might be caused by its neurotropy, cerebrotropy, and power of penetration into cells of host, related to its surfactant properties.

(5) The compound is of promise for the treatment of diseases caused by the Japanese encephalitis virus.

(6) It may be claimed that this is the only compound which has been confirmed to have chemotherapeutic effect on patients suffering from the so-called small viruses such as the Japanese encephalitis virus.

(Received September 24, 1953)

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93. Takeo Ueda, Isao Nakata, and Shigeshi Toyoshima: Researches on Quaternary Ammonium Salts as Chemotherapeutic Drugs. I. Syntheses of Trialkyl-*p*-alkylanilinium Salts.

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

A number of long-chain quaternary ammonium salts have been reported concerning their germicidal activity since their high potency and usefulness in this field was pointed out by Domagk in 1935.[1] It had already been known that some quaternary nitrogen compounds, pyridinium salts, quinolinium salts, dyestuffs, and so on, were effective against microbes but the study of the utilization of quaternary ammonium salts as germicides was greatly stimulated by his improvement of the germicidal activity in attaching long-chain aliphatic residues to the quaternary nitrogen atom. It was also found that lower members in the series of alcohols and alkylphenols were useful as germicides but attempts to test higher members as to their activity were fruitless because of their low solubility in germicidal concentration. Fortunately, quaternary ammonium salts, even though of high molecular weight, in general, were found to be remarkably soluble in water.

Among those quaternary nitrogen compounds, the effective ones were found to possess long-chain alkyl groups and in general, surface active properties, though their germicidal activity did not run parallel with their surface active properties.

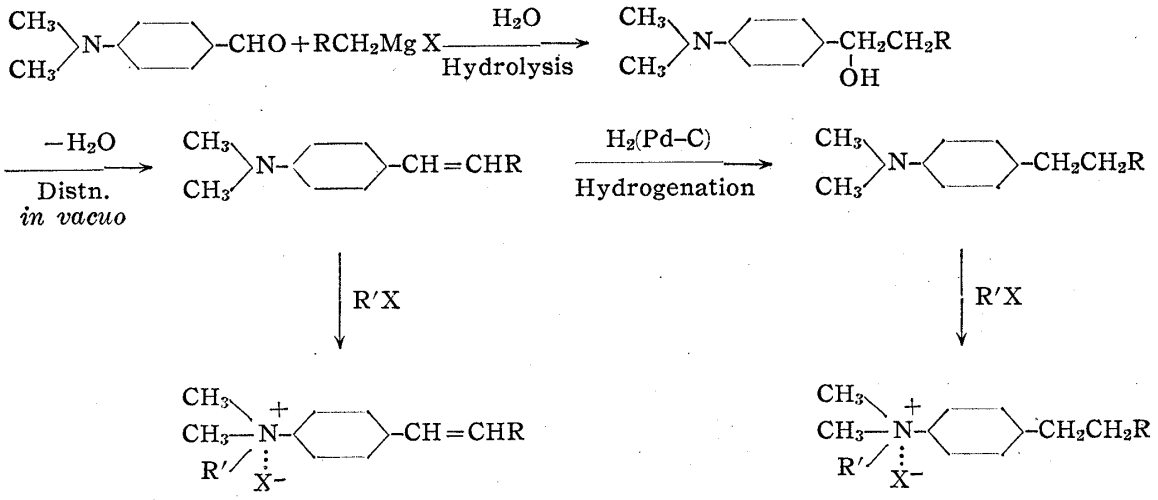
As reported in previous papers,[2] 3-alkylphenylazo-4-hydroxynaphthalenesulfonic acids were observed to be more effective against the Japanese encephalitis virus than other compounds in this series, and their virucidal activity was shown to increase with lengthening of alkyl group and then reach the optimum with the octyl group. It might be deduced thereby that alkylphenyl residue should be an important factor in increasing the activity of the compounds of this type. In order to examine whether this assumption was in point or not, some quaternary ammonium salts were synthesized by converting N,N-dimethyl-*p*-alkylanilines.

N,N-Dimethyl-*p*-alkylaniline was prepared by various methods, for instance, by alkylation of *p*-alkylaniline, by condensation of dimethylaniline with alcohol in the presence of catalysts,[3] and so on. However, these methods were not always suitable in laboratories because of low yields or of difficulty in the purification of resulting substances. N,N-

* Shinano-machi, Shinjuku-ku, Tokyo (上田武雄, 中田 公, 豊島 滋).

1) G. Damagk: Med. Wochshr., **61**, 829(1935).
2) T. Ito, S. Toyoshima, M. Taniguchi, T. Ueda: This Bulletin, **1**, 275(1953).
3) W. Cule Davies, F. L. Hulbert: J. Soc. Chem. Ind., **57**, 349(1938), *et seq.*

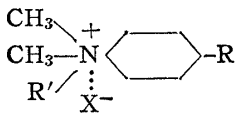
Dimethyl-*p*-alkylanilines were obtained easily and with good yields by the following method. Through reaction of *p*-dimethylaminobenzaldehyde with alkylmagnesium halide, N,N-dimethylaminophenyl-*p*-alkylcarbinol (I) was obtained, which was readily dehydrated to N,N-dimethyl-*p*-alken-1-ylaniline (II) by vacuum distillation.[4] N,N-Dimethyl-*p*-alkylaniline (III) was obtained by hydrogenation of the double bond in N,N-dimethyl-*p*-alken-1-ylaniline (II) with hydrogen in the presence of palladium charcoal as a catalyst. The tertiary amines (II and III) thereby obtained were converted into the quaternary ammonium salts (IV and V) by reaction with alkyl or aralkyl halide. The whole process of the reaction is illustrated as follows:



R=H or alkyl, R′=methyl or benzyl, X=Br or I.

The quaternary ammonium salts prepared above are summarized in Tables I and II.

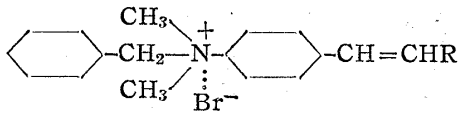
TABLE I



R	R′	X	Appearance	m.p. (°C)	Solubility in water
CH_3-	$C_6H_5CH_2$-	Br	Colorless prisms	166～167	Freely Soluble
C_2H_5-	$C_6H_5CH_2$-	Br	Colorless prisms	158～159	Freely Soluble
n-C_3H_7-	$C_6H_5CH_2$-	Br	Colorless prisms	153～154	Freely Soluble
n-C_4H_9-	$C_6H_5CH_2$-	Br	Colorless prisms	136～137	Freely Soluble
n-C_5H_{11}-	$C_6H_5CH_2$-	Br	Colorless plates	107～108	Freely Soluble
n-C_6H_{13}-	$C_6H_5CH_2$-	Br	Colorless plates	84～85	Freely Soluble
n-C_7H_{15}-	$C_6H_5CH_2$-	Br	Colorless plates	89～90	Soluble
n-C_8H_{17}-	$C_6H_5CH_2$-	Br	Colorless plates	87～88	Soluble
n-C_9H_{19}-	$C_6H_5CH_2$-	Br	Colorless plates	98～99	Soluble
n-$C_{10}H_{21}$-	$C_6H_5CH_2$-	Br	Colorless plates	88～89	Soluble
n-$C_{11}H_{23}$-	$C_6H_5CH_2$-	Br	Colorless plates	86～87	Soluble
n-C_5H_{11}-	CH_3-	I	Colorless plates	184.5～185.5	Soluble
n-C_6H_{13}-	CH_3-	I	Colorless plates	179.5～180.5	Sparingly Soluble
n-C_7H_{15}-	CH_3-	I	Colorless plates	173～174	Sparingly Soluble
n-C_8H_{17}-	CH_3-	I	Colorless plates	174～175	Sparingly Soluble
n-C_9H_{19}-	CH_3-	I	Colorless plates	180～181	Sparingly Soluble
n-$C_{10}H_{21}$-	CH_3-	I	Colorless plates	176～177	Sparingly Soluble

4) Similar methods have been adopted for the synthesis of lower members in this series by the following authors: F. Sachs, L. Sachs: Ber., 38, 511(1905); F. Sachs, W. Weigert: *Ibid.*, 40, 4361(1907).

TABLE II



R	Appearance	m.p. (°C)	Solubility in water
CH_3-	Colorless prisms	149.5～150.5	Freely soluble
C_2H_5-	Colorless prisms	104～105	Freely soluble
C_3H_7-	Colorless prisms	114～115	Soluble
C_4H_9-	Colorless plates	100～101	Soluble
C_5H_{11}-	Colorless plates	105～106	Soluble
C_6H_{13}-	Colorless plates	100～101	Soluble
C_7H_{15}-	Colorless plates	103～104	Soluble
C_8H_{17}-	Colorless plates	90～91	Soluble
C_9H_{19}-	Colorless plates	94～95	Soluble

The compounds shown in Table I and II were examined as to their activities *in vitro* against *Encephalitis japonica* according to the experimental procedures described in the previous work.[5]

Among both alkyl and alkenylphenyl series, the compounds possessing chains longer than C_8 were observed to exert weak activities, which were approximately equal to that of PAN-No. 25. None of other compounds showed any activity on the virus.

Antibacterial properties of the above compounds will be described in this Bulletin in the near future.

Experimental

Syntheses of Materials—A solution of 0.03 mole of *p*-dimethylaminobenzaldehyde in 70 cc. of dehydrated ether was added dropwise, with efficient stirring, during 1 hour into a solution of alkylmagnesium halide prepared in the usual manner by reacting 1.22 g. of magnesium metal with a mixture of 0.05 mole of alkyl halide in 3～4 times its volume of dehydrated ether. After gentle boiling on a water bath to complete the reaction, the reaction mixture was poured into 100 g. of chipped ice, hydrolyzed completely with diluted sulfuric acid, and then made alkaline with aqueous ammonia, and extracted with ether. On evaporation of ether, corresponding crude N,N-dimethylaminophenyl-*p*-alkylcarbinol was obtained. N,N-Dimethyl-*p*-alken-1-ylaniline was obtained by distillation of N,N-dimethylaminophenyl-*p*-alkylcarbinol under a diminished pressure accompanied with dehydration. The yields were 75～85% of the theoretical based on *p*-dimethylaminobenzaldehyde, with the exception of the poor yield of N,N-dimethyl-*p*-vinylaniline due to its high polymerizability. Among the compounds containing double bonds thus obtained, the lower members were soluble in common organic solvents but the higher ones were hardly soluble in ethanol, methanol, or acetone.

N,N-Dimethyl-*p*-vinylaniline—Pale yellow oil, $b.p_{10}$ 110～112°.

N,N-Dimethyl-*p*-propen-1-ylaniline—Yellowish white prisms, m.p. 49～50°, $b.p_{10}$ 128～129°.

N,N-Dimethyl-*p*-buten-1-ylaniline—Yellowish white prisms, m.p. 25°, $b.p_{10}$ 138～140°.

N,N-Dimethyl-*p*-amylen-1-ylaniline—Yellowish white needles, m.p. 36～37°, $b.p_{10}$ 150～153.

N,N-Dimethyl-*p*-hexen-1-ylaniline—Pale yellow oil, $b.p_{10}$ 162～163°.

N,N-Dimethyl-*p*-hepten-1-ylaniline—Pale yellow oil, m.p. 6～7°, $b.p_{10}$ 174～175°.

N,N-Dimethyl-*p*-octen-1-ylaniline—Pale yellow oil, m.p. 5°, $b.p_{10}$ 187～189°.

N,N-Dimethyl-*p*-nonen-1-ylaniline—Pale yellow oill, m.p. 6°, $b.p_{10}$ 196～197°, $b.p_{3.5}$ 161～162°.

N,N-Dimethyl-*p*-decen-1-ylaniline—Pale yellow oil, m.p. 18.5°, $b.p_{4.5}$ 186～187°, $b.p_2$ 161～162°.

N,N-Dimethyl-*p*-undecen-1-ylaniline—Pale yellow oil, m.p. 20.5°, $b.p_{3.5}$ 186～187°.

N,N-Dimethyl-*p*-alkylaniline was prepared by the hydrogenation of N,N-dimethyl-*p*-alken-1-ylaniline in methanol or in glacial acetic acid, in the presence of palladium charcoal as a catalyst, where the calculated amount of hydrogen was rapidly absorbed. The compounds thereby obtained were colorless substances with aniline-like odor, and miscible with common organic solvents. The yields were nearly quantitative.

5) T. Ueda, S. Toyoshima, T. Wachi, M. Taniguchi, H. Tatsumi: J. Pharm. Soc. Japan, 72, 265 (1952).

N,N-Dimethyl-*p*-ethylaniline: b.p_{10} 96~97°.
N,N-Dimethyl-*p*-propylaniline: b.p_{10} 105~106°.
N,N-Dimethyl-*p*-butylaniline: b.p_{10} 124~125°.
N,N-Dimethyl-*p*-amylaniline: b.p_{10} 135~136°.
N,N-Dimethyl-*p*-hexylaniline: b.p_{10} 149~150°.
N,N-Dimethyl-*p*-heptylaniline: b.p_{10} 158~159°.
N,N-Dimethyl-*p*-octylaniline: b.p_{10} 174~175°.
N,N-Dimethyl-*p*-nonylaniline: b.p_{10} 181°.
N,N-Dimethyl-*p*-decylaniline: b.p_{10} 194°, b.p_1 150~151°, m.p. 8°.
N,N-Dimethyl-*p*-undecylaniline: b.$p_{1.5}$ 164~165°, m.p. 9.5°.

General Method of Syntheses of Anilinium Salts—A mixture of the tertiary amine obtained above and the equimolar amount of methyl iodide or benzyl bromide was warmed on a water bath for a few hours. Methiodide was recrystallized from diluted alcohol. In the case where benzyl bromide was employed, the reaction mixture was dissolved in a small amount of absolute alcohol, bone-blacked, filtered, and reprecipitated with dehydrated ether or petroleum ether. The lower members in this series easily crystallized, but the higher ones did not always crystallize with such ease. Following treatment was used: The reaction mixture was dissolved in water, shaken with ether to remove the unreacted materials, and the aqueous layer was concentrated to dryness *in vacuo*. The residue was reprecipitated from its alcoholic solution with ether or petroleum ether as described above. The yields were 70~80%.

The crude substances were somewhat hygroscopic but the pure ones were not. Anilinium salts thereby obtained were, in general, easily soluble in water though methiodides were comparatively less soluble.

Dimethylbenzyl-*p*-tolylammonium Bromide(I)—Colorless prisms, m.p. 166~167°. *Anal.* Calcd. for $C_{16}H_{20}NBr$: N, 4.57. Found: N, 4.56.

Dimethylbenzyl-*p*-ethylanilinium Bromide (II)—Colorless prisms, m.p. 158~159°. *Anal.* Calcd. for $C_{17}H_{22}NBr$: N, 4.37. Found: N, 4.40.

Dimethylbenzyl-*p*-propylanilinium Bromide (III)—Colorless prisms, m.p. 153~154°. *Anal.* Calcd. for $C_{18}H_{24}NBr$: N, 4.17. Found: N, 4.23.

Dimethylbenzyl-*p*-butylanilinium Bromide(IV)—Colorless prisms, m.p. 136~137°. *Anal.* Calcd. for $C_{19}H_{26}NBr$: N, 4.02. Found: N, 3.96.

Dimethylbenzyl-*p*-amylanilinium Bromide(V)—Colorless plates, m.p. 108~109°. *Anal.* Calcd. for $C_{20}H_{28}NBr$: N, 3.87. Found: N, 4.06.

Dimethylbenzyl-*p*-hexylanilinium Bromide(VI)—Colorless plates, m.p. 93°. *Anal.* Calcd. for $C_{21}H_{30}NBr$: N, 3.72. Found: N, 3.81.

Dimethylbenzyl-*p*-heptylanilinium Bromide(VII)—Colorless plates, m.p. 89~90°. *Anal* Calcd. for $C_{22}H_{32}NBr$: N, 3.59. Found: N, 3.62.

Dimethylbenzyl-*p*-octylanilinium Bromide(VIII)—Colorless plates, m.p. 87~88°. *Anal.* Calcd. for $C_{23}H_{34}NBr$: N, 3.46. Found: N, 3.56.

Dimethylbenzyl-*p*-nonylanilinium Bromide(IX)—Colorless plates, m.p. 98~99°. *Anal.* Calcd. for $C_{24}H_{36}NBr$: N, 3.35. Found: N, 3.44.

Dimethylbenzyl-*p*-decylanilinium Bromide(X)—Colorless plates, m.p. 88~89°. *Anal.* Calcd. for $C_{25}H_{38}NBr$: N, 3.23. Found: N, 3.21.

Dimethylbenzyl-*p*-undecylanilinium Bromide(XI)—Colorless plates, m.p. 86~87°. *Anal.* Calcd. for $C_{26}H_{40}NBr$: N, 3.14. Found: N, 3.17.

Trimethyl-*p*-amylanilinium Iodide(XII)—Colorless plates, m.p. 184.5~185.5°. *Anal.* Calcd. for $C_{14}H_{24}NI$: N, 4.20. Found: N, 4.15.

Trimethyl-*p*-hexylanilinium Iodide(XIII)—Colorless plates, m.p. 179~180.5°. *Anal.* Calcd. for $C_{15}H_{26}NI$: N, 4.03. Found: N, 4.06.

Trimethyl-*p*-heptylanilinium Iodide(XIV)—Colorless plates, m.p. 174°. *Anal.* Calcd. for $C_{16}H_{28}NI$: N, 3.88. Found: N, 3.98.

Trimethyl-*p*-octylanilinium Iodide(XV)—Colorless plates, m.p. 175°. *Anal.* Calcd. for $C_{17}H_{30}NI$: N, 3.73. Found: N, 3.80.

Trimethyl-*p*-nonylanilinium Iodide(XVI)—Colorless plates, m.p. 181.5°. *Anal.* Calcd. for $C_{18}H_{32}NI$: N, 3.60. Found: N, 3.63.

Trimethyl-*p*-decylanilinium Iodide(XVII)—Colorless plates, m.p. 177°. *Anal.* Calcd. for $C_{19}H_{34}NI$: N, 3.47. Found: N, 3.55.

Dimethylbenzyl-*p*-propen-1-ylanilinium Bromide(XVIII)—Colorless prisms, m.p. 149.5~150.5°. *Anal.* Calcd. for $C_{18}H_{22}NBr$: N, 4.22. Found: N, 4.14.

Dimethylbenzyl-*p*-buten-1-ylanilinium Bromide(XIX)—Colorless prisms, m.p. 104~105°. *Anal.* Calcd. for $C_{19}H_{24}NBr$: N, 4.05. Found: N, 4.01.

Dimethylbenzyl-*p*-amylen-1-ylanilinium Bromide(XX)—Colorless prisms, m.p. 114~115°. *Anal.* Calcd. for $C_{20}H_{26}NBr$: N, 3.89. Found: N, 4.01.

Dimethylbenzyl-*p*-hexen-1-ylanilinium Bromide(XXI)—Colorless plates, m.p. 100～101°. *Anal.* Calcd. for $C_{21}H_{28}NBr$: N, 3.74. Found: N, 3.85.

Dimethylbenzyl-*p*-hepten-1-ylanilinium Bromide(XXII)—Colorless plates, m.p. 105～106°. *Anal.* Calcd. for $C_{22}H_{30}NBr$: N, 3.61. Found. N, 3.69.

Dimethylbenzyl-*p*-octen-1-ylanilinium Bromide(XXIII)—Colorless plates, m.p. 100～101°. *Anal.* Calcd. for $C_{23}H_{32}NBr$: N, 3.48. Found: N, 3.51.

Dimethylbenzyl-*p*-nonen-1-ylanilinium Bromide(XXIV)—Colorless plates, m.p. 103～104°. *Anal.* Calcd. for $C_{24}H_{34}NBr$: N, 3.36. Found: N, 3.35.

Dimethylbenzyl-*p*-decen-1-ylanilinium Bromide(XXV)—Colorless plates, m.p. 90～91°. *Anal.* Calcd. for $C_{25}H_{36}NBr$: N, 3.25. Found: N, 3.26.

Dimethylbenzyl-*p*-undecen-1-ylanilinium Bromide(XXVI)—Colorless plates, m.p. 94～95°. *Anal.* Calcd. for $C_{26}H_{38}NBr$: N, 3.15. Found: N, 3.23.

Summary

In accordance with the assumption that the alkylphenyl groups might play an important rôle in increasing the activity of 3-alkylphenylazo-4-aminonaphthalenesulfonic acids against Japanese encephalitis virus, some alkylanilinium salts were synthesized by combining alkyl or aralkyl halides with N,N-dimethyl-*p*-alkylanilines, which were readily prepared by following reactions, *viz.*, syntheses of N,N-dimethylaminophenyl-*p*-alkylcarbinols with *p*-dimethylaminobenzaldehyde and alkylmagnesium halides, the dehydration of the carbinols by vacuum distillation to N,N-dimethyl-*p*-alken-1-ylanilines, and then the hydrogenation of the double bonds of the resulting substance by catalytic reduction to N,N-dimethyl-*p*-alkylanilines.

(Received September 24, 1953)

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94. Masaru Hasegawa: Über die Bromierung von Methylpyrimidin-Derivaten mittels N-Bromsuccinimides.

(*Pharmaz. Institut d. Medizin. Fakultät d. Universität Tokyo**)

Durch eine Reihe von voraufgelaufenen Versuchen wurde es bestätigt, dass die Methyl-Kette auf der α- bzw. γ-Stellung der Pyridin- und Chinolin-Homologen durch N-Bromsuccinimid (N. B. S.) leicht bromierbar ist.[1] Die Reaktion verläuft dabei weit glatter, wenn man die Basizität des Kernstickstoffes durch eine Chlor Gruppe unterdrückt. Durch Erweiterung der Versuche auf der Pyrimidin-Reihe wurde es nun gezeigt, dass beim Pyrimidin die Methyl-Kette der 5-Stellung vorzüglich bromiert wird.

4-Methyl-2,6-dichlor- bzw. 2,4,-Dimethyl-6-chlor-pyrimidin zeigt nämlich gegen die Reaktion einen Widerstand. Bei der Einwirkung von N.B.S. in Tetrachlorkohlenstoff verbrauchte es bis zur Beendigung der Reaktion mehr als 10 Stunden und es wurde ausser dem Ausgangsmaterial nichts sicheres erfasst. Die Reaktion mit 5-Methyl-2,4,6-trichlor- und 2,5-Dimethyl-4,6-dichlor-pyrimidin verläuft dagegen weit glatter. Innerhalb von 1 Stunde war die Reaktion beendet, und es entstand das entsprechende 5-Brommethyl-Derivat mit ca. 75～80 proz. Ausbeute. Das 5-Brommethyl-Derivat des ersteren bildete Tafeln vom Schmp. 134～135° und das entsprechende Derivat des letzterens Tafeln vom Schmp. 109～110°.

* Hongo, Tokyo (長谷川 賢).

1) Hasegawa: J. Pharm. Soc. Japan, **71**, 256(1951); Diese Zeitschr., **1**, 47, 293 (1953).