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152. Fumio Ueda, Takeo Ueda, and Shigeshi Toyoshima : Researches on Chemotherapeutic Drugs against Viruses. XXV.[1] Studies on the Syntheses and Antiviral Effect of 2-Dimethylaminoethyl Alkylphenyl Ethers.

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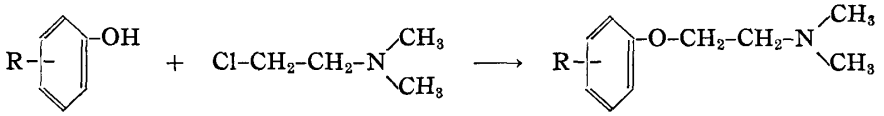
In the previous papers of this series,[1,2] it was reported that some compounds of 3-alkylphenoxy-1,2-propanediol, 3-alkanoylaminophenoxy-1,2-propanediol, and 2-alkylphenoxy-alkanoic acid series exerted antiviral activity against Japanese B encephalitis virus *in vivo*, and against poliomyelitis virus and influenza A virus *in vitro*. It was thereby observed that in the structure of these compounds, phenoxyl group having hydrophobic groups, such as alkyl and alkanoylamino, might be important.

The same type of compounds, possessing a dimethylaminoethyl group in place of a propanediol or carboxylic group were synthesized and their antiviral activities tested. This paper describes the synthesis of 2-dimethylaminoethyl alkylphenyl ethers and their antiviral activity against Japanese B encephalitis and poliomyelitis virus.

2-Dimethylaminoethyl alkylphenyl ethers are not known yet, but the parent compound, 2-dimethylaminoethyl phenyl ether, had been synthesized[3] by condensation of phenol with 2-dimethylaminoethyl chloride hydrochloride to obtain Adrenaline-like compounds. 2-Dimethylaminoethyl alkylphenyl ether, however, could not be obtained by this method. Alkyl derivatives of 2-dimethylaminoethyl phenyl ether, having alkyl chains of 8~14 carbon atoms, were synthesized through the reaction of alkylphenol and 2-dimethylaminoethyl chloride, liberated from its hydrochloride, in the presence of metallic sodium in xylene. The free bases of 2-dimethylaminoethyl alkylphenyl ethers were obtained as a light yellow oil in 70~85% yield. By treatment of these bases with oxalic acid in ethanol, the oxalates were obtained as colorless crystals, which were purified by recrystallization. The maleates of these ethers were prepared by treating the free base, liberated from oxalates, with maleic acid, and were submitted to antiviral tests.



$R = CH_3(CH_2)_n$ n : 7, 9, 11, 13

2-Dimethylaminoethyl *o*-alkylphenyl ethers and 2-dimethylaminoethyl *p*-alkylphenyl ethers thus obtained are summarized in Table I.

The antiviral activities of the compounds thus obtained were examined *in vivo* against the Nakayama strain of Japanese B encephalitis virus and *in vitro* against the Lansing strain of poliomyelitis virus. The experimental procedures were the same as those described in a previous paper.[1] The results are shown in Tables II and III.

Table II shows that 2-dimethylaminoethyl *o*-octylphenyl ether and 2-dimethylaminoethyl *p*-octylphenyl ether were active against the Nakayama strain of Japanese B encephalitis virus *in vivo*, but the others were ineffective.

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1) Part XXIII. F. Ueda : This Bulletin, 7, 823(1959).
2) Part XXIV. F. Ueda, T. Ueda, S. Toyoshima : *Ibid.*, 7, 829(1959).
3) L. Knorr : Ber., 38, 3148(1905).

Table I. R-C6H4-O-CH2-CH2-N(CH3)2

Compd. No.	R	Salt	m.p.(°C)	Appearance
1	*o*-$CH_3(CH_2)_7$	oxalate	115~116	needles
		maleate	84~ 85	needles
2	*o*-$CH_3(CH_2)_9$	oxalate	114~115	needles
		maleate	91~ 92	needles
3	*o*-$CH_3(CH_2)_{11}$	oxalate	113~114	needles
		maleate	74~ 75	needles
4	*o*-$CH_3(CH_2)_{13}$	oxalate	109~110	needles
		maleate	74~ 75	needles
5	*p*-$CH_3(CH_2)_7$	oxalate	130~131	plates
		maleate	90~ 92	needles
6	*p*-$CH_3(CH_2)_9$	oxalate	130~131	plates
		maleate	92~ 93	needles
7	*p*-$CH_3(CH_2)_{11}$	oxalate	130~131	plates
		maleate	93~ 94	needles
8	*p*-$CH_3(CH_2)_{13}$	oxalate	128~129	plates
		maleate	93~ 94	needles

Table III shows that 2-dimethylaminoethyl *o*-octylphenyl ether, *o*-decylphenyl ether, and *p*-octylphenyl ether were effective against poliomyelitis virus *in vitro*.

Thus, some of the compounds of this series were active on the Nakayama strain and the Lansing strain. Alkylphenoxyl derivatives with hydrophilic group would be of interest in seeking a more effective antiviral drugs, since it was made clear by the studies of this series that several 3-alkylphenoxy-1,2-propanediols, 2-alkylphenoxy-alkanoic acids, and 2-dimethylaminoethyl alkylphenyl ethers possessed antiviral activity.

Table II. Antiviral Activity against Japanese B Encephalitis Virus

Compd. No.	Dose (mg./kg.)	Treated group[a]	Untreated group[a]	χ^{2}[b]
1	40	18/40	7/40	5.82
2	22	5/30	2/30	0.65
3	60	5/30	2/30	0.65
4	80	6/30	2/30	1.32
5	53	9/30	2/30	4.01
6	40	5/30	2/30	0.65
7	80	9/40	6/40	0.33
8	100	10/40	6/40	0.69

a) The numerator represents the number of mice that survived and the denominator, total number injected.
b) $P(\chi^2>3.84)=0.05$.

Table III. Antiviral Activity against Poliomyelitis Virus

Compd. No.	LD_{50}		
	Treated group (Compd. concn.)		Untreated group
	500 γ/cc.	200 γ/cc.	
1	$10^{-2.0}$	$10^{-2.16}$	$10^{-3.5}$
2	$10^{-2.2}$	$10^{-2.5}$	
3	$10^{-2.8}$	$10^{-3.0}$	
4	$10^{-2.9}$	$10^{-3.0}$	
5	$10^{-2.3}$	$10^{-2.5}$	
6	$10^{-2.8}$	$10^{-2.8}$	
7	$10^{-2.9}$	$10^{-3.0}$	
8	$10^{-3.0}$	$10^{-3.0}$	

Experimental

General Method for Synthesis of 2-Dimethylaminoethyl Alkylphenyl Ethers—To a suspension of 0.5 g. of metallic Na in 10 cc. of xylene, 0.02 mole of alkylphenol was added and the mixture was heated on a steam bath until metallic Na completely dissolved. To this solution 2-dimethyl-aminoethyl chloride, liberated from 4.0 g. of the hydrochloride, in 50 cc. of xylene was added and the mixture was refluxed for 8 hr. After cool, the separated NaCl was filtered off and xylene was removed from the filtrate *in vacuo*. The residue was dissolved in ether, washed with water, and dried over Na_2SO_4. On evaporation of ether, an oily substance was obtained. To this residue 2.5 g. of oxalic acid in ethanol was added and the oxalate, separated as crystals, was collected by filtration and recrystallized from AcOEt.

The maleate was prepared by treating the free base, liberated from the oxalate, with maleic acid. The maleate was purified by recrystallization from *iso*-PrOH.

The analytical data are given in Table IV.

Table IV.

Compd. No.	Salt	Mol. formula	C(%)		H(%)		N(%)	
			Calcd.	Found	Calcd.	Found	Calcd.	Found
1	oxalate	$C_{20}H_{33}O_5N$	65.37	65.34	9.05	9.12	3.81	3.61
	maleate	$C_{22}H_{35}O_5N$	67.14	66.86	8.97	9.02	3.56	3.45
2	oxalate	$C_{22}H_{37}O_5N$	66.80	66.57	9.43	9.52	3.54	3.59
	maleate	$C_{24}H_{39}O_5N$	68.37	68.05	9.33	9.30	3.32	3.36
3	oxalate	$C_{24}H_{41}O_5N$	68.05	68.02	9.76	9.83	3.31	3.30
	maleate	$C_{26}H_{43}O_5N$	69.45	69.07	9.64	9.61	3.12	2.85
4	oxalate	$C_{26}H_{45}O_5N$	69.14	68.96	10.04	10.24	3.10	3.08
	maleate	$C_{28}H_{47}O_5N$	70.40	70.15	9.92	9.78	2.93	2.65
5	oxalate	$C_{20}H_{33}O_5N$	65.37	65.47	9.05	9.12	3.81	3.51
	maleate	$C_{22}H_{35}O_5N$	67.14	67.30	8.97	9.09	3.56	3.63
6	oxalate	$C_{22}H_{37}O_5N$	66.80	66.48	9.43	9.59	3.54	3.30
	maleate	$C_{24}H_{39}O_5N$	68.37	68.32	9.33	9.35	3.32	3.39
7	oxalate	$C_{24}H_{41}O_5N$	68.05	68.41	9.76	9.95	3.31	3.31
	maleate	$C_{26}H_{43}O_5N$	69.45	69.72	9.64	9.75	3.12	3.12
8	oxalate	$C_{26}H_{45}O_5N$	69.14	68.76	10.04	10.16	3.10	3.09
	maleate	$C_{28}H_{47}O_5N$	70.40	70.22	9.92	10.04	2.93	2.84

Summary

2-Dimethylaminoethyl phenyl ether, having alkyl chain of 8~14 carbon atoms on the benzene ring in *ortho*- or *para*-position, were synthesized by condensation of alkylphenol with 2-dimethylaminoethyl chloride. The antiviral effects of these compounds were tested against the Nakayama strain of Japanese B encephalitis virus and the Lansing strain of poliomyelitis virus.

2-Dimethylaminoethyl *o*-octylphenyl ether and *p*-octylphenyl ether had antiviral activity against the Nakayama strain *in vivo*.

2-Dimethylaminoethyl *o*-octylphenyl ether, *o*-decylphenyl ether, and *p*-octylphenyl ether had antiviral activity against the Lansing strain *in vitro*.

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