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154. Junzo Kawahata, Hiroko Koibuchi, and Shigeshi Toyoshima: Researches on Chemotherapeutic Drugs against Viruses. XXXII.*1 Studies on the Synthesis and the Antiviral Effect of N-Alkanoyl-5-acetamido-8-quinolinesulfonamide.

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As described in the preceding paper,[1] derivatives of N-alkanoyl-quinolinesulfonamide were synthesized to find improved drugs of PANS-610. Among the compounds of N-alkanoyl-8-ethoxy-5-quinolinesulfonamide, the decanoyl derivative was found to be more effective against Japanese B encephalitis than PANS-610. This fact shows that quinoline ring was able to contribute to antiviral activity as well as that of naphthalene. Encouraged by this finding, the present work was undertaken to introduce acetamido or alkanoylsulfanilamido group into the quinoline ring. Thus, N-alkanoyl-5-acetamido-8-quinolinesulfonamide was synthesized and its effect on the Nakayama strain of Japanese B encephalitis virus was examined.

This report describes the synthesis and antiviral effect of N-alkanoyl-5-acetamido-8-quinolinesulfonamide.

Synthesis of N-Alkanoyl-5-acetamido-8-quinolinesulfonamide

N-Alkanoyl-5-acetamido-8-quinolinesulfonamide is unknown to date but its synthetic intermediate, 5-amino-8-quinolinesulfonamide has already been synthesized by Urist and Jenkins[2] and the process of their method is shown in Chart 1.

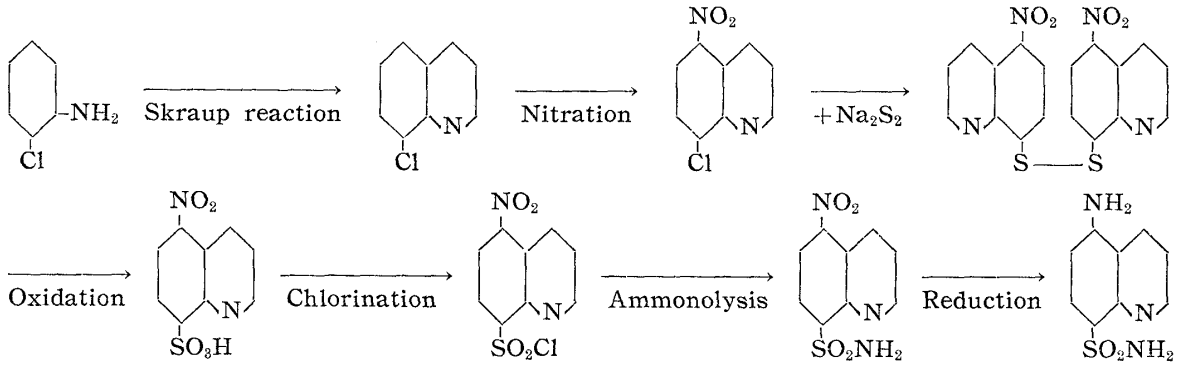

Chart 1.

Though this method was tried, the yield of 5-amino-8-quinolinesulfonamide was found very low.

Processes other than that described above were examined for synthesis of 5-amino- or 5-acetamido-8-quinolinesulfonamide in a better yield, but any better method was not found. Thus, 5-amino-8-quinolinesulfonamide was prepared in a low yield according to the method of Urist and Jenkins.

Next, 5-amino-8-quinolinesulfonamide was acetylated with acetic anhydride and the resulting 5-acetamido derivative was reacted with alkanoyl chloride in anhydrous pyridine to yield N-alkanoyl-5-acetamido-8-quinolinesulfonamide as illustrated in Chart 2.

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*1 This paper constitutes part of a series entitled "Researches on Chemotherapeutic Drugs against Viruses" by Takeo Ueda. Part XXXI. This Bulletin, 8, 921(1960).

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1) Part XXIX. This Bulletin, 8, 788(1960).

2) H. Urist, G. L. Jenkins: J. Am. Chem. Soc., **63**, 2943(1941).

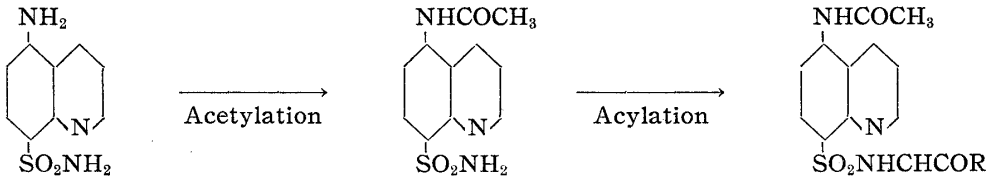

Chart 2.

The compounds synthesized are summarized in Table I.

TABLE I.

Compd. No.	R	Mol. formula	Analyses (%) C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
Q-4	C_4H_9	$C_{16}H_{19}O_4N_3S$	55.03	55.10	5.43	5.41	12.03	11.91
Q-6	C_6H_{13}	$C_{18}H_{23}O_4N_3S$	57.27	57.34	6.14	6.19	11.13	11.04
Q-7	C_7H_{15}	$C_{19}H_{25}O_4N_3S$	58.29	58.39	6.44	6.41	10.73	10.73
Q-9	C_9H_{19}	$C_{21}H_{29}O_4N_3S$	60.12	60.21	6.97	6.85	10.02	9.95
Q-11	$C_{11}H_{23}$	$C_{23}H_{33}O_4N_3S$	61.70	61.81	7.43	7.37	9.39	9.43
Q-13	$C_{13}H_{27}$	$C_{25}H_{37}O_4N_3S$	63.07	63.21	7.83	7.85	8.83	8.91

All the compounds, recrystallized from hydr. EtOH, are colorless plates.

Screening Test of N-Alkanoyl-5-acetamido-8-quinolinesulfonamide

Antiviral effect of the compounds synthesized was tested *in vitro* employing the Nakayama strain in mice. The experimental procedures were the same as those described in the preceding report.[1]

The experimental results obtained are shown in Table II. As can be seen from Table II,

TABLE II. Antiviral Activity *in vitro* against Japanese B Encephalitis Virus

Compd. No.	Compd. concn. (γ/cc.)	LD_{50} (10^{-x}) Treated group x	Untreated group x
Q-4	500	5.8	8.4
Q-6	500	4.5	8.6
	250	5.6	8.6
Q-7	500	3.4	8.6
	250	5.2	8.6
Q-9	500	2.8	8.6
	250	3.0	8.6
	100	3.2	8.6
Q-11	500	3.0	8.6
	250	3.5	8.6
	100	5.0	8.6
Q-13	500	4.8	8.6
	250	5.6	8.6

Various dilutions of the Nakayama strain of Japanese B encephalitis virus were prepared. Each 0.1 cc. of the dilution was placed in a test tube containing 0.1 cc. of a sterilized solution of a compound and 0.8 cc. of the Lush solution. After incubation at 22° for 10 min., 0.03 cc. each of this mixture was inoculated intracerebrally into mice. After daily observations for 2 weeks, LD_{50} of the treated and untreated groups was calculated by the method of Reed and Munch.

the octanoyl and dodecanoyl derivatives were found to have effect nearly equal to that of PANS-610, the decanoyl derivative being stronger than PANS-610, and the other compounds weaker than PANS-610. It may be said from these results that the decanoyl derivative was stronger *in vitro* than PANS-610 and N-decanoyl-8-ethoxy-5-quinolinesulfonamide by the test in a dose of 250 γ/cc. and 100 γ/cc.

The *in vivo* effect of decanoyl and dodecanoyl derivatives was tested using the Nakayama strain in mice. The experimental procedures were the same as those described in the preceding report[1] and experimental results are shown in Table III.

Table III. Antiviral Effect *in vivo* against Japanese B Encephalitis Virus

Compd. No.	LD_{50} (mg./kg. *i. v.*)	Dose (mg./kg.)	Treated group	Untreated group
Q-9	140	70	22/50	13/50
		46	14/50	
Q-11	160	80	18/49	13/50
		53	15/49	

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

$10^{-1.5}(4 \times LD_{50})$ of the Nakayama strain was inoculated intraperitoneally into groups of mice and 72 hr. later, 1/2 dose of LD_{50} of each compound was injected intravenously into the mice in a single dose. After daily observations for 2 weeks, the ratio of survived and total mice used was recorded.

As seen in Table III, both derivatives were found to possess significant *in vivo* effect and the decanoyl derivative was particularly more effective than N-decanoyl-8-ethoxy-5-quinolinesulfonamide and PANS-610.

From these findings, it was assumed that the ring of quinoline could contribute to antiviral activity, as well as that of naphthalene.

Detailed chemotherapeutic studies on N-decanoyl-5-acetamido-8-quinolinesulfonamide will be published in a medical journal in the near future.

Experimental

General Method for Synthesis of N-Alkanoyl-5-acatamido-8-quinolinesulfonamide

a) **5-Amino-8-quinolinesulfonamide**—Prepared from 5-nitro-8-chloroquinoline via bis(5-nitro-8-quinolyl) disulfide, 5-nitro-8-quinolinesulfonic acid, 5-nitro-8-quinolinesulfonyl chloride, and 5-nitro-8-quinolinesulfonamide according to the method of Urist and Jenkins.

b) **5-Acetamido-8-quinolinesulfonamide**—To a suspension of 0.86 g. of 5-amino-8-quinolinesulfonamide in 20 cc. of glacial AcOH, 0.52 g. of Ac_2O was added and refluxed for 15 hr. After concentration and cooling the reaction mixture, precipitated 5-acetamido-8-quinolinesulfonamide was collected, washed with Et_2O, and recrystallized from hydr. EtOH to colorless needles, m.p. 270~272° (decomp.). Yield, 0.8 g. *Anal.* Calcd. for $C_{11}H_{11}O_3N_3S$: N, 15.84. Found: N, 15.72.

c) **N-Alkanoyl-5-acetamido-8-quinolinesulfonamide**—To a mixture of 0.005 mole of 5-acetamido-8-quinolinesulfonamide and 5 cc. of pyridine, 0.007 mole of alkanoyl chloride was added dropwise at 100° with agitation and the mixture was heated for 7 hr. The reaction mixture was poured into 100 cc. of cold water, allowed to stand, and the crude product was collected by filtration. It was washed with petr. ether and toluene, and recrystallized from hydr. EtOH.

Summary

The six compounds of N-alkanoyl-5-acetamido-8-quinolinesulfonamide were synthesized and their antiviral effect was tested by employing the Nakayama strain of Japanese B encephalitis virus.

The decanoyl derivative was more effective *in vitro* than PANS-610 or N-decanoyl-8-ethoxy-5-quinolinesulfonamide. Moreover, the decanoyl derivative was found to possess significant *in vivo* effect against the Nakayama strain.

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