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140. Masako Muraoka, Tomoo Itoh, Toyoharu Mizuma, and Shigeshi Toyoshima: Researches on Chemotherapeutic Drugs against Viruses. XXX.*2 Synthesis and Antiviral Activity of 2-Dimethylaminoethyl Alkylbenzhydryl Ether.

*(Pharmaceutical Institute, Keio-Gijuku University*1)*

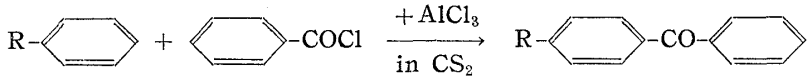
As described in a previous paper,[1] it was found that several compounds of 2-dimethylaminoethyl *p*-alkylbenzhydryl thioether series and 2-dimethylaminoethyl *p*-alkylthiobenzhydryl thioether series possessed antiviral effect on Japanese B encephalitis virus and the compounds of 2-dimethylaminoethyl alkylbenzhydryl ether were synthesized by introducing one or two alkyl groups into the structure of antihistamine drug, Diphenhydramine, and their activity against viruses was examined.

This paper describes the syntheses and antiviral activities of 2-dimethylaminoethyl *p*-alkylbenzhydryl ether and *p,p'*-dialkylbenzhydryl ether.

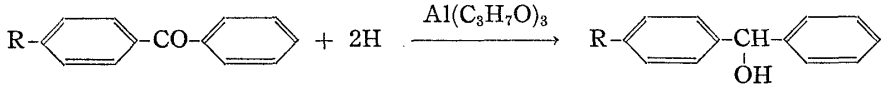
Synthesis of 2-Dimethylaminoethyl *p*-Alkylbenzhydryl Ether

Among compounds of 2-dimethylaminoethyl *p*-alkylbenzhydryl ether, methyl and ethyl derivatives are known.[2] These known compounds were synthesized according to the route shown in Chart 1.

Process 1. Synthesis of *p*-Alkylbenzophenone.



Process 2. Synthesis of *p*-Alkylbenzhydrol.



Process 3. Synthesis of 2-Dimethylaminoethyl *p*-Methyl- and *p*-Ethylbenzhydryl Ether.

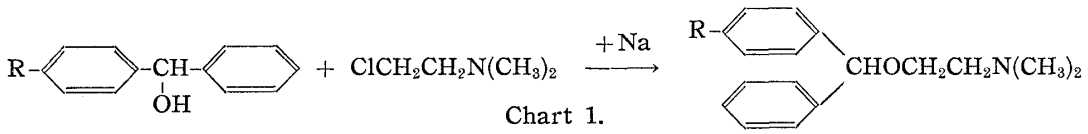


Chart 1.

Compounds of *p*-alkylbenzophenone containing methyl, ethyl, and higher alkyls to hexadecyl were synthesized, as expected, by Process 1.

p-Alkylbenzhydrol was obtained according to Process 2, by the reduction of the ketone with aluminium isopropoxide. In the case of 2-dimethylaminoethyl *p*-alkylbenzhydryl ether, only methyl and ethyl derivatives were prepared by the Process 3. The other higher alkyl derivatives failed to be produced. As an improved method, these derivatives were obtained by the bromination of *p*-alkylbenzhydrol in benzene solution with hydrogen bromide and treatment of the resulting bromide solution with the suspension of 2-dimethylaminoethanol and anhydrous sodium carbonate.

Among the compounds synthesized, methyl and ethyl derivatives afforded crystalline hydrochloride and the other higher alkyl derivatives formed crystalline maleates, but not crystalline hydrochloride.

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*1 Shinano-machi, Shinjuku-ku, Tokyo (村岡全子, 伊藤知男, 水間豊治, 豊島 滋).

*2 This constitutes part of a series entitled "Researches on Chemotherapeutic Drugs against Viruses" by Takeo Ueda. Part XXIX: This Bulletin, 8, 788(1960).

1) K. Takahashi, K. Ohki, T. Mizuma, S. Toyoshima: *Ibid.*, 8, 757(1960).
2) J. Büchi, *et al.*: Helv. Chim. Acta, **34**, 1657(1951).

Synthesis of 2-Dimethylaminoethyl *p,p'*-Dialkylbenzhydryl Ether

Regarding the synthesis of 2-dimethylaminoethyl *p,p'*-dialkylbenzhydryl ether, *p,p'*-dialkylbenzophenone should be taken up as the primary intermediate. This compound may be prepared by the Friedel-Crafts reaction of alkylbenzene with phosgene, oxalyl chloride, or alkylbenzoyl chloride, as shown in Chart 2.

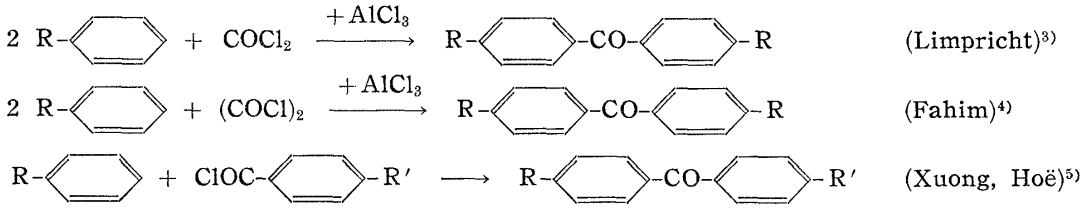


Chart 2.

The result of the three reactions showed that the method of Limpricht was available for only *p,p'*-dimethylbenzophenone but not for the higher dialkyl members, the method of Fahim suitable for the synthesis of dimethyl to dihexyl derivatives, and the method of Xuong and Hoë, applicable to the synthesis of *p,p'*-dialkylbenzophenone having different alkyl groups. Thus, diethyl to dihexyl derivatives were synthesized by the method of Fahim, and *p,p'*-dioctyl, *p*-butyl-*p'*-ethyl, *p*-butyl-*p'*-hexyl, and *p*-butyl-*p'*-octyl derivatives, by the method of Xuong and Hoë.

Next *p,p'*-dialkylbenzhydrol was prepared by the reduction of *p,p'*-dialkylbenzophenone with aluminium isopropoxide as described for the synthesis of *p*-alkylbenzhydrol. Finally, the following three methods were considered for synthesis of 2-dimethylaminoethyl *p,p'*-dialkylbenzhydryl ether.

The first method was analogous to that of 2-dimethylaminoethyl benzhydryl ether, reacting *p,p'*-dialkylbenzhydrol with dimethylaminoethanol in the presence of metallic sodium. However, this method was able to synthesize only *p,p'*-dimethyl derivatives and none of the higher dialkyl derivatives. Regarding this method, the corresponding dialkylbenzophenones were identified as 2,4-dinitrophenylhydrazones in the case of *p,p'*-dipropyl- and *p,p'*-dihexyl-benzhydrol. Therefore, this method may be not suitable for the synthesis of higher alkyl derivatives.

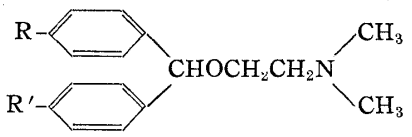
The second method was to synthesize 2-dimethylaminoethyl *p,p'*-dialkylbenzhydryl ether by condensation of *p,p'*-dialkylbenzhydrol with 2-dimethylaminoethanol in the presence of sodium amide. This method did not afford any of the expected ethers.

The third method was to react dimethylaminoethanol with dialkylbenzhydryl halide, which had been prepared by the halogenation of *p,p'*-dialkylbenzhydrol with hydrogen halide. In this case, it was difficult to purify the resulting halide by distillation *in vacuo*, because the halides decomposed to *p,p'*-dialkylphenylmethane during distillation. Therefore, the crude dialkylbenzhydryl halide was employed for the reaction. However, reaction of dialkylbenzhydryl halide with 2-dimethylaminoethanol in the presence of metallic sodium did not afford any of the expected ethers and the anticipated compounds were obtained by the reaction of *p,p'*-dialkylbenzhydryl bromide with 2-dimethylaminoethanol, using anhydrous sodium carbonate as a milder condensation agent.

The compounds thus synthesized were new bases having higher boiling points and they were difficult to be purified by distillation. They were purified by the salt-formation with maleic acid.

3) H. Limpricht: Ann., **312**, 92(1900).
4) H. A. Fahim: J. Chem. Soc., **1949**, 520.
5) N. D. Xuong, N. P. Bum Hoë: *Ibid.*, **1952**, 3744.

TABLE I(a). Antiviral Activity on Japanese B Encephalitis Virus in Mice



R	R′	Dose (mg./kg.)	Treated group[a]	Untreated group[a]	χ^{2}[b]
CH_3	H	17.5	6/40	3/40	1.13
		12	3/40		0
C_2H_5	H	18	5/40	3/40	0.43
		12	5/40		0.43
n-C_3H_7	H	15	4/40	3/40	0.16
		10	4/40		0.16
n-C_4H_9	H	22.5	6/40	3/40	1.13
		15	3/40		0
n-C_5H_{11}	H	22.5	7/40	3/40	1.83
		15	7/40		1.83
n-C_6H_{13}	H	15	5/40	3/40	0.43
		10	3/40		0
n-C_8H_{17}	H	40	14/40	10/40	1.03
		28	16/40		2.05
n-$C_{10}H_{21}$	H	50	15/40	10/40	1.45
		35	15/40		1.45
n-$C_{12}H_{25}$	H	15	20/40	8/40	7.91
n-$C_{14}H_{29}$	H	7.5	14/40	8/40	2.26
		5	8/40		0
n-$C_{16}H_{33}$	H	6	15/40	8/40	2.99
		4	15/40		2.99
CH_3	CH_3	20	3/18	1/20	1.11
		15	3/20		1.11
C_2H_5	C_2H_5	20	4/50	2/50	0.71
		14	1/50		0.03
n-C_3H_7	n-C_3H_7	15	4/40	2/40	0.72
		10	3/40		0.21
n-C_4H_9	n-C_4H_9	20	4/40	2/40	0.72
		13	3/40		0.21
n-C_5H_{11}	n-C_5H_{11}	25	8/40	2/40	4.11
		18	7/40		3.13
n-C_6H_{13}	n-C_6H_{13}	30	8/40	2/40	4.11
		20	6/40		2.22
n-C_8H_{17}	n-C_8H_{17}	50	6/40	2/40	2.22
		33	3/40		0.21
n-C_4H_9	C_2H_5	20	3/40	2/40	0.21
n-C_4H_9	n-C_6H_{13}	20	6/40	2/40	2.22

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

b) $P(\chi^2 > 3.84) = 0.05$

$10^{-1.5}(4 \times LD_{50})$ of the Nakayama strain of Japanese B encephalitis virus was inoculated intraperitoneally into groups of mice, and 72 hr. later, 1/2 or 1/3 dose of LD_{50} of each compound was injected intravenously into the mice in a single dose. After daily observation for 2 weeks, χ^2 was calculated for the treated and untreated groups. If χ^2 was over 3.8 ($P=0.05$), it was considered to be significant.

Table I(b). Antiviral Activity on PR-8 Strain of Influenza Virus in Membrane Culture

R	R′	final concn. of compd.	HA value 2^{-x}			
			$10^{-4}M$	$2\times10^{-5}M$	$10^{-5}M$	control
n-C_4H_9	H		7.0	9.0	9.0	9.0
n-C_8H_{17}	H		8.0	8.0	8.0	8.0
n-$C_{10}H_{21}$	H		9.0	9.0	9.0	9.0
n-$C_{12}H_{25}$	H		7.0	8.0	8.0	8.0
n-C_3H_7	n-C_3H_7		2.5	7.0	7.5	8.5
n-C_4H_9	n-C_4H_9		1.5	7.0	7.0	7.0
n-C_5H_{11}	n-C_5H_{11}		3.0	8.0	8.0	8.5
n-C_4H_9	C_2H_5		4.0	9.0	9.0	9.0

The PR-8 egg-adapted strain of influenza virus (Type A) was employed. Chorioallantoic membrane of 15-day embryonated egg was cut into pieces of 1.0 cm. in diameter. 0.1 cc. of 10^{-2} dilution of the virus was placed in a test tube containing 0.8 cc. of Hanks solution and a piece of the cut chorioallantoic membrane, 0.1 cc. of a sterillized solution of a compound was added to the test tube immediately after the viral inoculation. After shaking the culture at 37° for 18 hr., the viral content of the fluid in the test tube was estimated by chicken-cell agglutination. For chicken-cell agglutination, Horsfall's method was employed.

Screening Test of 2-Dimethylaminoethyl Alkylbenzhydryl Ether

The compounds described above were tested for their antiviral activity, using the Nakayama strain of Japanese B encephalitis virus and the PR-8 strain of influenza A virus. The experimental procedures were the same as those described in the previous report.[6]

None of these compounds of both β-dimethylaminoethyl *p*-alkylbenzhydryl ether and *p*,*p*′-dialkylbenzhydryl ether, except *p*-dodecyl derivative, was effective against the Nakayama strain. This fact shows that the basal structure of 2-dimethylaminoethyl benzhydryl ether did not contribute to the effect on the virus, inspite of the presence of alkyl group, as observed among the compounds of 2-dimethylaminoethyl alkylthiobenzhydryl thioether.[7]

Against the PR-8 strain, dipropyl, dibutyl, and dipentyl derivatives showed considerable effect by the membrane culture test, as can be seen in Table I, while none of compound of the monoalkyl series did. It is of interest that there are compounds effective to the influenza virus and this might give a clue to finding drugs against influenza.

Experimental

I) General Procedure for Synthesis of *p*-Alkylbenzophenone—To a mixture of 0.25 mole of *p*-alkylbenzene and 0.25 mole of powdered anhyd. $AlCl_3$ in 30 cc. of CS_2, 0.3 mole of BzCl was added slowly with rapid stirring. The mixture was then warmed on a water bath and stirring was continued until no more HCl gas evolved. When cool, the reaction mixture was poured on crushed ice and extracted with Et_2O. The CS_2-Et_2O layer was washed successively with H_2O, saturated $NaHCO_3$ solution, and H_2O, and dried over $CaCl_2$. After the solvent was removed by evaporation, the residue was distilled *in vacuo*. The higher homologs, (C_8~C_{16}) were purified by the following procedure: A mixture of 0.025 mole of *p*-alkylbenzophenone, 5 cc. of AcOH, and 0.025 mole of Girard T reagent in 50 cc. of dehyd. EtOH was heated on water bath under reflux for 4 hr. The reaction mixture was then poured into 500 cc. of ice-water containing 4.2 g. of Na_2CO_3 and washed with Et_2O. 25 cc. of conc. HCl was added to the aqueous solution and the solution was heated on a water bath for 1 hr. The oily layer was taken up with Et_2O, washed with H_2O, and dried over $MgSO_4$. The Et_2O residue was identified as the 2,4-dinitrophenylhydrazone.

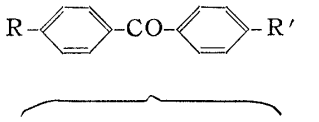
II) General Procedure for Synthesis of *p*,*p*′-Dialkylbenzophenone—a) With cooling, 0.5 mole of anhyd. $AlCl_3$ was added with stirring into a mixture of 0.21 mole of alkylbenzene and 0.20 mole of oxalyl chloride in 40 cc. of CS_2. After standing overnight, CS_2 was evaporated, the residue was

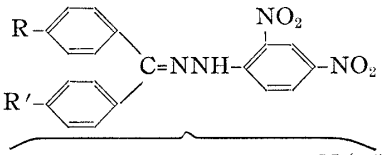
6) Part XXIV. F. Ueda, *et al.*: This Bulletin, **7**, 833(1959).
7) Prat XXVI. K. Takahashi, *et al.*: *Ibid.*, **8**, 757(1960).

poured on ice, and extracted with Et_2O. The Et_2O extract was washed with H_2O and 10% K_2CO_3 solution, and dried over $CaCl_2$. The Et_2O residue was purified by distillation and identified as the 2,4-dinitrophenylhydrazone.

b) A mixture of 0.07 mole of alkyl benzene and 0.06 mole of *p*-alkylbenzoyl chloride was added with stirring into 0.41 mole of anhyd. $AlCl_3$ in 30 cc. of CS_2 and the mixture was refluxed on a water bath. The reaction mixture was poured into ice-water and extracted with Et_2O, which was washed with H_2O and 10% K_2CO_3 solution, and dried over $CaCl_2$. The crude ketone was purified by distillation *in vacuo*, or chromatography over Al_2O_3, elution with petr. ether, and identified as the 2,4-dinitrophenylhydrazone.

Table II.



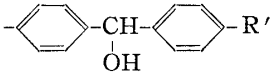


R	R′	b.p. (°C/mm. Hg)	m.p. (°C)	Method	m.p. (°C)	Mol. formula	N (%) Calcd.	N (%) Found
CH_3	H	153~155/5	53	I	220~221	$C_{20}H_{16}O_4N_4$	14.89	14.97
C_2H_5	H	155~156/4		〃	167~168	$C_{21}H_{18}O_4N_4$	14.35	14.32
n-C_3H_7	H	170~172/3		〃	152~153	$C_{22}H_{20}O_4N_4$	13.86	13.76
n-C_4H_9	H	176~178/2		〃	142~143	$C_{23}H_{22}O_4N_4$	13.39	13.33
n-C_5H_{11}	H	190~192/2		〃	137~138	$C_{24}H_{24}O_4N_4$	12.96	12.89
n-C_6H_{13}	H	213~214/3		〃	123~124	$C_{25}H_{26}O_4N_4$	12.55	12.43
n-C_8H_{17}	H			〃	115~116	$C_{27}H_{30}O_4N_4$	11.81	11.79
n-$C_{10}H_{21}$	H			〃	107~108	$C_{29}H_{34}O_4N_4$	11.15	11.27
n-$C_{12}H_{25}$	H			〃	108~109	$C_{31}H_{38}O_4N_4$	10.56	10.36
n-$C_{14}H_{29}$	H			〃	96~97	$C_{33}H_{42}O_4N_4$	10.03	10.26
n-$C_{16}H_{33}$	H			〃	91~93	$C_{35}H_{46}O_4N_4$	9.55	9.53
CH_3	CH_3	149~151/4	95	II-a				
C_2H_5	C_2H_5	152~153/3	47	〃	183~185	$C_{23}H_{22}O_4N_4$	13.52	13.76
n-C_3H_7	*n*-C_3H_7		69	〃				
n-C_4H_9	*n*-C_4H_9	203~206/3		〃	159~161	$C_{27}H_{30}O_4N_4$	11.81	11.54
n-C_5H_{11}	*n*-C_5H_{11}	220~222/4		〃	146~148	$C_{29}H_{34}O_4N_4$	11.15	10.91
n-C_6H_{13}	*n*-C_6H_{13}	243~245/2		〃	131~132	$C_{31}H_{38}O_4N_4$	10.56	10.32
n-C_8H_{17}	*n*-C_8H_{17}			II-b	119~120	$C_{35}H_{46}O_4N_4$	9.55	9.70
n-C_4H_9	C_2H_5	207~209/4		〃	144~145	$C_{25}H_{26}O_4N_4$	12.55	12.54
n-C_4H_9	*n*-C_6H_{13}	220~222/2		〃	131~132	$C_{29}H_{34}O_4N_4$	11.15	10.92
n-C_4H_9	*n*-C_8H_{17}			〃	124~125	$C_{31}H_{38}O_4N_4$	10.56	10.74

2,4-Dinitrophenylhydrazones are orange plates.

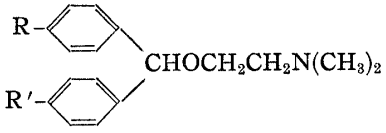
III) General Procedure for Syntheses of *p*-Alkylbenzhydrol and *p,p′*-Dialkylbenzhydrol—A mixture of 10 g. of $(iso\text{-}PrO)_3Al$ in 50 cc. of dehyd. iso-PrOH and 0.05 mole of *p*-alkyl- or *p,p′*-dialkylbenzophenone was refluxed on a water bath at such a rate that 5~10 drops of the distillate were collected per min. When the Me_2CO test became negative, most of the excess iso-PrOH was removed under a reduced pressure. The cooled residue was hydrolyzed with cold dil. HCl (prepared from 17.5 cc. of conc. HCl and 88 cc. of H_2O) and dissolved in Et_2O. The Et_2O solution was washed with dil. HCl and H_2O, and dried over anhyd. Na_2SO_4. *p*-Methyl-, *p*-ethyl-, *p,p′*-dimethyl-, *p,p′*-diethyl-*p,p′*-dipropyl-, and *p,p′*-dibutyl-benzhydrols were obtained as crystals. The higher homologs were obtained as oily substances and submitted to the next step of the reaction without further purification.

Table III.



R	R′	m.p. (°C)	Appearance	Mol. formula	C (%) Calcd.	C (%) Found	H (%) Calcd.	H (%) Found
CH_3	H	52	colorless needles	$C_{14}H_{14}O$	84.81	84.67	7.12	7.13
C_2H_5	H	33	〃	$C_{15}H_{16}O$	84.87	84.78	7.60	7.43
CH_3	CH_3	69	colorless plates	$C_{15}H_{16}O$	84.87	84.75	7.60	7.62
C_2H_5	C_2H_5	59~60	〃	$C_{17}H_{20}O$	84.95	84.91	8.39	8.18
n-C_3H_7	*n*-C_3H_7	50~52	〃	$C_{19}H_{24}O$	85.02	84.95	9.01	9.16
n-C_4H_9	*n*-C_4H_9	30	colorless needles	$C_{21}H_{28}O$	85.08	84.52	9.52	9.84

Table IV.



Compd. No.	R	R′	Method	Free amine b.p. (°C/mm. Hg)		m.p. (°C)	Appearance	Recrystn. solvent
1	CH_3	H	IV-a		HCl	150～152	colorless needles	EtOH+Et_2O
2	C_2H_5	H	〃		〃	164～165	〃	〃
3	C_2H_5	H	〃		maleate	124～125	colorless plates	AcOEt
4	n-C_3H_7	H	IV-b	60～62/10^{-4}	〃	61～63	〃	Et_2O
5	n-C_4H_9	H	〃	66～68/10^{-4}	〃	64～66	〃	〃
6	n-C_5H_{11}	H	〃	71～75/10^{-4}	〃	56～58	colorless needles	〃
7	n-C_6H_{13}	H	〃	85～86/10^{-4}	〃	68～70	〃	〃
8	n-C_8H_{17}	H	〃	100～1/10^{-4}	〃	71～73	colorless plates	〃
9	n-$C_{10}H_{21}$	H	〃	116～8/10^{-4}	〃	74～75	〃	〃
10	n-$C_{12}H_{25}$	H	〃		〃	78～80	〃	〃
11	n-$C_{14}H_{29}$	H	〃		〃	75～77	〃	AcOEt+Et_2O
12	n-$C_{16}H_{33}$	H	〃		〃	72～74	〃	〃
13	CH_3	CH_3	IV-a		HCl	148	〃	iso-PrOH+Et_2O
14	C_2H_5	C_2H_5	IV-b		oxalate	135～137	〃	iso-PrOH
15	n-C_3H_7	n-C_3H_7	〃		〃	129～130	〃	〃
16	n-C_3H_7	n-C_3H_7	〃		picrate	146～147	yellow needles	EtOH
17	n-C_3H_7	n-C_3H_7	〃		maleate	106～108	colorless plates	iso-PrOH
18	n-C_4H_9	n-C_4H_9	〃		〃	103～104	〃	AcOEt
19	n-C_5H_{11}	n-C_5H_{11}	〃		〃	104～106	colorless needles	〃
20	n-C_6H_{13}	n-O_6H_{13}	〃		〃	98～99	〃	Et_2O
21	n-C_8H_{17}	n-C_8H_{17}	〃		〃	88～89	〃	Et_2O+Petr. ether
22	n-C_4H_9	n-C_2H_5	〃		〃	85～87	〃	Et_2O+AcOEt
23	n-C_4H_9	n-C_6H_{13}	〃		〃	72～74	colorless plates	Et_2O

Table V.

Compd. No.	Mol. formula	C (%)		H (%)		N (%)	
		Calcd.	Found	Calcd.	Found	Calcd.	Found
1	$C_{18}H_{23}ONCl$	70.63	70.90	7.91	7.86	4.58	4.54
2	$C_{19}H_{26}ONCl$	71.28	71.47	8.19	8.34	4.48	4.57
3	$C_{23}H_{29}O_5N$	69.15	69.14	7.32	7.42	3.51	3.57
4	$C_{24}H_{31}O_5N$	69.71	69.59	7.56	7.39	3.39	3.45
5	$C_{25}H_{33}O_5N$	70.23	70.33	7.78	7.62	3.28	3.19
6	$C_{26}H_{35}O_5N$	70.71	70.55	7.99	7.80	3.17	3.09
7	$C_{27}H_{37}O_5N$	71.18	71.17	8.19	8.04	3.07	3.04
8	$C_{29}H_{41}O_5N$	72.02	72.51	8.55	8.47	2.90	2.78
9	$C_{31}H_{45}O_5N$	72.76	72.25	8.86	8.68	2.74	2.64
10	$C_{33}H_{49}O_5N$	73.43	73.83	9.15	9.08	2.60	2.72
11	$C_{35}H_{53}O_5N$	74.03	74.36	9.41	9.63	2.47	2.39
12	$C_{37}H_{57}O_5N$	74.58	74.29	9.64	9.44	2.35	2.25
13	$C_{19}H_{26}ONCl$	71.28	71.32	8.19	8.02	4.38	4.21
14	$C_{23}H_{31}O_5N$	68.80	68.68	7.79	7.56	3.49	3.52
15	$C_{25}H_{35}O_5N$	69.90	69.62	8.21	8.00	3.26	3.18
16	$C_{29}H_{36}O_8N_4$	61.25	61.39	6.38	6.34	9.85	9.75
17	$C_{27}H_{37}O_5N$	71.18	70.66	8.19	7.96	3.07	2.98
18	$C_{29}H_{41}O_5N$	72.02	71.86	8.55	8.48	2.90	2.83
19	$C_{31}H_{45}O_5N$	72.76	72.95	8.86	8.65	2.74	2.65
20	$C_{33}H_{49}O_5N$	73.43	73.24	9.15	9.48	2.60	2.54
21	$C_{37}H_{57}O_5N$	74.58	74.63	9.64	9.47	2.35	2.28
22	$C_{27}H_{37}O_5N$	71.18	71.47	8.19	8.08	3.07	2.97
23	$C_{31}H_{45}O_5N$	72.76	72.27	8.86	8.75	2.74	2.68

IV) General Procedure for Syntheses of 2-Dimethylaminoethyl *p*-Alkylbenzhydryl Ether and 2-Dimethyaminoethyl *p,p'*-Dialkylbenzhydryl Ether—a) A mixture of 0.035 mole of *p*-alkyl- or *p,p'*-dialkylbenzhydrol and 0.8 g. of metallic Na in 100 cc. of toluene was refluxed under stirring for 16 hr. at 100~110°, 0.045 mole of 2-dimethylaminoethyl chloride in 40 cc. of toluene was added slowly, and refluxed for 20 hr. After cool, the reaction mixture was extracted with 5% HCl, the aqueous extract was washed with Et_2O, and made alkaline with K_2CO_3. The separated oily amine was extracted with Et_2O and dried over anhyd. K_2CO_3. The hydrochloride of the amine was prepared by the usual method.

b) A stream of HBr gas was introduced for 2 hr. into 0.05 mole of *p*-alkyl- or *p,p'*-dialkylbenzhydrol in benzene. The treated solution was dried over $CaCl_2$ and the decanted benzene layer was repeated with the same treatment again. After washing with H_2O and 10% Na_2CO_3 solution, and dried over $CaCl_2$, the solution was added to a suspension of 0.05 mole of anhyd. Na_2CO_3 in 0.055 mole of 2-dimethylaminoethanol and heated at 110°. The reaction mixture was heated with stirring in an oil bath at 125° for 13 hr., the cooled reaction mixture was washed with H_2O, and dried over anhyd. $MgSO_4$. After removal of the solvent, the residue was purified by distillation in high vacuum or by chromatography over Al_2O_3 and elution with petr. ether and benzene. The purified product was converted to the maleate with maleic acid in iso-PrOH.

Summary

Compounds of 2-dimethylaminoethyl *p*-alkylbenzhydryl ether and *p,p'*-dialkylbenzhydryl ether series were synthesized and their activity was examined using the Nakayama strain of Japanese B encephalitis and the PR-8 strain of influenza A virus. *p,p'*-Dipropyl-, *p,p'*-dibutyl, and *p,p'*-dipentyl derivatives were found to have considerable activity on the PR-8 strain in membrane culture, and *p*-dodecyl derivative was recognized to be effective on the Japanese B encephalitis virus in mice.

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