96. Tsuneo Wachi and Takako Wada : Researches on Chemotherapeutic Drugs against Viruses.* XXII.[1] Syntheses and Antiviral Activities of 4-Acylaminonaphthalenesulfonamide and N^1-Dodecanoyl-4-acylaminonaphthalenesulfonamide.

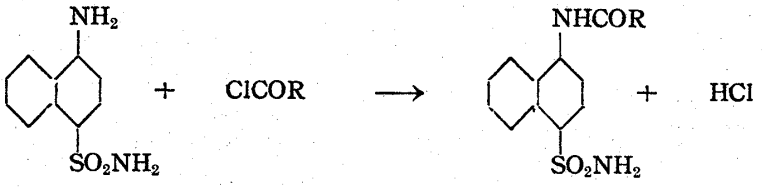
(*Pharmaceutical Institute, Keio-Gijuku University***)

In the foregoing paper,[1] it was pointed out that N^1-acyl-4-acetylaminonaphthalenesulfonamides were of interest in exerting antiviral and surfactant activities and that among them, N^1-dodecanoyl-4-acetylaminonaphthalenesulfonamide, named PANS-No. 610, was of promise for antiviral administration.

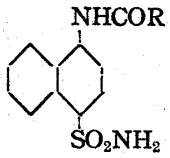
Since the antiviral activities of these compounds might be associated with their surfactant properties, it was of interest for the search of new antiviral drugs to change the balance of surfactant acyl groups in these compounds.

On consideration of such relationship, 4-acylaminonaphthalenesulfonamides and N^1-dodecanoyl-4-acylaminonaphthalenesulfonamides were synthesized. This paper describes the synthesis and antiviral activities of these new compounds.

Synthesis of 4-Acylaminonaphthalenesulfonamides 4-Acylaminonaphthalenesulfonamides have not hitherto been synthesized. It was noted that N^4-acylsulfanilamide or N^1,N^4-diacylsulfanilamide was obtained by the respective condensation of one mole of sulfanilamide with one or two moles of acyl chloride. By referring to this reaction, 4-acylaminonaphthalenesulfonamides were synthesized by condensing 4-aminonaphthalenesulfonamide with equimolar amount of acyl chlorides in a cold mixture of acetone and dry pyridine, as shown in the following :



The compounds thus obtained are summarized in Table I.

Table I. 

R	Mol. formula	m.p. °C (decomp.)	Appearance	Soly. of Na salt in water
$-COCH_2CH_3$	$C_{13}H_{14}O_3N_2S$	249.5~251	Needles	Very sol.
$-CO(CH_2)_2CH_3$	$C_{14}H_{16}O_3N_2S$	239~241.5	〃	〃
$-CO(CH_2)_4CH_3$	$C_{16}H_{20}O_3N_2S$	196~197.5	〃	Sol.
$-CO(CH_2)_6CH_3$	$C_{18}H_{24}O_3N_2S$	191~192	〃	Fairly sol.
$-CO(CH_2)_8CH_3$	$C_{20}H_{28}O_3N_2S$	193.5~195	Fine needles	〃
$-CO(CH_2)_{10}CH_3$	$C_{22}H_{32}O_3N_2S$	193~195.5	Needles	Slightly sol.
$-CO(CH_2)_{12}CH_3$	$C_{24}H_{36}O_3N_2S$	196~197	Fine needles	〃
$-CO(CH_2)_{14}CH_3$	$C_{26}H_{40}O_3N_2S$	192~193	Needles	〃
$-CO(CH_2)_{16}CH_3$	$C_{28}H_{44}O_3N_2S$	190~191	Fine needles	〃
$-CO(CH_2)_8CH=CH_2$	$C_{21}H_{28}O_3N_2S$	190~191	Needles	Sol.

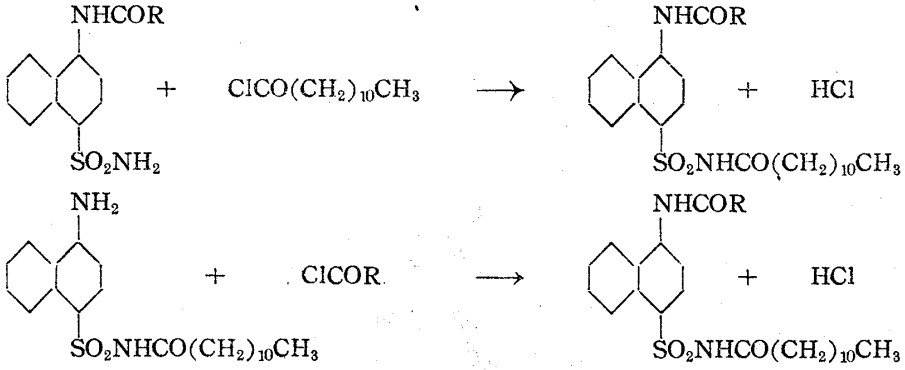
Synthesis of N^1-Dodecanoyl-4-acylaminonaphthalenesulfonamides These compounds also have not been reported. N^1-Dodecanoyl-4-acylaminonaphthalenesulfonamides

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

** Shinano-machi, Shinjuku-ku, Tokyo (和智恒雄, 和田多嘉子).

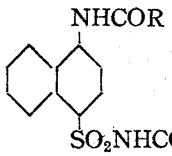
1) Part XXI : This Bulletin, **2**, 423(1954).

were synthesized either by the reaction of 4-acylaminonaphthalenesulfonamide possessing lower acyl groups with dodecanoyl chloride in pyridine, or by the condensation of N^1-dodecanoyl-4-aminonaphthalenesulfonamide with acyl chloride containing higher acyl group in a mixture of pyridine and acetone as illustrated in the following:



The compounds thus obtained are summarized in Table II.

TABLE II.



R	Mol. formula	m.p. °C(decomp.)	Appearance	Soly. of Na salt in water
$-COCH_2CH_3$	$C_{25}H_{36}O_4N_2S$	152.5~154.5	Plates	Sol.
$-CO(CH_2)_2CH_3$	$C_{26}H_{38}O_4N_2S$	141~143.5	〃	〃
$-CO(CH_2)_4CH_3$	$C_{28}H_{42}O_4N_2S$	140.5~142	〃	Fairly sol.
$-CO(CH_2)_6CH_3$	$C_{30}H_{46}O_4N_2S$	142~145	〃	〃
$-CO(CH_2)_8CH_3$	$C_{32}H_{50}O_4N_2S$	144.5~147	〃	〃
$-CO(CH_2)_{10}CH_3$	$C_{34}H_{54}O_4N_2S$	144~146	〃	Slightly sol.
$-CO(CH_2)_{12}CH_3$	$C_{36}H_{58}O_4N_2S$	143~145.5	〃	〃
$-CO(CH_2)_{14}CH_3$	$C_{38}H_{62}O_4N_2S$	140~144	〃	〃
$-CO(CH_2)_{16}CH_3$	$C_{40}H_{66}O_4N_2S$	145~148.5	〃	〃
$-CO(CH_2)_8CH=CH_2$	$C_{33}H_{50}O_4N_2S$	141~145.5	Prisms	Fairly sol.

Conditions for the syntheses of the compounds of the two series were studied by using various modified methods deduced from those for sulfanilamides and the methods described above were found to be the most effective for these two series.

Both 4-acylaminonaphthalenesulfonamides and N^1-dodecanoyl-4-acylaminonaphthalenesulfonamides came in colorless crystals, hardly soluble in water but soluble in aqueous alkali solutions with formation of the sodium salts. Their solubility in alkaline solution decreased on lengthening their carbon chain.

Antiviral Activities of 4-Acylaminonaphthalenesulfonamides and N^1-Dodecanoyl-4-acylamionaphthalenesulfonamides For the test of antiviral activities of these

TABLE III.

Compound	pH	Drug concentration(%) 0.05	0.025	0.01
N^1-Dodecanoyl-4-propionylaminonaphthalenesulfonamide	8.2	8/10	3/10	0/9
N^1-Dodecanoyl-4-butanoylaminonaphthalenesulfonamide	8.2	10/10	3/10	0/10
N^1-Dodecanoyl-4-hexanoylaminonaphthalenesulfonamide	8.2	9/10	5/10	0/9
N^1-Dodecanoyl-4-octanoylaminonaphthalenesulfonamide	8.2	7/10	6/10	0/10
N^1-Dodecanoyl-4-decanoylaminonaphthalenesulfonamide	8.2	10/10	3/10	0/9
N^1-Dodecanoyl-4-undecylenoylaminonaphthalenesulfonamide	8.2	5/9	3/11	0/8
N^1-Dodecanoyl-4-acetylaminonaphthalenesulfonamide(PANS-No. 610)	8.2	9/10	4/10	0/10
Control	7.6	0/10		

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

compounds *in vitro* against the Nakayama strain of *Encephalitis japonica*, the same procedures as described in Part V[2] were employed. The results are shown in Table III.

From the results thus obtained, it may be said that such compounds having acyl groups at N^4-position but not any substituent at N^1-position as 4-acylaminonaphthalenesulfonamides, were less effective against the virus than N^1-acyl-4-acylamino- and N^1-acyl-4-aminonaphthalenesulfonamides. This fact might be due to the decrease of both adsorption and penetration properties of the compounds caused by the lowering of surface activity. Thus, it was deduced that the existence of acyl group at N^1-position was preferable for the exertion of an antiviral activity.

In the series of N^1-dodecanoyl-4-acylaminonaphthalenesulfonamides it was found that the antiviral activities *in vitro* were similar when the number of carbon atoms of the acyl group at N^4-position was 3~12, and were nearly equal to that of PANS-No. 610. This fact suggests that their *in vitro* activities, related to direct action on the virus, might remain almost invariable until their acyl groups became very large. In other words, the existence of a lauroyl group at N^1-position as well as an acyl group of a not very large size at N^4-position was considered requisite in showing a strong activity *in vitro*. Hereupon, *in vivo* effects of the six active compounds described above were tested by using the test method described in the foregoing paper[1], but none were as effective as PANS-No. 610. Consequently it may be said that the introduction of an acyl group of not so large a size at N^4-position was preferable for the exertion of *in vivo* effect. That the *in vivo* effect of N^1-dodecanoyl-4-acylaminonaphthalenesulfonamide having an acyl larger than a propionoyl group was inferior to that of PANS-No. 610 might at least be partially due to the difference of surfactant property, especially penetration activity between the former and the latter. The relationship between the antiviral and surfactant property of these compounds will be discussed in the near future.

Experimental

General Method of Synthesis of 4-Acylaminonaphthalenesulfonamides—4.5 g. of 4-aminonaphthalenesulfonamide was dissolved in a mixture of 100 cc. of acetone and 5 cc. of pyridine. Agitation was started and mixture was cooled to 5° to 0°, and 0.02 mole of acyl chloride was added in small portions. After 15 mins.' stirring, 50 cc. of acetone was removed by evaporation, and the precipitate, produced by adding 100 cc. water and 5 cc. conc. HCl, was filtered, and 4-acylaminonaphthalenesulfonamide was obtained after recrystallization.

General Method of Synthesis of N^1-Dodecanoyl-4-acylaminonaphthalenesulfonamides—(1) 0.005 mole of 4-acyl(propionoyl, butanoyl, hexanoyl, or octanoyl)-aminonaphthalenesulfonamide was mixed with 6 cc. of pyridine. The mixture was heated to 90~100°, agitation was started, and 1.1 g. of dodecanoyl chloride was added in portions. After 15 mins'. stirring at 100~110°, the reaction mixture was poured into a mixture of 30 cc. water and 6 cc. of conc. HCl, and the precipitate was collected by filtration. (2) 2 g. of N^1-dodecanoyl-4-aminonaphthalenesulfonamide was dissolved in 15 cc. of acetone and 1.5 cc. of pyridine. Under stirring, 0.005 mole of acyl (decanoyl, dodecanoyl, tetradecanoyl, hexadecanoyl, octadecanoyl, or undecylenoyl) chloride was added to the mixture at room temperature. After 15 mins.' stirring, most of the acetone was removed and the precipitate, produced by adding 30 cc. water and 1.5 cc. of conc. HCl, was filtered.

4-Propionoylaminonaphthalenesulfonamide—Recrystd. from 90% EtOH to needles, m.p. 249.5~251°. Yield, 69.5%. *Anal.* Calcd. for $C_{13}H_{14}O_3N_2S$: N, 10.09. Found: N, 10.12.

4-Butanoylaminonaphthalenesulfonamide—Recrystd. from 70% EtOH to needles, m.p. 239~241.5°. Yield, 63.5%. *Anal.* Calcd. for $C_{14}H_{16}O_3N_2S$: N, 9.59. Found: N, 9.39.

4-Hexanoylaminonaphthalenesulfonamide—Recrystd. from 70% EtOH to needles, m.p. 196~197.5°. Yield, 89%. *Anal.* Calcd. for $C_{16}H_{20}O_3N_2S$: N, 8.75. Found: N, 8.81.

4-Octanoylamimonaphthalenesulfonamide—Recrystd. from 90% EtOH to needles, m.p. 191~192°. Yield, 50%. *Anal.* Calcd. for $C_{18}H_{24}O_3N_2S$: N, 8.05. Found: N, 8.14.

4-Decanoylaminonaphthalenesulfonamide—Recrystd. from 90% EtOH to fine needles, m.p. 193.5~195°. Yield, 55.5%. *Anal.* Calcd. for $C_{20}H_{28}O_3N_2S$: N, 7.45. Found: N, 7.53.

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

4-Dodecanoylaminonaphthalenesulfonamide—Recrystd. from EtOH to needles, m.p. 193~195.5°. Yield, 71.5%. *Anal.* Calcd. for $C_{22}H_{32}O_3N_2S$: N, 6.93 Found : N, 7.02.

4-Tetradecanoylaminonaphthalenesulfonamide—Recrystd. from EtOH to fine needles, m.p 196~197°. Yield, 82.5%. *Anal.* Calcd. for $C_{24}H_{36}O_3N_2S$: N, 6.47. Found : N, 6.56.

4-Hexadecanoylaminonaphthalenesulfonamide—Recrystd. from EtOH to needles, m.p. 192~193°. Yield, 93%. *Anal.* Calcd. for $C_{26}H_{40}O_3N_2S$: N, 6.09. Found : N, 6.10.

4-Octadecanoylaminonaphthalenesulfonamide—Recrystd. from a mixture of abs. EtOH and benzene to fine needles, m.p. 190~191°. Yield, 83%. *Anal.* Calcd. for $C_{28}H_{44}O_3N_2S$: N, 5.73. Found : N, 5.79.

4-Undecylenoylaminonaphthalenesulfonamide—Recrystd. from 80% EtOH to needles, m.p. 190~191°. Yield, 71%. *Anal.* Calcd. for $C_{21}H_{28}O_3N_2S$: N, 7.21. Found : N, 7.29.

N^1-Dodecanoyl-4-propionoylaminonaphthalenesulfonamide—Recrystd. from 70% EtOH to plates, m.p. 152.5~154.5°. Yield, 52%. *Anal.* Calcd. for $C_{25}H_{36}O_4N_2S$: N, 6.09. Found : N, 6.11.

N^1-Dodecanoyl-4-butanoylaminonaphthalenesulfonamide—Recrystd. from 80% EtOH to plates, m.p. 141~143.5°. Yield, 34%. *Anal.* Calcd. $C_{26}H_{38}O_4N_2S$: N, 5.90. Found : N, 5.88.

N^1-Dodecanoyl-4-hexanoylaminonaphthalenesulfonamide—Recrystd. from 90% EtOH to plates, m.p. 140.5~142°. Yield, 36%. *Anal.* Calcd. for $C_{28}H_{42}O_4N_2S$: N, 5.58. Found N, 5.69.

N^1-Dodecanoyl-4-octanoylaminonaphthalenesulfonamide—Recrystd. from 90% EtOH to plates, m.p. 142~145°. Yield, 50%. *Anal.* Calcd. for $C_{30}H_{46}O_4N_2S$: N, 5.28. Found : N, 5.25.

N^1-Dodecanoyl-4-decanoylaminonaphthalenesulfonamide—Recrystd. from benzene and from 80% EtOH to plates, m.p. 144.5~147°. Yield, 22%. *Anal.* Calcd. for $C_{32}H_{50}O_4N_2S$: N, 5.02 Found : N, 5.10.

N^1-Dodecanoyl-4-dodecanoylaminonaphthalenesulfonamide—Recrystd. from 90% EtOH to plates, m.p. 144~146°. Yield, 24%. *Anal.* Calcd. for $C_{34}H_{54}O_4N_2S$: N, 4.78. Found : N, 4.64.

N^1-Dodecanoyl-4-tetradecanoylaminonaphthalenesulfonamide—Recrystd. from benzene and EtOH to plates, m.p. 143~145.5°. Yield, 43%. *Anal.* Calcd. for $C_{36}H_{58}O_4N_2S$: N, 4.56. Found : N, 4.44.

N^1-Dodecanoyl-4-hexadecanoylaminonaphthalenesulfonamide—Recrystd. from benzene and from EtOH to plates, m.p. 140~144°. Yield, 22%. *Anal.* Calcd. for $C_{38}H_{62}O_4N_2S$: N, 4.36. Found : N, 4.29.

N^1-Dodecanoyl-4-octadecanoylaminonaphthalenesulfonamide—Recrystd. from benzene and from EtOH to plates, m.p. 145~148.5°. Yield, 36%. *Anal.* Calcd. for $C_{40}H_{63}O_4N_2S$: N, 4.17. Found : N, 4.14.

N^1-Dodecanoyl-4-undecylenoylaminonaphthalenesulfonamide—Recrystd. from EtOH to prisms, m.p. 141~145.5°. Yield, 35%. *Anal.* Calcd. for $C_{33}H_{50}O_4N_2S$: N, 4.91. Found : N, 5.03.

Summary

1) 4-Acylaminonaphthalenesulfonamides were synthesized by condensing 4-aminonaphthalenesulfonamide with equimolar amount of acyl chlorides in a cold mixture of acetone and pyridine. N^1-Dodecanoyl-4-acylaminonaphthalenesulfonamides were synthesized either by the reaction of 4-acylaminonaphthalenesulfonamide possessing lower acyl groups with dodecanoyl chloride in pyridine or by the condensation of N^1-dodecanoyl-4-aminonaphthalenesulfonamide with acyl chlorides containing higher acyl groups in a mixture of pyridine and acetone.

2) The antiviral effects of these compounds were tested against the Nakayama strain of the Japanese encephalitis virus.

3) Antiviral activities *in vitro* of the series of N^1-dodecanoyl-4-acylaminonaphthalenesulfonamides were similar when the number of carbon atoms in the acyl group at N^4-position was 3~12 and were nearly equal to that of PANS-No. 610.

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