COC_{11}H_{23}$	60	2.95	2.93
$COC_{13}H_{27}$	90	2.97	3.07

Table XIV. Antiviral Activity against the Nakayama Strain of Japanese B Encephalitis Virus



R	R′	Dose (mg./kg.)	LD_{50} (−log)	
			Treated group	Untreated group
$COC_{11}H_{23}$	$COCH_3$	60	3.16	3.10
$COC_{11}H_{23}$	COC_3H_7	60	2.83	3.07
$COC_{11}H_{23}$	COC_5H_{11}	75	2.75	3.07
$COC_{11}H_{23}$	COC_7H_{15}	90	2.64	3.07
$COC_{11}H_{23}$	COC_9H_{19}	40	3.01	3.10
$COC_{11}H_{23}$	$COC_{11}H_{23}$	50	2.76	3.07
COC_2H_5	$COC_{11}H_{23}$	100	2.80	3.07
COC_3H_7	$COC_{11}H_{23}$	90	2.80	3.07
COC_5H_{11}	$COC_{11}H_{23}$	75	2.92	3.07
COC_7H_{15}	$COC_{11}H_{23}$	60	2.80	3.07

1-naphthylsulfonyl)-2-hexanoylhydrazine, 1-(4-amino-1-naphthylsulfonyl)-2-hexanoylhydrazine, hexanoyl, octanoyl, dodecanoyl derivatives of 1-acyl-2-(4-dodecanamido-1-naphthylsulfonyl)hydrazine, and propanoyl, butanoyl, octanoyl derivatives of 1-(4-acylamino-1-naphthylsulfonyl)-2-dodecanoylhydrazine were significantly effective *in vivo* against the virus, because each of them showed more than 0.2 difference, comparing their LD_{50} with that of the control. Particularly, 1-(4-amino-1-naphthylsulfonyl)-2-hexanoylhydrazine

and 1-(4-dodecanamido-1-naphthylsulfonyl)-2-octanoylhydrazine were considered to exert *in vivo* effect nearly equal to that of antiviral N-(4-acetamido-1-naphthylsulfonyl)dodecanamide.

From the relationship between antimicrobial activity and chemical structure of compounds of the two series, the following conclusion may be possible.

(1) Naphthalene ring seems to have graeter antimicrobial effect than a benzene ring.

(2) Higher alkyl group was essential for the appearance of antimicrobial activity, since the parent compounds of the two series lacked any activity.

(3) It was better for antituberculous activity to introduce doubly higher acyl groups into 4-amino-1-naphthalenesulfonic acid hydrazide. 1-(4-Dodecanamido-1-naphthylsulfonyl)-2-hexanoylhydrazine was the most promising compound among the two series.

(4) There were many significant antiviral compounds among the doubly acylated compounds of 4-amino-1-naphthalenesulfonic acid hydrazide series, but their effect was not so predominant over N-(4-acetamido-1-naphthylsulfonyl)dodecanamide.

Experimental

General Procedure for Synthesis of 1-(N-Acetylsulfanilyl)-2-acylhydrazine——a) To a solution of 0.01 mole of N^1-amino-N^4-acetylsulfanilamide in 12 cc. of dehyd. pyridine, 0.01 mole of acyl chloride was added dropwise with stirring in a cold bath. After warming on a water bath for 5 min., the reaction mixture was poured into ice water and acidified with dil. HCl. The precipitate was dissolved in dil. NaOH, reprecipitated with AcOH, and recrystallized from EtOH.
b) To a solution of 0.01 mole of acylhydrazine in 15 cc. of dehyd. pyridine, 0.01 mole of N-acetylsulfanilyl chloride was added with stirring. After warming on a water bath for 1 hr., the reaction mixture was poured into ice water and acidified with dil. HCl. The precipitate was purified by reprecipitation.

General Procedure for Synthesis of 1-Acyl-2-sulfanilylhydrazine——A solution of 0.01 mole of 1-(N-acetylsulfanilyl)-2-acylhydrazine in 2.2 cc. of EtOH and 3.8 cc. of 25% NaOH was refluxed for 2~3 hr. After acidification with AcOH, the precipitate was collected and recrystallized from EtOH.

General Procedure for Synthesis of 1-Acyl-2-(N-dodecanoylsulfanilyl)hydrazine——To a stirred solution of 0.01 mole of 1-acyl-2-sulfanilylhydrazine in 2 cc. of dehyd. pyridine, 0.01 mole of dodecanoyl chloride was added dropwise with cooling. After warming on a water bath for 5 min., the reaction mixture was poured into ice water and acidified with dil. HCl. The precipitate was collect and recrystallized from EtOH.

4-Acetamido-1-naphthalenesulfonic Acid Hydrazide——To a solution of 1 g. of $NH_2NH_2 \cdot H_2O$ in 5.8 cc. of MeOH, 2.84 g. of 4-acetamido-1-naphthalenesulfonyl chloride was added with stirring and the mixture was warmed on a water bath until the reaction mixture became clear. After standing for several hours at room temp., 8 cc. of H_2O was added. The precipitate was collected and recrystallized from EtOH, m.p. 162°(decomp.). Yield, 1.4 g.

General Procedure for Synthesis of 1-(4-Acetamido-1-naphthylsulfonyl)-2-acylhydrazine——To a solution of 0.025 mole of acylhydrazine in 25~30 cc. of dehyd. pyridine, 0.02 mole of 4-acetamido-1-naphthalenesulfonyl chloride was added. The resulting solution was warmed on a water bath for 2~3 hr. and poured into 300 cc. of 2% HCl. The precipitate was collected and recrystallized from EtOH.

1-(4-Acetamido-1-naphthylsulfonyl)-2-dodecanoylhydrazine——To a solution of 2 g. of 4-acetamido-1-naphthalenesulfonic acid hydrazide in 6 cc. of dehyd. pyridine, 1.54 g. of dodecanoyl chloride was added dropwise with cooling. After warming on a water bath at 80° for 30 min., the reaction mixture was poured into dil. HCl. The precipitate was collected and recrystallized from EtOH to colorless needles, m.p. 199~200°. Yield, 1.7 g. *Anal.* Calcd. for $C_{36}H_{57}O_5N_3S$: C, 67.19; H, 8.86; N, 6.53. Found : C, 67.63; H, 9.31; N, 6.43.

Sodium 4-Ethoxycarbonylamino-1-naphthalenesulfonate——Sodium 4-amino-1-naphthalenesulfonate (252 g.) was dissolved in 1600 cc. of 40% NaOH solution with warming on a water bath. After cool, 173 g. of ethyl chlorocarbonate was added to this solution at 20° with stirring. The whole solution was stirred for additional 5 hr., the precipitate was collected, and dried at 130°. The crude product was used for the following synthesis. For purification, the crude product was recrystallized from EtOH to colorless plates, m.p. >300°. *Anal.* Calcd. for $C_{13}H_{12}O_5NNaS$: N, 4.41. Found : N, 4.47.

4-Ethoxycarbonylamino-1-naphthalenesulfonyl Chloride——Sodium 4-ethoxycarbonylamino-1-naphthalenesulfonate (60 g.) was stirred with 60 g. of PCl_5 until the evolution of HCl gas ceased. The

reaction mixture was poured into ice water and the precipitate was washed with H_2O, $KHCO_3$ solution, and Me_2CO. The product was recrystallized from Me_2CO to colorless needles, m.p. 134~136°. Yield, 25.1 g. *Anal.* Calcd. for $C_{13}H_{12}O_4NClS$: N, 4.47. Found : N, 4.52.

General Procedure for Synthesis of 1-Acyl-2-(4-ethoxycarbonylamino-1-naphthylsulfonyl)hydrazine——To a solution of 0.01 mole of acylhydrazine in 15 cc. of dehyd. pyridine, 0.01 mole of 4-ethoxycarbonylamino-1-naphthalenesulfonyl chloride was added with stirring. After warming on a water bath for 1~2 hr., the reaction mixture was poured into 300 cc. of 2% HCl. The precipitate was collected and recrystallized from EtOH.

General Procedure for Synthesis of 1-Acyl-2-(4-amino-1-naphthylsulfonyl)hydrazine——A solution of 0.01 mole of 1-acyl-2-(4-ethoxycarbonylamino-1-naphthylsulfonyl)hydrazine in 2.2 cc. of EtOH and 4.8 cc. of 20% NaOH was warmed on a water bath for 30~40 min. at 80°. After acidification with AcOH, the precipitate was collected and recrystallized from EtOH. In higher homologs, the precipitate was extracted with hot benzene. After removal of benzene, the residue was recrystallized from EtOH.

General Procedure for Synthesis of 1-Acyl-2-(4-acylamino-1-naphthylsulfonyl)hydrazine——To an ice-cold solution of 0.01 mole of 1-acyl-2-(4-amino-1-naphthylsulfonyl)hydrazine in 12 cc. of dehyd. pyridine, 0.01 mole of acyl chloride was added dropwise. After warming on a water bath for 5 min., the reaction mixture was poured into dil. HCl. The precipitate was collected, and extracted with hot benzene. After removal of benzene, the residue was recrystallized from EtOH.

Summary

1-Acyl-2-sulfanilylhydrazine, 1-acyl-2-(4-amino-1-naphthylsulfonyl)hydrazine and their acyl derivatives were synthesized and their antimicrobial activity was examined. Among the derivatives of 1-acyl-2-sulfanilylhydrazine series, several compounds showed a weak *in vitro* activity on tubercle bacilli, but none of the compounds exerted any antibacterial or antiviral activity. On the contrary, there were found one compound having activity against tubercule bacilli comparable to that of INAH and dihydrostreptomycin, and two compounds having *in vivo* effect on Japanese B encephalitis virus equal to that of N-(4-amino-1-naphthylsulfonyl)dodecanamide, among the derivatives of 1-acyl-2-(4-amino-1-naphthylsulfonyl)hydrazine, but none of the compounds showed any activity against *Escherichia coli communi* or *Staphylococcus aureus*.

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