N^1-(4'-Azobenzene)-4-aminonaphthalenesulfonamide—3 g. of the acetyl compound was hydrolyzed with a mixture of 10% NaOH and 9 cc. EtOH by the same procedures as described above. Recrystd. from EtOH to reddish orange prisms, m.p. 182~183°. Yield, 81%. *Anal.* Calcd. for $C_{22}H_{18}O_2N_4S$: N, 13.93. Found: N, 14.10.

N^1-(*o*-Azotoluene)-4-aminonaphthalenesulfonamide—2 g. of the acetyl compound was hydrolyzed with a mixture of 20 cc. of 15% KOH and 12 cc. EtOH by the same procedures as above. Recrystd. from EtOH to orange plates, m.p. 195~196°. Yield, 83%. *Anal.* Calcd. for $C_{24}H_{22}O_2N_4S$: N, 13.00. Found: N, 12.85.

N^1-(4'-Sulfophenyl)-4-aminonaphthalenesulfonamide—8 g. of the acetyl compound was boiled with a mixture of 50 cc. of water and 50 cc. conc. HCl for 1 hr. After cooling, the precipitate was filtered and recrystallized from dil. EtOH to plates, m.p. over 270°(decomp.). Yield, 90%. *Anal.* Calcd. for $C_{16}H_{14}O_5N_2S_2$: N, 7.39. Found: N, 7.28.

N^1-(4'-Aminophenyl)-4-aminonaphthalenesulfonamide—A fine suspension of 7 g. of N^1-(4'-nitrophenyl)-4-aminonaphthalenesulfonamide[2] in 250 cc. MeOH was catalytically reduced in the presence of Pd-C prepared from 8 cc. of 1% $PdCl_2$ solution and 2.5 g. of activated carbon, and the calculated amount of hydrogen was absorbed. After reduction the catalyst was removed by filtration, the filtrate was evaporated, the residue was dissolved in dil. HCl, filtered, and reprecipitated by NH_4OH. The precipitate was recrystallized from dil. EtOH to plates, m.p. 192~193°. Yield, 62%. *Anal.* Calcd. for $C_{16}H_{15}O_2N_3S$: N, 13.88. Found: N, 13.92.

Summary

1) By the condensation of primary amines and 4-acetylaminonaphthalenesulfonyl chloride, N^1-substituted 4-acetylaminonaphthalenesulfonamides were obtained and were hydrolyzed to N^1-substituted 4-aminonaphthalenesulfonamides.

2) The activities of these compounds were tested *in vitro* against *Encephalitis japonica*.

3) Following effective substances were found: N^1-(4'-azobenzene)- and N^1-(*o*-azotoluene)-4-acetylaminonaphthalenesulfonamide, and N^1-(4'-azobenzene)- and N^1-(*o*-azotoluene)-4-aminonaphthalenesulfonamide.

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94. Tsuneo Wachi: Researches on Chemotherapeutic Drugs against Viruses.* XX[1]. Synthesis and Antiviral Effects of N^1-Alkylphenyl-4-acetylaminonaphthalenesulfonamides and N^1-Alkylphenyl-4-aminonaphthalenesulfonamides.

(*Pharmaceutical Institute, Keio-Gijuku University***)

It was reported by Ueda *et al.*[2] that the lengthening of an alkyl radical in 3-alkylphenylazo-4-aminonaphthalenesulfonic acid was accompanied with the change of its antiviral effect against *Encephalitis japonica*. It was also pointed out by Ito *et al.*[3] from the point of surface activities that the antiviral activity of these compounds was nearly parallel to their surface tension-lowering properties in the series of 3-alkylphenylazo-4-aminonaphthalenesulfonic acid. It was also found that 3-(*p*-octylphenylazo)-4-aminonaphthalenesulfonic acid possessing the strongest surfactant properties exerted the most marked activity *in vitro* among this series, but a weak effect *in vivo*, nearly equal to that of PAN-No. 25. That this compound was not so effective *in vitro* as anticipated from the results of the *in vitro* test might be attributable to its azo structure, which should be unfavorable for antiviral properties because of its chemical affinity with pro-

* Takeo Ueda and Shigeshi Toyoshima: Researches on Chemotherapeutic Drugs against Viruses. XX.

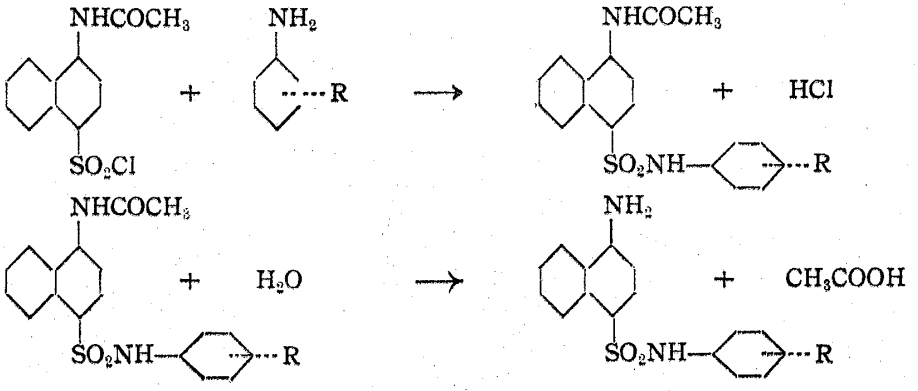
** Shinano-machi, Shinjuku-ku, Tokyo (和智恒雄).

1) Part XIX: This Bulletin, **2**, 415(1954).
2) T. Ueda, *et al.*: This Bulletin, **1**, 271(1953).
3) T. Ito, *et al.*: *Ibid.*, **1**, 278(1953).

teinous components in tissues. Therefore, attempts were made to find compounds related to aminonaphthalenesulfonamide without an azo structure and from such finding, it was thought advisable to introduce the alkylphenyl group, which is considered to be an important factor in increasing surface activities, into the N^1-position of 4-aminonaphthalenesulfonamide. This paper describes the synthesis of N^1-alkylphenyl-4-acetylamino- and N^1-alkylphenyl-4-aminonaphthalenesulfonamides, and their antiviral activity against the Nakayama strain of *Encephalitis japonica*.

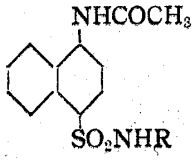
Antiviral activity of the alkylanilines, the starting materials for synthesis of these N^1-substitutes mentioned above, were tested by Ueda *et al.*[4] against the Nakayama strain of *Encephalitis japonica* and those which had more than seven carbon atoms were recognized to be effective *in vitro* against the virus, though they were generally highly toxic.

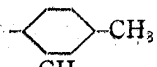
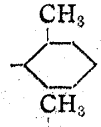
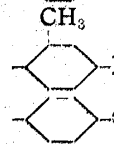
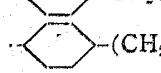
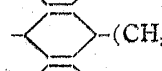
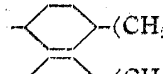
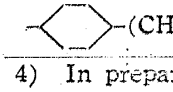
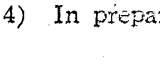
Synthesis of N^1-Alkylphenyl-4-acetylaminonaphthalenesulfonamides and N^1-Alkylphenyl-4-aminonaphthalenesulfonamides The condensation of 4-acetylaminonaphthalenesulfonyl chloride with alkylaniline in a mixture of acetone and pyridine afforded N^1-alkylphenyl-4-acetylaminonaphthalenesulfonamide, which was hydrolyzed to N^1-alkylphenyl-4-aminonaphthalenesulfonamide, as shown in the following:



The properties of the compounds obtained are summarized in Tables I and II.

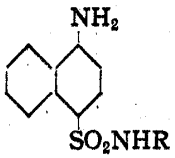
TABLE I.

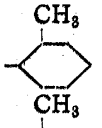
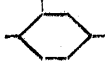


R	Mol. formula	m.p. °C. (decomp.)	Appearance	N% Calcd.	N% Found
	$C_{19}H_{18}O_3N_2S$	228.5~229.5	Plates	7.91	7.85
	$C_{19}H_{18}O_3N_2S$	231~233	〃	7.91	7.86
	$C_{19}H_{17}O_5N_3S$	(219~220.5)	Yellow Plates	10.53	10.74
	$C_{20}H_{20}O_3N_2S$	207~208	Plates	7.61	7.92
	$C_{21}H_{22}O_3N_2S$	165~166	〃	7.33	7.29
	$C_{22}H_{24}O_3N_2S$	152~153	Needles	7.07	7.33
	$C_{26}H_{32}O_3N_2S$	209~210.5	Prisms	6.20	6.34
	$C_{23}H_{36}O_3N_2S$	197~198.5	〃	5.84	5.99

4) In preparation.

Table II.



R	Mol. formula	m.p. °C. (decomp.)	Appearance	N% Calcd.	N% Found
	$C_{17}H_{16}O_2N_2S$	166~167	Needles	8.98	8.92
	$C_{17}H_{16}O_2N_2S$	169~171	Plates	8.98	9.02
	$C_{17}H_{15}O_4N_3S$	(175~177)	Yellow Plates	11.76	11.22
	$C_{18}H_{18}O_2N_2S$	164~165	Plates	8.59	8.57
	$C_{19}H_{20}O_2N_2S$	156~158	〃	8.24	8.35
	$C_{20}H_{22}O_2N_2S$	178~181	〃	7.91	8.06
	$C_{24}H_{30}O_2N_2S$	108~110	〃	6.83	6.68
	$C_{26}H_{34}O_2N_2S$	107~109	Needles	6.39	6.45

These compounds were colorless crystals, sparingly soluble in water but soluble in aqueous alkaline solution with formation of alkali salts. Solubilities of the compounds of this type in water decreased with the lengthening of the alkyl chain.

Antiviral Activities of N^1-Alkylphenyl-4-acetylaminonaphthalenesulfonamides and N^1-Alkylphenyl-4-aminonaphthalenesulfonamides The antiviral activities of the compounds thus obtained were examined *in vitro* against the Nakayama strain of *Encephalitis japonica*. The experimental procedures were the same as those described in Part V.[5] The results are shown in Table III.

Table III.

Compound	pH	Concentration of drug(%) 0.05	0.025	0.01
N^1-(4′-Methylphenyl)-4-acetylaminonaphthalenesulfonamide	8.0	8/10	5/10	3/10
N^1-(2′-Methylphenyl)-4-acetylaminonaphthalenesulfonamide	8.0	10/10	5/10	4/10
N^1-(4′-Methylphenyl)-4-aminonaphthalenesulfonamide	7.8	6/10	4/10	3/10
N^1-(2′-Methylphenyl)-4-aminonaphthalenesulfonamide	7.8	8/10	4/10	3/9
p-(3-Phenylazo-4-aminonaphthalenesulfonamido)-benzoic acid (PANS-No. 325)	8.2	10/10	—	4/10
Control	7.6	0/10		

The numerator represents the number of mice that survived and the denominator, total number injected.

Table III shows that N^1-(2′-methylphenyl)- and N^1-(4′-methylphenyl)-4-acetylaminonaphthalenesulfonamide, and N^1-(2′-methylphenyl)- and N^1-(4′-methylphenyl)-4-aminonaphthalenesulfonamide exerted activities nearly equal to that of PANS-No. 325, but the others were ineffective by the tests mentioned above.

It was reported by Ueda *et al.*[2] that the effectiveness of the compounds in the series of 3-phenylazo-4-aminonaphthalenesulfonic acids varied with the number of carbon atoms in the alkyl groups, and that the optimum point of the effectiveness was reached when the alkyl group was octyl. It was also found by Ueda *et al.*[4] that alkylanilines with more than eight carbon atoms showed considerable antiviral activities. From those

5) T. Ueda, *et al.*: J. Pharm. Soc. Japan, **72**, 265(1952); cf. p. 413 of this Bulletin.

findings it was expected that N^1-derivatives possessing alkyl groups of moderate length should show remarkable antiviral effects with synergy of alkylaniline and aminonaphthalenesulfonamide, but, as mentioned above, the results were negative with the exception of four compounds possessing N^1-methylphenyl groups.

These facts show that the antiviral activities of these compounds might depend upon the balance of substituents in their molecules, rather than the synergistic influence of both the antiviral structures of alkylanilines and aminonaphthalenesulfonamides. Thus, the surfactant property of the antiviral compound was considered to be a factor in the realization of antiviral activity. According to this assumption, above effective compounds might be considered to possess a better balancing of hydrophobic tolyl group and hydrophilic sulfonamido, amino, or acetylamino group.

Experimantal

General Method of Synthesis of N^1-Alkylphenyl-4-acetylaminonaphthalenesulfonamides—11 g. of 4-acetylaminonaphthalenesulfonyl chloride was added cautiously into a mixture of 0.04 mole of alkylaniline in 100 cc. of acetone and 10 cc. of pyridine with continuous stirring. After stirring for 1 hr. at 50~60°, acetone was removed by evaporation, and a precipitate, produced by adding 300 cc. water and 10 cc. conc. HCl, was filtered. The precipitate was dissolved in aq. NaOH solution, filtered, reprecipitated by AcOH, and N^1-alkyl-4-acetylaminonaphthalenesulfonamide was obtained after recrystallization (in N^1-(4'-octylphenyl)- and N^1-(4'-decylphenyl) compounds reprecipitation was omitted).

N^1-(4'-Methylphenyl)-4-acetylaminonaphthalenesulfonamide—Recrystd. from EtOH to plates, m.p. 228.5~229.5°. Yield, 87%. *Anal.* Calcd. for $C_{19}H_{18}O_3N_2S$: N, 7.91. Found: N, 7.85.

N^1-(2'-Methylphenyl)-4-acetylaminonaphthalenesulfonamide—Recrystd. from EtOH to plates, m.p. 231~233°. Yield, 90%. *Anal.* Calcd. for $C_{19}H_{18}O_3N_2S$: N, 7.91. Found: N, 7.86.

N^1-(2'-Methyl-4'-nitrophenyl)-4-acetylaminonaphthalenesulfonamide—Recrystd. from EtOH to yellow plates, m.p. 219~220.5°(decomp.). Yield, 45%. *Anal.* Calcd. for $C_{19}H_{17}O_5N_3S$: N, 10.53. Found: N, 10.74.

N^1-(4'-Ethylphenyl)-4-acetylaminonaphthalenesulfonamide—Recrystd. from 80% EtOH to plates, m.p. 207~208°. Yield, 80%. *Anal.* Calcd. for $C_{20}H_{20}O_3N_2S$: N, 7.61. Found: N, 7.92.

N^1-(4'-Propylphenyl)-4-acetylaminonaphthalenesulfonamide—Recrystd. from 80% EtOH to plates, m.p. 165~166°. Yield, 90%. *Anal.* Calcd. for $C_{21}H_{22}O_3N_2S$: N, 7.33. Found: N, 7.29.

N^1-(4'-Butylphenyl)-4-acetylaminonaphthalenesulfonamide—Recrystd. from 80% EtOH to needles, m.p. 152~153°. Yield, 92%. *Anal.* Calcd. for $C_{22}H_{24}O_3N_2S$: N, 7.07. Found: N, 7.33.

N^1-(4'-Octylphenyl)-4-acetylaminonaphthalenesulfonamide—Recrystd. from EtOH to prisms, m.p. 209~210.5°. Yield, 66%. *Anal.* Calcd. for $C_{26}H_{32}O_3N_2S$: N, 6.20. Found: N, 6.34.

N^1-(4'-Decylphenyl)-4-acetylaminonaphthalenesulfonamide—Recrystd. from EtOH to prisms, m.p. 197~198.5°. Yield, 85%. *Anal.* Calcd. for $C_{28}H_{36}O_3N_2S$: N, 5.84. Found: N, 5.99.

N^1-Alkylphenyl-4-aminonaphthalenesulfonamides

N^1-(4'-Methylphenyl)-4-aminonaphthalenesulfonamide—2 g. of the acetyl compound was warmed for 40 mins. with 20 cc. of 2.5 *N* NaOH on a water bath. The hydrolyzed solution was diluted with 100 cc. of water, neutralized with AcOH, and a precipitate was filtered. Recrystd. from 50% EtOH to needles, m.p. 166~167°. Yield, 1.4 g. *Anal.* Calcd. for $C_{17}H_{16}O_2N_2S$: N, 8.98. Found: N, 8.92.

N^1-(2'-Methylphenyl)-4-aminonaphthalenesulfonamide—2 g. of the acetyl compound was hydrolyzed by the same procedures as above. Recrystd. from 50% EtOH to plates, m.p. 169~171°. Yield, 1.7 g. *Anal.* Calcd. for $C_{17}H_{16}O_2N_2S$: N, 8.98. Found: N, 9.02.

N^1-(2'-Methyl-4'-nitrophenyl)-4-aminonaphthalenesulfonamide—0.5 g. of the acetyl compound was hydrolyzed with 0.9 cc. of 3.5*N* KOH, diluted with 20 cc. of water, and neutralized with AcOH. Recrystd. from EtOH to yellow plates, m.p. 175~177°(decomp.). Yield, 0.25 g. *Anal.* Calcd. for $C_{17}H_{15}O_4N_3S$: N, 11.76. Found: N, 11.22.

N^1-(4'-Ethylphenyl)-4-aminonaphthalenesulfonamide—2 g. of the acetyl compound was hydrolyzed with 4.5 cc. of 3.5 *N* KOH, diluted with 50 cc. of water, and reprecipitated with AcOH. Recrystd. from 60% MeOH to plates, m.p. 164~165°. Yield, 1.1 g. *Anal.* Calcd. for $C_{18}H_{18}O_2N_2S$: N, 8.59. Found: N, 8.57.

N^1-(4'-Propylphenyl)-4-aminonaphthalenesulfonamide—1 g. of the acetyl compound was hydrolyzed with 1.6 cc. of 5 *N* NaOH and 1.5 cc. EtOH, diluted with 30 cc. of water, and reprecipitated with AcOH. Recrystd. from 60% EtOH to plates, m.p. 156~158°. Yield, 0.55 g. *Anal.* Calcd. for $C_{19}H_{20}O_2N_2S$: N, 8.24. Found: N, 8.35.

N^1-(4'-Butylphenyl)-4-aminonaphthalenesulfonamide—2 g. of the acetyl compound was hydrolyzed

with 3 cc. of 5 *N* NaOH and 1.5 cc. EtOH, diluted with 30 cc. of water, and reprecipitated with AcOH. Recrystd. from 60% EtOH to plates, m.p. 178~181°. Yield, 0.9 g. *Anal.* Calcd. for $C_{20}H_{22}O_2N_2S$: N, 7.91. Found : N, 8.06.

N^1-(4'-Octylphenyl)-4-aminonaphthalenesulfonamide—1 g. of the acetyl compound was warmed with 15 cc. EtOH and 6 cc. conc. HCl for 1.5 hrs. on a water bath. The reaction mixture was poured into 30 cc. of water and the sticky amorphous precipitate was recrystallized from benzene to plates, m.p. 108~110°. Yield, 0.6 g. *Anal.* Calcd. for $C_{24}H_{30}O_2N_2S$: N, 6.83. Found : N, 6.68.

N^1-(4'-Decylphenyl)-4-aminonaphthalenesulfonamide—1 g. of the acetyl compound was hydrolyzed by the same procedures as described above. Recrystd. from benzene to fine needles, m.p. 107~109°. Yield, 0.5 g. *Anal.* Calcd. for $C_{26}H_{34}O_2N_2S$: N, 6.39. Found : N, 6.45.

Summary

1) By the condensation of alkylaniline and 4-acetylaminonaphthalenesulfonyl chloride, N^1-alkylphenyl-4-acetylaminonaphthalenesulfonamide was obtained, which was hydrolyzed to N^1-aklylphenyl-4-aminonaphthalenesulfonamide.

2) The antiviral activities of these compounds were tested *in vitro* against *Encephalitis japonica*.

3) N^1-(2'- and 4'-Methylphenyl)-4-acetylaminonaphthalenesulfonamide and N^1-(2'- and 4'-methylphenyl)-4-aminonaphthalenesulfonamide were found to be of promise.

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95. Tsuneo Wachi and Takako Wada : Researches on Chemotherapeutic Drugs against Viruses.* XXI.[1] Synthesis and Antiviral Effects of N^1-Acyl-4-acetylaminonaphthalenesulfonamides and N^1-Acyl-4-aminonaphthalenesulfonamides.

(*Pharmaceutical Institute, Keio-Gijuku University***)

As described in the preceding papers, it was shown by the present authors that among the compounds of the 4-aminonaphthalenesulfonamide series, N^1-(*p*-azobenzene)-, N^1-(*o*-azotoluene)-[2], N^1-(*p*-tolyl)-, and N^1-(*o*-tolyl)-4-aminonaphthalenesulfonamides[3] and their N^1-acetylated derivatives exerted remarkable activity *in vitro*, nearly equal to that of PANS-No. 325, but weak effects *in vivo* nearly equal to that of PAN-No. 25.

On the other hand, it was deduced by Ueda *et al.*[4] that the antiviral activity, especially *in vitro* effect, of the compounds of the 4-aminonaphthalenesulfonamide series might depend not only upon their surface-tension lowering activity, but also on their penetrating property. In taking the above into consideration, N^1-acyl-4-acetylamino- and N^1-acyl-4-aminonaphthalenesulfonamides were synthesized by introducing an acyl group, perhaps affording surface activity, into 4-aminonaphthalenesulfonamide. This paper describes the synthesis and antiviral activities of N^1-acyl-4-acetylamino- and N^1-acyl-4-aminonaphthalenesulfonamides.

Synthesis of N^1-Acyl-4-acetylaminonaphthalenesulfonamide N^1-Acyl-4-aminonaph-

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1) Part XX : This Bulletin, **2**, 419(1954).
2) T. Wachi : *Ibid.* **2**, 415(1954).
3) T. Wachi : *Ibid.* **2**, 419(1945).
4) T. Ito, *et al.* : *Ibid.*, **1**, 278(1953).