UDC 615.778[547.263'53'233]

125. Tadakazu Tsuji, Toyoharu Mizuma, and Shigeshi Toyoshima : Researches on Chemotherapeutic Drugs against Viruses.*1 XXVII.[1] Synthesis and Antiviral Activity of 1-(*p*-Alkylphenyl)-3-dimethylamino-1-propanol.

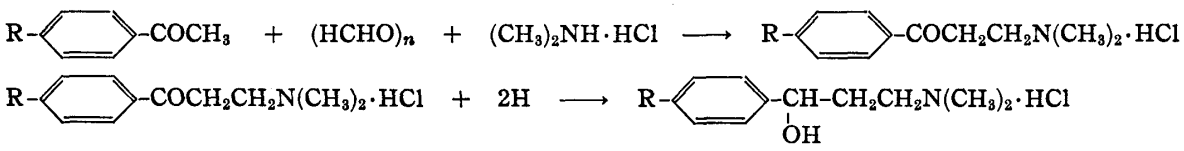
(*Pharmaceutical Institute, Keio-Gijuku University**2)

As described in previous papers,[1,2] Ueda, *et al.* prepared several compounds having antiviral activity by introducing alkyl group into the structure of neurotropic drugs. Among these compounds, norephedrine having alkyl group on the benzene ring[2] exerts a chemotherapeutic effect on Japanese B encephalitis. Based on this conception, attempts were made to introduce alkyl group into 1-phenyl-3-dimethylamino-1-propanol known as improved drug of ephedrine. Thus, 1-(*p*-alkylphenyl)-3-dimethylamino-1-propanol and related compounds were synthesized, and their antiviral activity was examined.

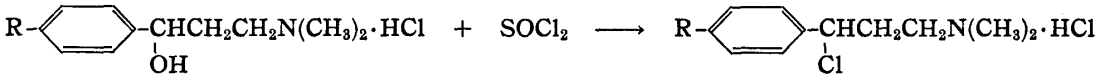
Synthesis of 1-(*p*-Alkylphenyl)-3-dimethylamino-1-propanol

Though 1-(*p*-alkylphenyl)-3-dimethylamino-1-propanol is unknown, 1-phenyl-3-(dimethylamino)-1-propanol was already reported by Mannich,[3] who prepared this compound by the reduction of Mannich base,[3] which was prepared from acetophenone, paraformaldehyde, and dimethylamine hydrochloride.

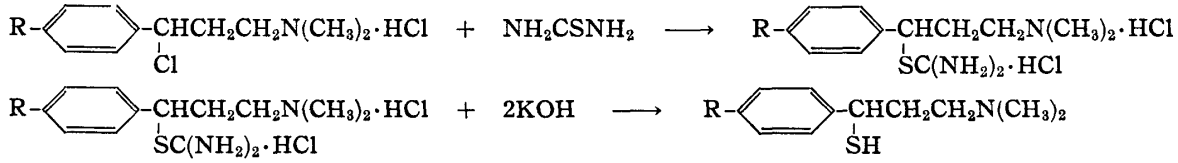
According to the methods of Mannich[3] and Okuda,[4] the Mannich base, 3-dimethylamino-4'-alkylpropiophenone hydrochloride was synthesized by reacting paraformaldehyde and dimethylamine hydrochloride with 4-alkylacetophenone, and 1-(*p*-alkylphenyl)-3-dimethylamino-1-propanol was obtained by reduction of the resulting Mannich base with palladium-carbon and hydrogen.



N,N-Dimethyl-3-(*p*-alkylphenyl)-3-chloropropylamine hydrochloride was prepared by reaction of 1-(*p*-alkylphenyl)-3-dimethylamino-1-propanol and thionyl chloride.



Further, 1-(*p*-alkylphenyl)-3-dimethylamino-1-propanethiol was prepared by reacting N,N-dimethyl-3-(*p*-alkylphenyl)-3-chloropropylamine with thiourea and hydrolysis of the resulting product with potassium hydroxide solution.



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

*2 Shinano-machi, Shinjuku-ku, Tokyo (辻 忠和, 水間豊治, 豊島 滋).

1) Part. XXVI. K. Takahashi, *et al.* : This Bulletin, 8, 757(1960).
2) T. Ueda, S. Toyoshima, K. Takahashi, M. Muraoka : Keio J. Med., 8, 182(1956).
3) C. Mannich, G. Heilner : Ber., **55**, 356(1922).
4) T. Okuda : Yakugaku Zasshi, **76**, 1(1956).

Table I. Antiviral Effect of 1-(*p*-Alkylphenyl)-3-dimethylamino-1-propanol against Nakayama Strain of *Encephalitis japonica*

No.	Alkyl	Dose (mg./kg.)	Treated group*	Untreated group*	Effect
9	CH_3	55	5/30	4/30	−
		40	6/30	4/30	
10	CH_3CH_2	45	5/30	3/30	−
		30	1/30	3/30	
11	$CH_3(CH_2)_2$	50	2/30	3/30	−
		40	1/30	3/30	
12	$CH_3(CH_2)_3$	32	2/30	4/30	−
		24	5/30	4/30	
13	$CH_3(CH_2)_5$	25	4/30	2/30	−
		20	5/30	2/30	
14	$CH_3(CH_2)_7$	50	1/30	3/30	−
		40	5/30	3/30	
15	$CH_3(CH_2)_9$	50	13/50	3/50	+
		33	9/50	3/50	
16	$CH_3(CH_2)_{11}$	45	4/50	3/50	+
		33	10/50	3/50	

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

Table II. Antiviral Effect of 1-(*p*-Alkylphenyl)-3-dimethylamino-1-propanol against PR-8 Strain of Influenza A Virus

No.	Alkyl	Compd. concn. (10^{-x} mole)	Chorioallantoic membrane culture method Hemaglutinin titer 2^x	Detn. of direct virus inactivating action EID_{50} 10^{-x}	Effect
9	CH_3	4	7.5	—	−
		5	7.0		
	Control	—	8.0	—	
10	CH_3CH_2	4	1.0	6.75	+
		5	1.0～2.0		
	Control	—	4.0	7.75	
11	$CH_3(CH_2)_2$	4	3.0		−
		5	4.0	7.0	
	Control	—	4.0	7.75	
12	$CH_3(CH_2)_3$	4	4.0	6.8	−
		5	4.0		
	Control	—	4.0	7.75	
13	$CH_3(CH_2)_5$	3	8.0	7.33	−
		4	8.0		
		5	8.0		
	Control	—	8.3	9.0	
14	$CH_3(CH_2)_7$	3.5	5.0	5.0	−
		4	6.0		
		5	7.5		
	Control	—	8.0	9.0	
15	$CH_3(CH_2)_9$	3	8.0	7.33	−
		4	8.0		
		5	8.0		
	Control	—	8.3	9.0	
16	$CH_3(CH_2)_{11}$	3	2.5	4.66	−
		4	6.5		
		5	7.0		
	Control	—	8.3	8.3	

Thus, eight compounds of 3-dimethylamino-4′-alkylpropiophenone hydrochloride, eight compounds of 1-(*p*-alkylphenyl)-3-dimethylamino-1-propanol, and two compounds of 1-(*p*-alkylphenyl)-3-dimethylamino-1-propanethiol series were obtained in remarkably good yield. These compounds are listed in Tables III, IV, V, and VI.

Screening Test on 1-(*p*-Alkylphenyl)-3-dimethylamino-1-propanol and Related Compounds

The *in vivo* effect of synthesized compounds was examined against the Nakayama strain of Japanese B encephalitis virus and *in ovo* activity against the PR-8 strain of influenza A virus. The experimental procedures are described in the experimental part. The results obtained are shown in Tables I and II.

As can be seen from Table I, among the compounds of 1-(*p*-alkylphenyl)-3-dimethylamino-1-propanol, the decyl and dodecyl derivatives were found to have *in vivo* effect on the Nakayama strain and as shown in Table II, the ethyl derivative was active against the PR-8 strain. Among the compounds of 1-(*p*-alkylphenyl)-3-dimethylaminopropanethiol and N,N-dimethyl-3-(*p*-alkylphenyl)-3-chloropropylamine, alkyl derivative effective against viruses was not found.

It has been found by this research group that the structure of neurotropic drugs on combination of alkyl group did not always give antiviral activity. In fact no compound effective on the Nakayama strain and other viruses has been found among the compounds of N,N-dimethyl-2-(*p*-alkylbenzhydryloxy)ethylamine, N,N-dimethyl-2-(*p*-alkylbenzhydrylthio)ethylamine, alkylated thiobarbituric acid, etc.

However, the results described above shows that the structure of 1-phenyl-3-(dimethylamino)-1-propanol was able to contribute to antiviral activity on combination with alkyl group of optimum carbon chain.

Therefore, it may be said that the introduction of alkyl group into the structure of neurotropic drugs might give clues for finding antiviral drugs. The works on alkyl derivatives of other types of neurotropic and cerebrotropic drugs will be reported in the near future.

Experimental

3-Dimethylamino-4-alkylpropiophenone Hydrochloride—To a mixture of 0.1 mole of *p*-alkylacetophenone, 10.54 g. of $Me_2NH \cdot HCl$, and 3.96 g. of $(HCHO)_n$, 16 cc. of EtOH and 0.2 cc. of conc. HCl were added and the mixture was refluxed for 8～10 hr. on a water bath. The solvent was distilled off in vacuum and the residue was recrystallized from EtOH-Me_2CO. Yield, 51～64%.

Table III. R-C$_6$H$_4$-$COCH_2CH_2N(CH_3)_2 \cdot HCl$

No.	R	Appearance	m.p. (°C)	Formula	N (%) Calcd.	N (%) Found
1	CH_3	Colorless needles	152～155	$C_{12}H_{18}ONCl$	—	—
2	CH_3CH_2	〃	146～147	$C_{13}H_{20}ONCl$	5.80	5.90
3	$CH_3(CH_2)_2$	〃	140～141	$C_{14}H_{22}ONCl$	5.48	5.69
4	$CH_3(CH_2)_3$	〃	142～143	$C_{15}H_{24}ONCl$	5.19	5.08
5	$CH_3(CH_2)_5$	〃	140～141.5	$C_{17}H_{28}ONCl$	4.71	4.86
6	$CH_3(CH_2)_7$	〃	144～145	$C_{19}H_{32}ONCl$	4.30	4.30
7	$CH_3(CH_2)_9$	Colorless plates	145～147	$C_{21}H_{36}ONCl$	3.96	3.76
8	$CH_3(CH_2)_{11}$	〃	143～145	$C_{23}H_{40}ONCl$	3.67	3.55

1-(*p*-Alkylphenyl)-3-dimethylamino-1-propanol Hydrochloride—3-Dimethylamino-4-alkylpropiophenone hydrochloride (0.01 mole) was reduced at atmospheric pressure in 50～100 cc. of MeOH with Pd-C as a catalyst. After removal of Pd-C and the solvent from the reaction mixture, the residue was recrystallized from Me_2CO. Yield, 53～61%.

Table IV. R-C$_6$H$_4$-CH(OH)CH$_2$CH$_2$N(CH$_3$)$_2$·HCl

No.	R	Appearance	m.p. (°C)	Formula	N (%) Calcd.	N (%) Found
9	CH_3	Colorless needles	131~132	$C_{12}H_{20}ONCl$	6.16	6.12
10	CH_3CH_2	Colorless plates	127~129	$C_{13}H_{22}ONCl$	5.75	5.55
11	$CH_3(CH_2)_2$	Colorless needles	128	$C_{14}H_{24}ONCl$	5.46	5.44
12	$CH_3(CH_2)_3$	Colorless plates	129~130	$C_{15}H_{26}ONCl$	5.16	5.04
13	$CH_3(CH_2)_5$	Colorless needles	125~127	$C_{17}H_{30}ONCl$	4.67	4.75
14	$CH_3(CH_2)_7$	〃	130~132	$C_{19}H_{34}ONCl$	4.27	4.24
15	$CH_3(CH_2)_9$	〃	138~140	$C_{21}H_{38}ONCl$	3.94	3.97
16	$CH_3(CH_2)_{11}$	〃	137~139	$C_{23}H_{42}ONCl$	3.65	3.53

N,N-Dimethyl-3-(*p*-alkylphenyl)-3-chloropropylamine Hydrochloride—To a cooled solution of 1/50 mole of 1-(*p*-alkylphenyl)-3-dimethylamino-1-propanol hydrochloride in 25 cc. of $CHCl_3$, 6.8 g. of $SOCl_2$ in 25 cc. of $CHCl_3$ was added. After the whole was warmed at 50° for 1 hr., the solvent was removed in vacuum and the residue was recrystallized from MeOH-Me_2CO.

Table V. R-C$_6$H$_4$-CH(Cl)CH$_2$CH$_2$N(CH$_3$)$_2$·HCl

No.	R	Appearance	m.p. (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
17	H	Colorless plates	184~185	$C_{11}H_{17}NCl_2$	56.42	7.33	5.98	55.97	7.06	6.16
18	CH_3	Colorless prisms	164~165	$C_{12}H_{19}NCl_2$	58.07	7.72	5.64	58.71	7.65	5.39
19	$CH_3(CH_2)_9$	Colorless plates	145.5~146	$C_{21}H_{37}NCl_2$	—	—	3.74	—	—	3.92
20	$CH_3(CH_2)_{11}$	〃	150~151	$C_{23}H_{41}NCl_2$	68.63	10.27	3.48	68.24	10.26	3.21

1-(*p*-Alkylphenyl)-3-dimethylamino-1-propanethiol—A mixture of 0.01 mole of N,N-dimethyl-3-(*p*-alkylphenyl)-3-chloropropylamine, 0.76 g. of thiourea, and 8 cc. of propanol was heated for 9 hr. on a water bath. After removal of the solvent in vacuum, 8 cc. of 10% NaOH was added to the residue and extracted with Et_2O. The Et_2O solution was dried and evaporated. The residue was converted to its salt by adding the acid immediately or after vacuum distillation with CO_2 stream. The salt was recrystallized from Me_2CO.

Table VI.

No.	Compound	Appearance	m.p. (°C)	Formula	N (%) Calcd.	N (%) Found
21	C$_6$H$_4$(CHSH-CH$_2$CH$_2$N(CH$_3$)$_2$·HCl)	Colorless plates	147~149	$C_{11}H_{18}NSCl$	6.05	6.24
22	$C_{12}H_{25}$-C$_6$H$_4$(CHSH-CH$_2$CH$_2$N(CH$_3$)$_2$·CHCOOH-CHCOOH)	〃	116~118	$C_{27}H_{45}O_4NS$	2.92	3.16

Experimental Procedures for Antiviral Tests—(1) Japanese B Encephalitis Virus : 0.3 cc. of 10 times the LD_{50} ($LD_{50}=10^{-2.5}$) of the Nakayama strain was inoculated intraperitoneally into the D. M. K. homogenous strain of mice (8~10 g. in weight) and 72 hr. later, 2/3 or 1/2 LD_{50} of the test compound was injected intravenously into these mice as a single dose. These mice were observed daily for symptoms for 14 days. From the survival ratio of treated group to the control, χ^2 value was calculated. When χ^2 was over 3.8, it was recognized as a significant value.

(2) Influenza Virus : For the screening test on the influenza virus, the chorioallantoic membrane culture and the determination of direct virus inactivating action were used.

i) Chorioallantoic Membrane Culture Method : The chorioallantoic membrane of fertilized eggs, which had been incubated at 37° for 11 days, was cut into pieces with diameter of 1.0 cm. and each piece of these cut membranes was added to a test tube containing 0.8 cc. of Hank's solution. Then 0.1 cc. of 10^{-2} of the egg-adapted PR-8 strain and 0.1 cc. of a dilution of the test compound were added into these tubes. After shaking the culture at 37° for 18 hr., the medium was removed and its HA value was estimated by using the pattern method. For the control group, 0.1 cc. of phosphate buffer solution (pH 7.6) was added instead of the dilution of a compound.

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).