Caffeine-<8′ azo 3>-4-aminonaphthalenesulfonic Acid—Recrystd. from glacial AcOH to dark purple amorphous powder. Yield, 1.2 g. *Anal.* Calcd. for $C_{18}H_{17}O_5N_7S$: N, 22.15. Found: N, 21.91.

Caffeine-<8′ azo 3>-4-hydroxynaphthalenesulfonic Acid—Recrystd. from AcOH to dark purple amorphous powder. Yield, 0.8 g. *Anal.* Calcd. for $C_{18}H_{16}O_6N_6S$: N, 18.91. Found: N, 19.20.

Caffeine-<8′ azo 3>-N^1-(*p*-carboxyphenyl)-4-aminonaphthalenesulfonamide—Recrystd. from glacial AcOH to fine red needles. Yield, 1.6 g. *Anal.* Calcd. for $C_{25}H_{22}O_6N_8S$: N, 19.91. Found: N, 20.14.

Summary

1) 3-Heterocylic azo-4-(amino or hydroxy)-naphthalenesulfonic acid and its derivatives were synthesized by coupling diazotized heterocyclic amines with 4-(amino or hydroxy)-naphthalenesulfonic acid and its derivatives.

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

3) It was found that among this series only the activity of sodium 3-(γ-pyridylazo)-4-aminonaphthalenesulfonate was nearly equal to that of PANS-No. 325.

(Received June 10, 1954)

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93. Tsuneo Wachi: Researches on Chemotherapeutic Drugs against Viruses.* XIX.[1] Synthesis and Antiviral Effects of N^1-Substituted 4-Acetylaminonaphthalenesulfonamide and 4-Aminonaphthalenesulfonamide.

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

Among the isomers of aminonaphthalenesulfonamide and its sulfonamido substitutes, 4-aminonaphthalenesulfonamide and its N^1-substitute, related to sulfanilamides in structure, were of interest in the search for chemotherapeutic drugs. Several compounds belonging to this series have already been synthesized by Hiyama[2] and their effects *in vitro* against the Nakayama strain of *Encephalitis japonica* were examined. According to his findings, N^1-phenyl-, N^1-(2′-carboxyphenyl)-, and N^1-(1′-naphthyl)-4-aminonaphthalenesulfonamide, of the sixteen compounds synthesized, showed a weak activity *in vitro* against the virus. However, it seemed wrong to conclude activities of this series from the results obtained with such a small number of compounds, and in order to examine more precisely the antiviral behavior of the compounds in this series, some unknown compounds of this series were synthesized and their antiviral activities tested. This paper describes the synthesis of these compounds and their antiviral activities against the Nakayama strain of *Encephalitis japonica*.

Synthesis of N^1-Substitutes of 4-Acetylaminonaphthalenesulfonamide and 4-Aminonaphthalenesulfonamide N^1-Substituted 4-acetylaminonaphthalenesulfonamides were synthesized by the condensation of 4-acetylaminonaphthalenesulfonyl chloride with the primary amines in a mixture of acetone and pyridine, and by hydrolyzing the acetyl compounds obtained by which, N^1-substituted 4-aminonaphthalenesulfonamides were obtained as illustrated in the following:

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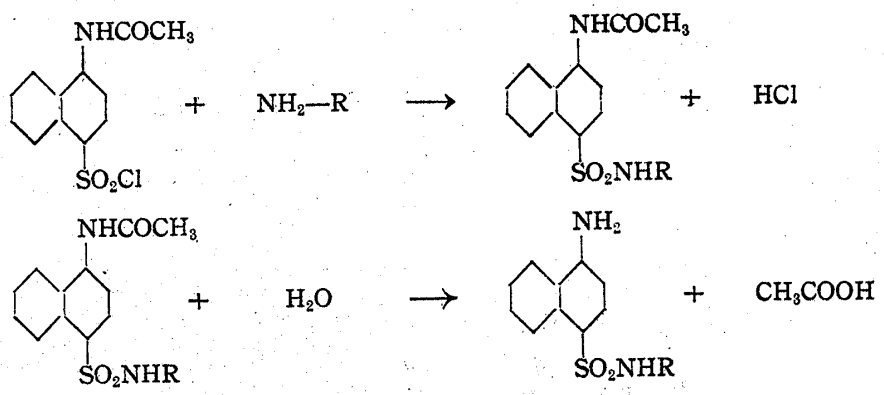
* Takeo Ueda and Shigeshi Toyoshima: Researches on Chemotherapeutic Drugs aginst Viruses. XIX.

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

1) Part XVIII: This Bulletin, **2**, 412(1954).

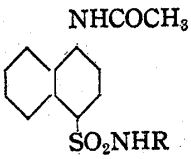
2) M. Hiyama: J. Pharm. Soc. Japan, **72**, 1370(1952).

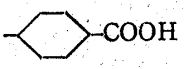
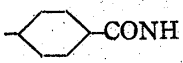
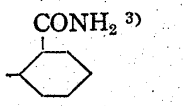
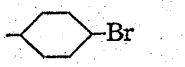
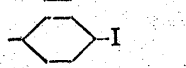
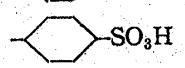
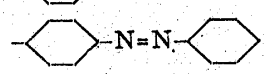
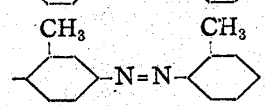


Deacetylation of the acetyl compound with aqueous or alcoholic hydrochloric acid or with caustic alkali solution afforded N^1-substituted 4-aminonaphthalenesulfonamide. N^1-(4'-Aminophenyl)-4-aminonaphthalenesulfonamide was prepared by the catalytic reduction of N^1-(4'-nitrophenyl)-4-aminonaphthaleneslfonamide in methanol in the presence of palladium charcoal.

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

TABLE I.



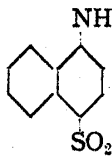
R	Mol. Formula	m.p. °C. (decomp.)	Appearance	N% Calcd.	N% Found
$-CH_3$	$C_{13}H_{14}O_3N_2S$	228~230	Prisms	10.08	10.14
	$C_{19}H_{16}O_5N_2S$	(248~249)	Needles	7.29	7.31
	$C_{19}H_{17}O_4N_3S$	257.5	Prisms	10.96	10.80
 [3]	$C_{19}H_{17}O_4N_3S$	236.5	Needles	10.96	11.08
	$C_{18}H_{15}O_3N_2SBr$	219.5~220	〃	6.68	6.77
	$C_{18}H_{15}O_3N_2SI$	(226.5~227.5)	Plates	6.02	6.11
	$C_{18}H_{16}O_6N_2S_2$	(227~228)	Prisms	6.67	6.66
	$C_{24}H_{20}O_3N_4S$	223~224.5	Orange Prisms	12.60	12.46
	$C_{26}H_{24}O_3N_4S$	243~246	〃	11.83	11.76

All of these compounds synthesized were new and came as colorless crystals, soluble in aqueous alkaline solution.

Antiviral Activities of N^1-Substituted 4-Acetylaminonaphthalenesulfonamide and 4-Aminonaphthalenesulfonamide For the test of the antiviral activities of these compounds *in vitro* against the Nakayama strain of *Encephalitis japonica*, the same procedures as described in Part V[4] were employed : The results are shown in Table III.

3) T. Ueda, S. Toyoshima, T. Wachi : J. Pharm. Soc. Japan, **72**, 1349(1952).
4) T. Ueda, *et al.* : *Ibid.*, **72**, 265(1952); cf. p. 413 of this Bulletin.

TABLE II.



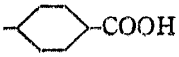
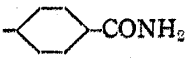
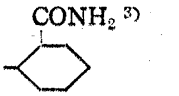
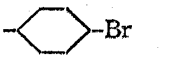
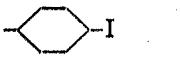
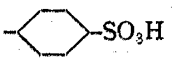
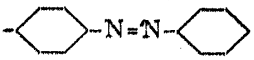
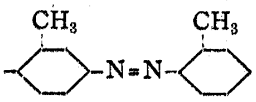
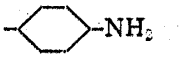
R	Mol. Formula	m.p. °C. (decomp.)	Appearance	N% Calcd.	N% Found
$-CH_3$	$C_{11}H_{12}O_2N_2S$	184~185	Plates	11.84	11.91
	$C_{17}H_{14}O_4N_2S$	(ca. 220)	Needles	8.18	8.16
	$C_{17}H_{15}O_3N_3S$	223~224	〃	12.31	12.44
 [3]	$C_{17}H_{15}O_3N_3S$	208	Plates	12.31	12.25
	$C_{16}H_{13}O_2N_2SBr$	176~178	〃	7.44	7.39
	$C_{16}H_{13}O_2N_2SI$	190~191.5	〃	6.60	6.76
	$C_{16}H_{14}O_5N_2S_2$	(>270)	〃	7.39	7.28
	$C_{22}H_{18}O_2N_4S$	182~183	Reddish Orange Prisms	13.93	14.10
	$C_{24}H_{22}O_2N_4S$	195~196	Orange Plates	13.00	12.85
	$C_{16}H_{15}O_2N_3S$	192~193	Plates	13.88	13.92

TABLE III.

Compound	pH	Concentration of Drug (%) 0.1	0.05	0.01
N^1-(4′-Azobenzene)-4-acetyl-aminonaphthalenesulfonamide	8.0	6/9	5/9	3/10
N^1-(*o*-Azotoluene)-4-acetyl-aminonaphthalenesulfonamide	8.0	8/9	5/10	4/10
N^1-(4′-Azobenzene)-4-aminonaphthalenesulfonamide	7.8	6/10	5/10	3/10
N^1-(*o*-Azotoluene)-4-aminonaphthalenesulfonamide	7.8	7/8	7/10	4/10
Control	7.6	0/10		

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

These results indicated that N^1-(4′-azobenzene)- and N^1-(*o*-azotoluene)-4-acetylaminonaphthalenesulfonamide, and N^1-(4′-azobenzene)- and N^1-(*o*-azotoluene)-4-aminonaphthalenesulfonamide were effective but others were ineffective.

It was pointed out by Hiyama[2] that among these compounds N^1-(2′-carboxyphenyl)- and N^1-(1′-naphthyl)-4-aminonaphthalenesulfonamide showed antiviral activities, but none of these N^1-substitutes prepared here, except N^1-azophenyl compounds, was effective. It may be said that the present negative results are due to the more strict procedures of the test (Ueda-Toyoshima method) than that of Hiyama. None of the compounds pointed out by Hiyama showed antiviral effect when tested by the Ueda-Toyoshima method.

N^1-Azopheyl-4-aminonaphthalenesulfonamide was more effective than PANS-No. 325 against the virus *in vitro* and so it may be of promise as an antiviral drug.

In the present stage, it is difficult to show the reasons why N^1-azophenyl compounds were more effective than N^1-phenyl compounds in spite of the resemblance of their chemical structures. However, it may be said that the increase of surface activities of

these substances by attaching hydrophobic groups such as phenylazo or tolylazo groups to the benzene ring of the parent sulfonamide resulted in intensifying the antiviral activities of these compounds, according to assumptions on the relationship between antiviral effects and surface activities being conducted by Ueda, *et al.*[5]

Experimental

General Method of Syntheses of N¹-Substituted 4-Acetylaminonaphthalenesulfonamide—Ten g. of 4-acetylaminonaphthalenesulfonyl chloride was added cautiously into a mixture of 0.04 mole of primary amine in 10 cc. pyridine and 100 cc. acetone with efficient stirring. After 2 hrs.' stirring at 50~60°, 50 cc. of acetone was removed by evaporation and the precipitate, produced by adding 200 cc. water and 10 cc. conc. HCl, was filtered. The precipitate was dissolved in aq. NaOH solution, filtered, and reprecipitated with AcOH. After recrystallizations, N¹-substituted 4-acetylaminonaphthalenesulfonamide was obtained.

N¹-(4'-Carboxyphenyl)-4-acetylaminonaphthalenesulfonamide—Recrystd. from 70% EtOH to needles, m.p. 248~249°(decomp.). Yield, 93%. *Anal.* Calcd. for $C_{19}H_{16}O_5N_2S$: N, 7.29. Found: N, 7.31.

N¹-(4'-Carbamylphenyl)-4-acetylaminonaphthalenesulfonamide—Recrystd. from 70% EtOH to prisms, m.p. 257.5°. Yield, 90%. *Anal.* Calcd. for $C_{19}H_{17}O_4N_3S$: N, 10.96. Found: N, 10.80.

N¹-(4'-Bromophenyl)-4-acetylaminonaphthalenesulfonamide—Recrystd. from 80% EtOH to needles, m.p. 219.5~220°. Yield, 48%. *Anal.* Calcd. for $C_{18}H_{15}O_3N_2BrS$: N, 6.68. Found: N, 6.77.

N¹-(4'-Iodophenyl)-4-acetylaminonaphthalenesulfonamide—Recrystd. from 85% EtOH to plates, m.p. 226.5~227.5°(decomp.). Yield, 91%. *Anal.* Calcd. for $C_{18}H_{15}O_3N_2IS$: N, 6.02. Found: N, 6.11.

N¹-(4'-Sulfophenyl)-4-acetylaminonaphthalenesulfonamide—Recrystd. from dil. EtOH to prisms, m.p. 227~228°(decomp.). Soluble in hot water. Yield, 55%. *Anal.* Calcd. for $C_{18}H_{16}O_6N_2S_2$: N, 6.67. Found: N, 6.66.

N¹-(4'Azobenzene)-4-acetylaminonaphthalenesulfonamide—Recrystd. from dil. EtOH to orange prisms, m.p. 223~224.5°. Yield, 73.5%. *Anal.* Calcd. for $C_{24}H_{20}O_3N_4S$: N, 12.60. Found: N, 12.46.

N¹-(*o*-Azotoluene)-4-acetylaminonaphthalenesulfonamide—Recrystd. from AcOH to orange prisms, m.p. 243~246°. Yield, 81%. *Anal.* Calcd. for $C_{25}H_{24}O_3N_4S$: N, 11.83. Found: N, 11.76.

N¹-Methyl-4-acetylaminonaphthalenesulfonamide—10 g. of 4-acetylaminonaphthalenesulfonyl chloride was added in portions into a mixture of 5 g. of methylamine hydrochloride in 50 cc. EtOH and 6 cc. of 40% NaOH solution with continuous stirring. After the reaction mixture was warmed for 20 mins. on a water bath, a precipitate, produced by adding 100 cc. of water, was filtered. Recrystd. from EtOH to prisms, m.p. 228~230°. Yield, 61%. *Anal.* Calcd. for $C_{13}H_{14}O_3N_2S$: N, 10.08. Found: N, 10.14.

N¹-Methyl-4-aminonaphthalenesulfonamide—2 g. of the crude acetyl compound was warmed with 30 cc. EtOH and 6 cc. of conc. HCl on a water bath. After 20 mins.' boiling, the reaction mixture was diluted with 150 cc. of water, neutralized with Na_2CO_3, and filtered. Recrystd. from dil. EtOH to plates, m.p. 184~185°. Yield, 70%. *Anal.* Calcd. for $C_{11}H_{12}O_2N_2S$: N, 11.84. Found: N, 11.91.

N¹-(4'-Carboxyphenyl)-4-aminonaphthalenesulfonamide—13.5 g. of the crude acetyl compound was warmed with a mixture of 46 cc. of 15% KOH and 10 cc. of water on a water bath. After 1 hr.'s warming, the hydrolyzed mixture was poured into 200 cc. of water, reprecipitated with AcOH, filtered, and recrystallized from EtOH to needles, m.p. ca. 220°(decomp.). Yield, 83%. *Anal.* Calcd. for $C_{17}H_{14}O_4N_2S$: N, 8.18. Found: N, 8.16.

N¹-(4'-Carbamylphenyl)-4-aminonaphthalenesulfonamide—10 g. of the crude acetyl compound was warmed with a mixture of 100 cc. of EtOH and 50 cc. conc. HCl on a water bath. After refluxing for 1.5 hrs., the hydrolyzed mixture was diluted with 200 cc. of water, the precipitate was collected by filtration, dissolved in NaOH solution, reprecipitated by AcOH, and filtered. Recrystd. from 60% EtOH to needles, m.p. 223~224°. Yield, 67%. *Anal.* Calcd. for $C_{17}H_{15}O_3N_3S$: N, 12.31. Found: N, 12.44.

N¹-(4'-Bromophenyl)-4-aminonaphthalenesulfonamide—0.9 g. of the acetyl compound was warmed with a mixture of 1.76 cc. of 20% NaOH and 1 cc. EtOH on a water bath. After 40 mins.' boiling, the hydrolyzed solution was diluted with water, neutralized with AcOH, and filtered. Recrystd. from dil. EtOH to plates, m.p. 176~178°. Yield, 49%. *Anal.* Calcd. for $C_{16}H_{13}O_2N_2BrS$: N, 7.44. Found: N, 7.39.

N¹-(4'-Iodophenyl)-4-aminonaphthalenesulfonamide—2 g. of the acetyl compound was hydrolyzed with a mixture of 2.13 cc. of 20% NaOH and 1.5 cc. EtOH by the same procedures as described above. Recrystd. from 60% EtOH to plates, m.p. 190~191.5°. Yield, 44%. *Anal.* Calcd. for $C_{16}H_{13}O_2N_2IS$: N, 6.60. Found: N, 6.76.

5) T. Ito, *et al.*: This Bulletin, **1**, 278(1953).

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.

(Received June 19, 1954)

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.

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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).