ii) Determination of the Direct Virus Inactivating Action : Each dilution of the egg-adapted PR-8 strain and the maximal non-toxic dose of test compound were mixed in a test tube and the tube was incubated at 22° for 24 hr. Then 0.1 cc. of this mixture was inoculated into chorioallantoic sack and the eggs were further incubated at 37° for 24 hr. After the incubation, these inoculated eggs were kept at 4° for 2 hr., the chorioallantoic fluid was removed, and ELD_{50} was determined.

Summary

In order to find antiviral compounds, alkyl group was introduced into the neurotropic structure of 1-phenyl-3-dimethylamino-1-propanol and activity of the resulting alkyl derivatives were examined against the Nakayama strain of Japanese B encephalitis virus and the PR-8 strain of influenza A virus. 1-(*p*-Decylphenyl)-3-dimethylamino-1-propanol and 1-(*p*-dodecylphenyl)-3-dimethylamino-1-propanol showed *in vivo* effect on the Nakayama strain, and 1-(*p*-ethylphenyl)-3-dimethylamino-1-propanol exerted *in ovo* activity on the PR-8 strain.

(Received December 19, 1959)

UDC 615.778〔547.263'53'233〕

126. Atsushi Takada and Shigeshi Toyoshima : Researches on Chemotherapeutic Drugs against Viruses. XXVIII.*1 Synthesis and Antiviral Effect of 1-(*p*-Alkylphenyl)-1-phenyl-2-methylamino-1-propanol.

(*Pharmaceutical Institute, Keio-Gijuku University**2)

In the previous papers,[1] it was reported that several antiviral compounds were found by the introduction of alkyl group into the structure of neurotropic drugs. It is of interest that among these compounds, *p*-methylephedrine showed an inhibitory effect on Japanese B encephalitis virus and some of alkylated amine having benzhydryl group, on Japanese B encephalitis and influenza viruses. Based on this conception, the present work was promoted to find new antiviral compounds by introduction of alkylphenyl group into the structure of ephedrine. Thus, 1-(*p*-alkylphenyl)-1-phenyl-2-methylamino-1-propanol was synthesized and their antiviral properties examined. This paper describes the synthesis and antiviral activity of 1-(*p*-alkylphenyl)-1-phenyl-2-methylamino-1-propanol.

None of the derivatives of 1-(*p*-alkylphenyl)-1-phenyl-2-methylamino-1-propanol has been synthesized, but their parent compound, 1,1-diphenyl-2-methylamino-1-propanol was already reported by Skita[2] and Takamatsu.[3] By the modification of the method of Takamatsu, 1-(*p*-alkylphenyl)-1-phenyl-2-methylamino-1-propanol was synthesized according to the scheme shown in Chart 1.

---

*1 This paper constitutes a part of a series entitled "Researches on Chemotherapeutic Drugs against Viruses" by Takeo Ueda.

*2 Shinano-machi, Shinjuku-ku, Tokyo (高田 純, 豊島 滋).

1) T. Ueda, S. Toyoshima, K. Takahashi, M. Muraoka : Keio J. Med., 8, 199(1959); K. Takahashi, K. Ohki, T. Mizuma, S. Toyoshima : This Bulletin, 8, 757(1960).
2) A. Skita, F. Keil, E. Baesler : Ber., **66**, 6858(1933).
3) H. Takamatsu, Y. Minaki : Yakugaku Zasshi, **76**, 1234(1956).

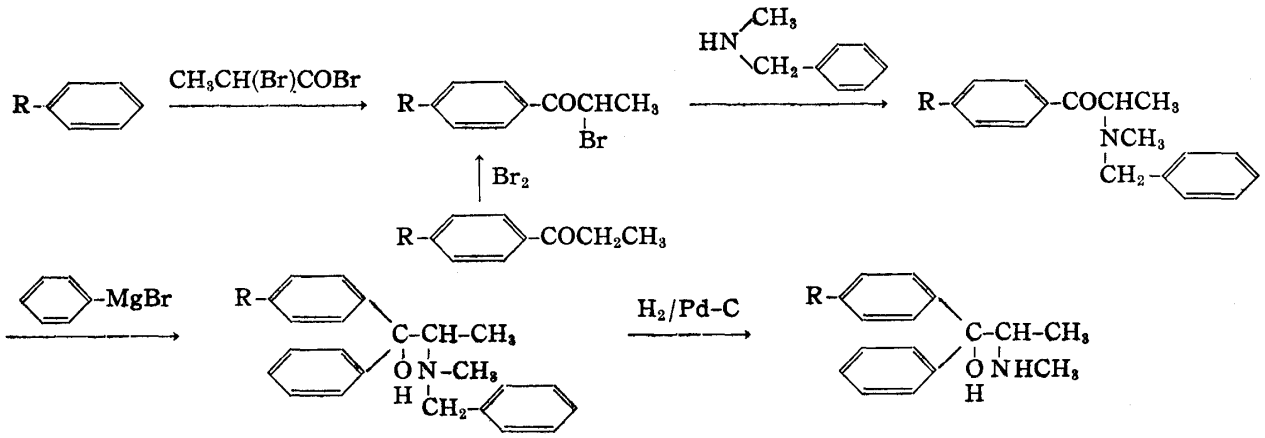


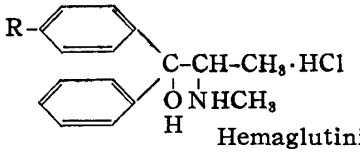
Chart 1.

2-Bromo-4′-alkylpropiophenone, employed as the starting material, was prepared by the following two methods: Lower homologs, such as methyl, ethyl, propyl, and butyl derivatives, were prepared by the condensation of alkylbenzene with 2-bromopropionyl bromide. Higher homologs were not obtained by this method because of their decomposition during distillation and they were prepared by the direct bromination of *p*-alkylpropiophenone with bromine. 2-Bromo-4′-alkylpropiophenone was converted into 2-(N-methylbenzylamino)-4′-alkylpropiophenone by treatment with N-methylbenzylamine. By the Grignard reaction in usual manner, 1-(*p*-alkylphenyl)-1-phenyl-2-(N-methylbenzylamino)-1-propanol was obtained from 2-(N-methylbenzylamino)-4-alkylpropiophenone and phenylmagnesium bromide.

Finally, 1-(*p*-alkylphenyl)-1-phenyl-2-(N-methylbenzylamino)-1-propanol was submitted to debenzylation by catalytic hydrogenation in the presence of palladium-charcoal. Thus, eight compounds of 1-(*p*-alkylphenyl)-1-phenyl-2-methylamino-1-propanol series having alkyl chain of 1~10 carbon atoms were synthesized.

Screening tests of the synthesized compounds were carried out by using the PR-8 strain of influenza A virus and the Nakayama strain of Japanese B encephalitis virus, by the methods described in the previous papers.[4] The experimental results are shown in Tables I and II.

Table I. Antiviral Activity on the PR-8 Strain of Influenza A Virus

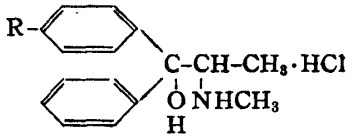


Hemaglutinin titer 2^n

No.	R	Compd. concn. (M) $10^{-3.5}$	10^{-4}	$10^{-4.5}$	10^{-5}	Untreated group
1	CH_3	5.0	5.0	6.0	6.0	6.0
2	C_2H_5	7.0	7.0	8.0	9.0	9.0
3	C_3H_7	7.0	7.0	8.0	8.0	9.0
4	C_4H_9	3.0	8.0	8.0	9.0	9.0
5	C_5H_{11}	3.0	5.5	9.0	9.0	9.0
6	C_6H_{13}	3.0	8.5	8.5	9.0	9.0
7	C_8H_{17}	4.0	8.0	9.0	9.0	9.0
8	$C_{10}H_{21}$	4.0	9.0	9.0	9.0	9.0

4) Part XXIII. F. Ueda: This Bulletin, **7**, 823(1959); Part XXIV. F. Ueda, T. Ueda, S. Toyoshima: *Ibid.*, **7**, 829(1959).

Table II. Antiviral Activity on the Nakayama Strain of Japanese B Encephalitis Virus (*in vivo*)



No.	R	Dose (mg./kg.)	Treated group[a]	Untreated group[a]	χ^2[b]
1	CH_3	15	3/40	3/40	—
		10	2/39		—
2	C_2H_5	15	4/40	3/40	—
		10	3/38		—
3	C_3H_7	15	4/40	3/40	—
		10	4/40		—
4	C_4H_9	20	9/28	6/30	0.57
		15	10/29		0.91
5	C_5H_{11}	22.5	7/31	1/30	3.41
		15	8/30		4.70
6	C_6H_{13}	30	6/28	1/30	2.99
		20	7/30		3.62
7	C_8H_{17}	45	6/30	1/30	2.58
		30	8/30		4.70
8	$C_{10}H_{21}$	30	10/30	1/30	7.12
		20	9/29		6.18

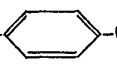
a) The numerator represents the number of mice that survived and the denominator, total number injected.
b) $P(\chi^2>3.84)=0.05$

As can be seen in Table I, all compounds except lower alkyl derivatives, such as 1-*p*-tolyl-, 1-(*p*-ethylphenyl), and 1-(*p*-propylphenyl)-1-phenyl-2-methylamino-1-propanol, which did not exert any effect on influenza virus, were slightly effective on the PR-8 strain in the chorioallantoic membrane. From Table II, it may be said that 1-(*p*-pentylphenyl)-, 1-(*p*-octylphenyl)-, and 1-(*p*-decylphenyl)-1-phenyl-2-methylamino-1-propanol were fairly effective on the Nakayama strain *in vivo*. The effect of these compounds, however, was not so marked, on comparison with those of the compounds which have already been reported.

The pharmacological properties as to the sympathomimetic effect of these compounds will be described in another report.

Experimental

General Procedure for Preparation of 2-Bromo-4'-alkylpropiophenone—(a) To a mixture of 0.23 mole of alkylbenzene and 30 g. of $AlCl_3$ in 70 cc. of CS_2, 42 g. of 2-bromopropionyl bromide was added dropwise with stirring. After stirring for 1 hr. on a steam bath, the reaction mixture was poured on crushed ice and extracted with Et_2O. The Et_2O extract was washed with water and dried over $CaCl_2$. After removal of Et_2O, the residue was distilled *in vacuo*. Boiling point and yield are shown in Table III.

Table III. R-  -COCH(Br)CH_3

R	b.p. (°C/mm. Hg)	Yield	R	b.p. (°C/mm. Hg)	Yield
CH_3	129~134/8	79	C_3H_7	146~148/6	87
C_2H_5	130~133/5	82	C_4H_9	164~170/6	85

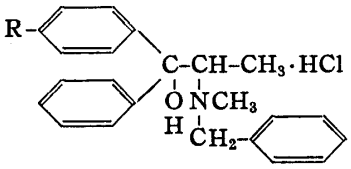
(b) To a solution of 0.18 mole of 4'-alkylpropiophenone in 40 cc. of benzene, 31.6 g. of Br_2 was added with stirring and stirring was continued until no more HBr evolved. The reaction mixture was washed with water and cold 10% NaOH, and submitted to the next reaction without further purification.

General Procedure for Preparation of 2-(N-Methylbenzylamino)-4'-alkylpropiophenone—To a mixture of 0.18 mole of 2-bromo-4'-alkylpropiophenone in benzene and 16 cc. of 36% NaOH, 24 g. of N-methylbenzylamine was added with stirring. The mixture was warmed on a steam bath for 3 hr., the benzene layer was separated, and washed with water. After evaporation of benzene, the residue

was submitted to the next reaction without further purification.
2-(N-Methylbenzylamino)-4-methylpropiophenone : b.p_3 176°
2-(N-Methylbenzylamino)-4-ethylpropiophenone : b.p_4 192~199°

General Procedure for Preparation of 1-(*p*-Alkylphenyl)-1-phenyl-2-(N-methylbenzylamino)-1-propanol Hydrochloride—To a solution of PhMgBr (prepared from 3.4 g. of Mg, 21.4 g. of bromobenzene, and 60 cc. of dry Et_2O) 0.009 mole of 2-(N-methylbenzylamino)-4-alkylpropiophenone in 10 cc. of Et_2O was added gradually with stirring in an ice bath. After stirring in a cold bath for 1 hr. and heating under reflux for 3 hr., the reaction mixture was cooled and poured into a mixture of crushed ice and HCl. The crude 1-(*p*-alkylphenyl)-1-phenyl-2-(N-methylbenzylamino)-1-propanol hydrochloride precipitated from the mixture was collected by filtration, washed with Et_2O, and recrystallized from the solvent shown in Table IV, together with analytical data.

TABLE IV.

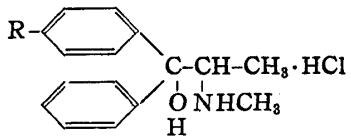


R	m.p. (°C)	Recrystn. solvent	Mol. formula	N (%) Calcd.	N (%) Found
CH_3	211 (dec.)	EtOH	$C_{24}H_{28}ONCl$	3.66	3.73
C_2H_5	209 (dec.)	〃	$C_{25}H_{30}ONCl$	3.54	3.48
C_3H_7	164~165	Me_2CO	$C_{26}H_{32}ONCl$	3.30	3.30
C_4H_9	93~94	〃	$C_{27}H_{34}ONCl$	3.20	3.27
C_5H_{11}	92~93	〃	$C_{28}H_{36}ONCl$	3.10	3.15
C_6H_{13}	54~55	Me_2CO-Et_2O	$C_{29}H_{38}ONCl$	3.09	3.01
C_8H_{17}	81~83	〃	$C_{31}H_{42}ONCl$	2.92	2.95
$C_{10}H_{21}$	87~89	〃	$C_{33}H_{46}ONCl$	2.75	2.86

All compounds are colorless plates.

General Procedure for Preparation of 1-(*p*-Alkylphenyl)-1-phenyl-2-(methylamino)-1-propanol Hydrochloride—A solution of 0.006 mole of 1-(*p*-alkylphenyl)-1-phenyl-2-(N-methylbenzylamino)-1-propanol hydrochloride in 50 cc. of MeOH was shaken in H_2 atmosphere in the presence of Pd-C catatlyst at room temp., until 134 cc. of H_2 was absorbed. After removal of the catalyst by filtration, the filtrate was concentrated to dryness and the residue was recrystallized from a suitable solvent. Analytical data are shown in Table V.

TABLE V.



R	m.p. (°C)	Recrystn. solvent	Yield (%)	Mol. formula	N (%) Calcd.	N (%) Found
CH_3	218~219	EtOH-Et_2O	94	$C_{17}H_{22}ONCl$	4.79	4.97
C_2H_5	238	〃	93	$C_{18}H_{24}ONCl$	4.58	4.45
C_3H_7	205	Me_2CO-Et_2O	92	$C_{19}H_{26}ONCl$	4.38	4.29
C_4H_9	180	EtOH-Et_2O	92	$C_{20}H_{28}ONCl$	4.02	3.87
C_5H_{11}	192	Me_2CO	93	$C_{21}H_{30}ONCl$	3.90	3.91
C_6H_{13}	188~190	〃	84	$C_{22}H_{32}ONCl$	3.87	3.81
C_8H_{17}	165~166	〃	68	$C_{24}H_{36}ONCl$	3.59	3.68
$C_{10}H_{21}$	162~163	〃	69	$C_{26}H_{40}ONCl$	3.35	3.06

All compounds are colorless needles.

Summary

Eight compounds of 1-(*p*-alkylphenyl)-1-phenyl-2-methylamino-1-propanol were synthesized and their antiviral activities were examined. Several compounds in this series were found to be slightly effective on the PR-8 strain of influenza A virus in chorioallantoic membrane and fairly effective on the Nakayama strain of Japanese B encephalitis virus *in vivo*.

(Received December 19, 1959)