UDC 615.778[547.263'53'233]

140. Atsushi Takada : Researches on Chemotherapeutic Drugs against Viruses. XXXIII.*1 Syntheses and Antiviral Activity of 1-Phenyl-3-amino-1-propanol Derivatives.

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The author and Toyoshima[1] found several compounds active on the Nakayama strain of Japanese B encephalitis virus and the PR-8 strain of influenza A virus by introducing alkyl group into the benzene ring of 1,1-diphenyl-2-methylamino-1-propanol. Also, Tsuji, Mizuma, and Toyoshima[2] obtained some compounds active on the viruses described above by introducing alkyl group into the benzene ring of 1-phenyl-3-dimethylamino-1-propanol. These finding suggested the introduction of alkyl, alkylthio, or phenyl group into 1-phenyl-3-amino-propanol to obtain antiviral compounds.

Several compounds of N,N-disubstituted 1-alkyl-1-phenyl-3-amino-1-propanol and 1,1-diphenyl-3-amino-1-propanol were already reported by Mannich,[3] Kawabata,[4] Ruddy,[5] Adamson,[6] and Benton[7] through the reaction of Mannich base with Grignard reagent. Derivatives which were substituted with alkyl or alkylthio group in their benzene ring have not been synthesized yet, except 1-ethyl-1-(*p*-tolyl)- and 1-ethyl-1-(*p*-ethylphenyl)-3-(1-piperidyl)-1-propanol.[8] Taking the method of Mannich[3] and Kawabata[4] into consideration, N,N-disubstituted 1-(*p*-alkylphenyl)-1-phenyl-3-amino-1-propanol, 1-(*p*-alkylthiophenyl)-1-phenyl-3-(1-piperidyl)-1-propanol, and 1-alkyl-1-(*p*-alkylphenyl)-3-(1-piperidyl)-1-propanol were synthesized. The derivatives of 1-phenyl-3-amino-1-propanol were also screened for their activity on viruses.

Synthesis of N,N-Disubstituted 1-(*p*-Alkylphenyl)-1-phenyl-3-amino-1-propanol

As a starting material, N,N-disubstituted 3-amino-4′-alkylpropiophenone was employed, among which 3-dimethylamino-4′-alkylpropiophenone was already described in one of the previous papers.[2] These intermediates were prepared by the condensation of paraformaldehyde and dialkylamine hydrochloride with *p*-alkylacetophenone according to the method of Mannich. N,N-Disubstituted 1-(*p*-alkylphenyl)-1-phenyl-3-amino-1-propanol was synthesized by the reaction of excess of phenylmagnesium bromide with Mannich base hydrochloride without conversion to a free base. The whole synthetic process is shown in Chart 1.

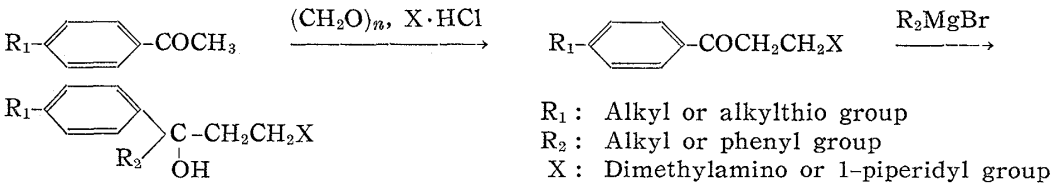

Chart 1.

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*1 This paper constitutes part of a series entitled "Researches on Chemotherapeutic Drugs against Viruses" by Takeo Ueda. Part XXXII : This Bulletin, 8, 930 (1960).

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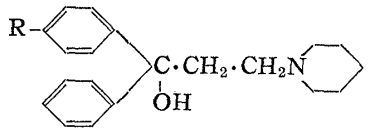
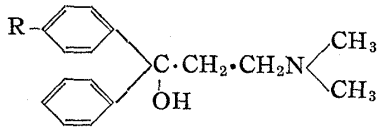
1) A. Takada, S. Toyoshima : This Bulletin, 8, 767 (1960).
2) T. Tsuji, T. Mizuma, S. Toyoshima : *Ibid.*, 8, 763 (1960).
3) C. Mannich, G. Heilner : Ber., **55**, 356 (1922).
4) H. Kawabata, Y. Nitta, T. Kasai : Yakugaku Zasshi, **69**, 190 (1949).
5) A. W. Ruddy, J. S. Buckley : J. Am. Chem. Soc., **72**, 718 (1950).
6) D. W. Adamson, P. A. Barrett, S. Wilkinson : J. Chem. Soc., **1951**, 52.
7) J. J. Benton : Brit. Pat. 776,061.
8) R. J. Turner, W. B. Neier, V. A. Lawson, H. P. Schedl : J. Am. Chem. Soc., **71**, 2053 (1949).

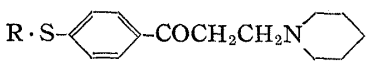
Table I. Antiviral Activity on the PR-8 Strain of Influenza A Virus



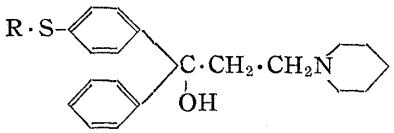
No.	R	Hemaglutinin titer 2^n Compound concn. (M) $10^{-3.5}$	$10^{-4.0}$	$10^{-4.5}$	10^{-5}	Untreated group	Effect
1	CH_3	7.0	7.0	7.0	7.0	7.0	—
2	C_2H_5	7.0	7.0	7.0	7.0	7.0	—
3	C_3H_7	3.0	7.0	7.0	7.0	7.0	+
4	C_4H_9	2.0	7.0	7.0	7.0	7.0	+
5	C_6H_{13}	2.0	8.0	8.0	8.0	9.0	+
6	C_8H_{17}	4.0	9.0	9.0	9.0	9.0	+
7	$C_{10}H_{21}$	6.5	9.0	9.0	9.0	9.0	—
8	$C_{12}H_{25}$	6.5	8.0	8.0	8.0	8.0	—



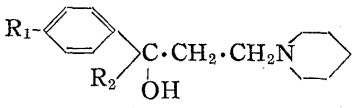
No.	R	$10^{-3.5}$	$10^{-4.0}$	$10^{-4.5}$	10^{-5}	Untreated group	Effect
9	CH_3	8.0	8.0	8.0	8.0	8.0	—
10	C_2H_5	7.0	7.0	8.0	8.0	8.0	—
11	C_4H_9	2.0	7.0	9.0	9.0	9.0	+
12	C_5H_{11}	4.0	8.0	8.0	9.0	9.0	+
13	C_6H_{13}	8.0	8.0	8.0	8.0	9.0	—
14	C_8H_{17}	3.0	8.5	8.0	8.0	8.0	+
15	$C_{10}H_{21}$	1.0	9.0	8.0	9.0	9.0	+



No.	R	$10^{-3.5}$	$10^{-4.0}$	$10^{-4.5}$	10^{-5}	Untreated group	Effect
16	CH_3	4.0	6.0	8.0	8.0	8.0	—
17	C_2H_5	4.0	6.0	8.0	8.0	8.0	—
18	C_4H_9	2.0	6.0	8.0	8.0	8.0	+
19	C_6H_{13}	1.0	4.0	7.0	8.0	8.0	++
20	C_8H_{17}	1.0	1.0	3.0	5.0	6.0	+++

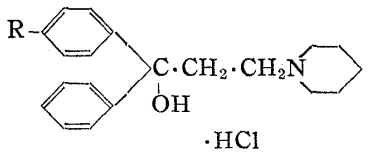


No.	R	$10^{-3.5}$	$10^{-4.0}$	$10^{-4.5}$	10^{-5}	Untreated group	Effect
21	C_2H_5	4.0	6.0	6.0	6.0	6.0	—
22	C_4H_9	2.0	3.0	6.0	6.0	6.0	++
23	C_6H_{13}	1.0	1.0	6.0	6.0	7.0	++
24	C_8H_{17}	1.0	1.0	6.0	6.0	6.0	++



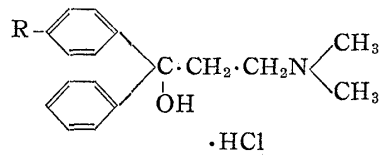
No.	R_1	R_2	$10^{-3.5}$	$10^{-4.0}$	$10^{-4.5}$	10^{-5}	Untreated group	Effect
25	CH_3	⬭	1.0	1.0	3.0	4.0	6.0	+++
26	CH_3	C_6H_{13}	1.0	4.0	4.0	4.0	6.0	+
27	CH_3	C_8H_{17}	1.0	4.0	4.0	6.0	6.0	+
28	CH_3	$C_{12}H_{25}$	4.0	6.0	6.0	6.0	6.0	—
29	C_2H_5	⬭	6.0	7.0	7.0	7.0	7.0	—
30	C_2H_5	$C_{12}H_{25}$	4.0	6.0	6.0	6.0	7.0	—
31	$C_{10}H_{21}$	⬭	4.0	7.0	7.0	8.0	8.0	—

Table II. Antiviral Effect on the Nakayama Strain of Japanese B Encephalitis Virus (*in vivo*) (1)

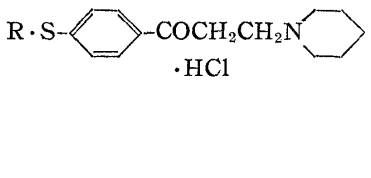


No.	R	Dose (mg./kg.)	Treated group[a]	Untreated group[a]	χ^{2b}
1	CH_3	20	10/38	10/40	—
		15	13/38		—
2	C_2H_5	22	16/40	10/40	2.05
		14	19/40		4.37
3	C_3H_7	20	13/40	10/40	—
		13	15/40		1.39
4	C_4H_9	22.5	18/40	9/40	5.53
		15	15/40		2.14
5	C_6H_{13}	20	15/40	10/40	1.39
		15	12/40		—
6	C_8H_{17}	25	10/40	10/40	—
		18	11/39		—
7	$C_{10}H_{21}$	45	10/40	10/40	—
		30	11/40		—
8	$C_{12}H_{25}$	45	10/39	10/40	—
		30	10/40		—

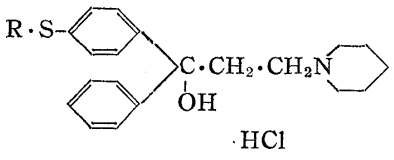
Table II. Antiviral Effect on the Nakayama Strain of Japanese B Encephalitis Virus (*in vivo*) (2)



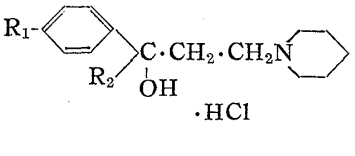
No.	R	Dose (mg./kg.)	Treated group[a]	Untreated group[a]	χ^{2} [b]
9	CH_3	17.5	6/40	1/40	2.50
		12	3/40		—
10	C_2H_5	18	5/40	3/40	—
		12	5/40		—
11	C_4H_9	22.5	6/40	3/40	—
		15	3/40		—
12	C_5H_{11}	22.5	7/40	3/40	—
		15	2/40		—
13	C_6H_{13}	15	5/40	3/40	—
		10	3/40		—
14	C_8H_{17}	40	14/40	10/40	0.95
		28	16/40		2.05
15	$C_{10}H_{21}$	30	9/40	4/40	1.46
		20	15/40		6.90



16	CH_3	15	11/40	9/40	—
		10	14/40		1.14
17	C_2H_5	12.5	8/40	9/40	—
		8	11/40		—
18	C_4H_9	15	8/39	9/40	—
		10	10/38		—
19	C_6H_{13}	20	10/40	8/40	—
		13	11/40		—
20	C_8H_{17}	20	11/40	8/40	—
		13	10/40		—



21	C_2H_5	20	8/40	8/40	—
		13	6/40		—
22	C_4H_9	24	6/40	8/40	—
		16	7/40		—
23	C_6H_{13}	25	5/30	1/30	0.89
		16	4/30		—
24	C_8H_{17}	30	8/30	1/30	4.70
		20	8/30		4.70



No.	R_1	R_2	Dose (mg./kg.)	Treated group[a]	Untreated group[a]	χ^{2} [b]
25	CH_3		20	11/30	5/30	2.13
			13	6/30		—
26	CH_3	C_6H_{13}	13	4/30	1/30	—
			8	3/30		—
27	CH_3	C_8H_{17}	15	4/30	1/30	—
			10	4/30		—
28	CH_3	$C_{12}H_{25}$	22.5	3/30	1/30	—
			15	6/30		2.58
29	C_2H_5		15	8/39	7/40	—
			10	11/40		1.14
30	C_2H_5	$C_{12}H_{25}$	20	4/30	1/30	—
			13	7/30		3.62
31	$C_{10}H_{21}$		22	2/30	1/30	—
			14	7/30		3.62

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

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

Eight compounds of 1-(*p*-alkylphenyl)-1-phenyl-3-(1-piperidyl)-1-propanol hydrochloride and seven compounds of 1-(*p*-alkylphenyl)-1-phenyl-3-dimethylamino-1-propanol hydrochloride were obtained by this reaction.

Synthesis of 1-(*p*-Alkylthiophenyl)-1-phenyl-3-(1-piperidyl)-1-propanol

According to the method similar to the synthesis of N,N-disubstituted 1-(*p*-alkylphenyl)-1-phenyl-3-amino-1-propanol, *p*-alkylthioacetophenone was prepared by the condensation of alkylthiobenzene with acetyl chloride in the presence of aluminium chloride, resulting *p*-alkylthioacetophenone condensed with paraformaldehyde and piperidine hydrochloride, and the resulting Mannich base hydrochloride was reacted with phenylmagnesium bromide. Five compounds of 3-(1-piperidyl)-4′-alkylthiopropiophenone hydrochloride and four compounds of 1-(*p*-alkylthiophenyl)-1-phenyl-3-(1-piperidyl)-1-propanol hydrochloride were obtained by this reaction.

Synthesis of 1-Alkyl-1-(*p*-alkylphenyl)-3-(1-piperidyl)-1-propanol

The synthetic method employed is similar to the synthesis of N,N-disubstituted 1-(*p*-alkylphenyl)-1-phenyl-3-amino-1-propanol. 3-(1-Piperidyl)-4′-alkylpropiophenone hydrochloride obtained as above, without conversion to its free base, was reacted with excess of appropriate alkylmagnesium bromide and seven compounds of 1-alkyl-1-(*p*-alkylphenyl)-3-(1-piperidyl)-1-propanol hydrochloride were obtained.

Screening Tests with 1-Phenyl-3-amino-1-propanol Derivatives

The compounds synthesized were examined for their antiviral activity in chorioallantoic membrane on the PR-8 strain of influenza A virus and *in vivo* on the Nakayama strain of Japanese B encephalitis virus according to the method described in the previous papers.[9]

As can be seen in Table I, several compounds synthesized were effective on the PR-8 strain in chorioallantoic membrane. Especially, 3-(1-piperidyl)-4′-octylthiopropiophenone and 1-(*p*-tolyl)-1-cyclohexyl-3-(1-piperidyl)-1-propanol were found to possess a marked effect on the virus. From Table II it may be said that majority of the compounds did not show much effect on the Nakayama strain, except 1-(*p*-ethylphenyl)- and 1-(*p*-butylphenyl)-1-phenyl-3-(1-piperidyl)-1-propanol, 1-(*p*-decylphenyl)-1-phenyl-3-dimethylamino-1-propanol, and 1-(*p*-octylthiophenyl)-1-phenyl-3-(1-piperidyl)-1-propanol which showed a significant value by using χ^2 calculation.

Tsuji, *et al.*[2] reported that 1-(*p*-ethylphenyl)-3-dimethylamino-1-propanol prossesses a marked effect on the PR-8 strain. The fact that 3-(1-piperidyl)-4′-octylthiopropiophenone and 1-cyclohexyl-1-(*p*-tolyl)-3-(1-piperidyl)-1-propanol are effective on the PR-8 strain, together with the results reported by Tsuji, *et al.*,[2] suggests further investigations on antiviral drugs. Of course, it is difficult, in the present stage, to discuss the relationship between antiviral activity and chemical structure in these compounds, but compounds more effective on influenza virus might be found by further investigations on 1-alkylphenyl-3-amino-1-propanol derivatives and their related compounds.

Experimental

General Procedure for Synthesis of N,N-Disubstituted 1-(*p*-Alkylphenyl)-1-phenyl-3-amino-1-propanol

a) 3-(1-Piperidyl)-4′-alkylpropiophenone Hydrochloride——A mixture of 0.086 mole of *p*-alkylacetophenone, 0.11 mole of piperidine hydrochloride, and 3.4 g. of $(CH_2O)_n$ in 14 cc. of EtOH containing 0.2 cc. of conc. HCl was refluxed in a water bath for 20 hr. After removal of EtOH *in vacuo*, residual crude material was recrystallized from Me_2CO or AcOEt. Analytical data are summarized in Table III.

9) F. Ueda : This Bulletin, **7**, 824 (1959); F. Ueda, T. Ueda, S. Toyoshima : *Ibid.*, **7**, 834 (1959).

Table III. R-C$_6$H$_4$-COCH$_2$CH$_2$N(C$_5$H$_{10}$)·HCl

R	m.p. (°C)	Appearance	Yield (%)	Recrystn. solvent	Formula	Analysis (%) C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
CH_3	177~178	Colorless prisms	57.8	EtOH	$C_{15}H_{22}ONCl$	67.27	67.31	8.28	8.30	5.23	5.16
C_2H_5	178	Colorless needles	52.6	〃	$C_{16}H_{24}ONCl$	68.18	67.98	8.58	8.61	4.97	4.89
C_3H_7	176	〃	33.1	EtOH-Me_2CO	$C_{17}H_{26}ONCl$	69.01	68.98	8.86	8.58	4.74	4.82
C_4H_9	164~165	〃	26.5	EtOH	$C_{18}H_{28}ONCl$	69.76	69.64	9.11	9.26	4.52	4.53
C_6H_{13}	155~156	〃	34.9	EtOH-Me_2CO	$C_{21}H_{32}ONCl$	71.08	71.08	9.54	9.74	4.14	4.11
C_8H_{17}	153	〃	47.6	〃	$C_{22}H_{36}ONCl$	72.19	72.23	9.91	9.86	3.82	3.76
$C_{10}H_{21}$	151~152	〃	53.3	〃	$C_{24}H_{40}ONCl$	73.15	72.71	10.23	10.33	3.56	3.58
$C_{12}H_{25}$	145~146	〃	44.2	〃	$C_{26}H_{44}ONCl$	73.98	74.03	10.51	10.48	3.32	3.37

b) 1-(*p*-Alkylphenyl)-1-phenyl-3-(1-piperidyl)-1-propanol Hydrochloride——To a solution of PhMgBr (prepared from 1.6 g. of Mg, 1.01 g. of PhBr, and 30 cc. of Et_2O), 0.021 mole of 3-(1-piperidyl)-4′-alkylpropiophenone hydrochloride was added slowly with vigorous stirring at 0° to 5°. 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 saturated solution of NH_4Cl. The crude 1-(*p*-alkylphenyl)-1-phenyl-3-(1-piperidyl)-1-propanol hydrochloride, which was precipitated from Et_2O layer by treatment with cold 10% HCl or by introducing HCl gas, was recrystallized from EtOH or AcOEt. Analytical data are summarized in Table IV.

Table IV. R-C$_6$H$_4$-C(OH)·CH$_2$·CH$_2$N(C$_5$H$_{10}$)·HCl

R	m.p. (°C)	Yield (%)	Recrystn. solvent	Formula	Analysis (%) C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
CH_3	225(decomp.)	84.9	H_2O	$C_{21}H_{28}ONCl$	72.91	72.86	8.16	8.07	4.05	4.13
C_2H_5	216(〃)	65.6	〃	$C_{22}H_{30}ONCl$	73.41	73.60	8.40	8.40	3.89	3.86
C_3H_7	206(〃)	50.0	Me_2CO	$C_{23}H_{32}ONCl$	73.87	74.25	8.62	8.75	3.74	3.66
C_4H_9	196~197	58.4	〃	$C_{24}H_{34}ONCl$	74.29	74.32	8.83	8.96	3.61	3.56
C_6H_{13}	192	60.7	〃	$C_{26}H_{38}ONCl$	75.06	75.04	9.21	8.80	3.37	3.34
C_8H_{17}	179	59.8	〃	$C_{28}H_{42}ONCl$	75.92	76.03	9.53	9.71	3.15	3.14
$C_{10}H_{21}$	155~156	69.7	〃	$C_{30}H_{46}ONCl$	76.31	76.50	9.82	9.76	2.97	2.98
$C_{12}H_{25}$	171~172	38.7	〃	$C_{32}H_{50}ONCl$	76.83	76.69	10.07	10.18	2.80	2.69

All compounds are colorless plates.

1-(*p*-Alkylphenyl)-1-phenyl-3-dimethylamino-1-propanol Hydrochloride——Prepared from the corresponding 3-dimethylamino-4′-alkylpropiophenone hydrochloride by the same procedure as (b). Data are listed in Table V.

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

R	m.p. (°C)	Yield (%)	Recrystn. solvent	Formula	Analysis (%) C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
CH_3	188	42.2	H_2O	$C_{18}H_{24}ONCl$	70.68	70.98	7.91	7.55	4.58	4.41
C_2H_5	229	83.3	〃	$C_{19}H_{26}ONCl$	71.34	71.24	8.19	8.01	4.38	4.22
C_4H_9	147~149	77.4	〃	$C_{31}H_{30}ONCl$	72.49	72.32	8.69	8.41	4.02	4.01
C_5H_{11}	148~149	56.3	AcOEt	$C_{32}H_{32}ONCl$	73.00	73.44	8.91	9.05	3.87	3.66
C_6H_{13}	149~150	34.9	〃	$C_{34}H_{34}ONCl$	73.47	73.58	9.11	9.23	3.73	3.46
C_8H_{17}	141~142	92.0	〃	$C_{36}H_{38}ONCl$	74.32	74.30	9.48	9.51	3.47	3.56
$C_{10}H_{21}$	133~134	33.2	〃	$C_{38}H_{42}ONCl$	75.05	75.03	9.80	9.76	3.24	2.89

All compounds are colorless plates.

General Procedure for Synthesis of 1-(*p*-Alkylthiophenyl)-1-phenyl-3-(1-piperidyl)-1-propanol ***p*-Alkylthioacetophenone**——To a mixture of 0.2 mole of alkylthiobenzene and 0.25 mole of anhyd. $AlCl_3$ in 60 cc. of CS_2, 0.22 mole of AcCl was added dropwise with stirring. Stirring was continued until no more HCl gas evolved. The reaction mixture was poured on crushed ice and extracted with Et_2O. The Et_2O extract was washed with H_2O and dried over $CaCl_2$. After removal of Et_2O, the residue was distilled *in vacuo*. Data are listed in Table VI, together with their semicarbazones.

Table VI. R·S-C$_6$H$_4$-COCH$_3$

R	m.p. (°C)	b.p. (°C/mm. Hg)	Yield (%)	Semicarbazone m.p. (°C)	Semicarbazone Formula	Semicarbazone N (%) Calcd.	Semicarbazone N (%) Found
C_4H_9	24～25	167～169/9	58.4	191～192	$C_{13}H_{19}N_3OS$	15.84	15.68
C_6H_{13}	40～41	170～172/4	63.8	186～187	$C_{15}H_{23}ON_3S$	14.33	14.13
C_8H_{17}		190～192/5	59.0	182～183	$C_{17}H_{27}ON_3S$	13.08	13.00

All compounds of *p*-alkylthioacetophenone are colorless prisms and their semicarbazones are colorless plates.

3-(1-Piperidyl)-4′-alkylthiopropiophenone Hydrochloride——Prepared from corresponding *p*-alkylthioacetophenone, $(CH_2O)_n$, and piperidine hydrochloride by the same procedure as (a).

Table VII. R·S-C$_6$H$_4$-COCH$_2$CH$_2$N(C$_5$H$_{10}$)·HCl

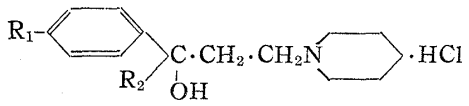
R	m.p. (°C)	Appearance	Yield (%)	Recrystn. solvent	Formula	Analysis (%) C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
CH_3	203～204	Colorless prisms	40.6	EtOH	$C_{15}H_{22}OHClS$	60.09	60.02	7.38	7.07	4.67	4.44
C_2H_5	176	〃	34.4	〃	$C_{16}H_{24}ONClS$	61.22	61.71	7.70	7.49	4.46	4.52
C_4H_9	142～143	Colorless plates	50.0	EtOH-AcOEt	$C_{18}H_{28}ONClS$	63.22	63.68	8.25	8.31	4.10	4.06
C_6H_{13}	128～129	〃	39.7	〃	$C_{20}H_{32}ONClS$	64.92	64.86	8.71	8.59	3.78	3.78
C_8H_{17}	139～140	〃	61.5	〃	$C_{22}H_{36}ONClS$	66.38	66.36	9.11	9.03	3.52	3.65

1-(*p*-Alkylthiophenyl)-1-phenyl-3-(1-piperidyl)-1-propanol Hydrochloride——Prepared from the corresponding 3-(1-piperidyl)-4′-alkylthiopropiophenone by the same procedure as (b). Analytical data are summarized in Table VIII.

Table VIII. R·S-C$_6$H$_4$-C(OH)·CH$_2$·CH$_2$N(C$_5$H$_{10}$)·HCl

R	m.p. (°C)	Appearance	Yield (%)	Recrystn. solvent	Formula	Analysis (%) C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
C_2H_5	215(decomp.)	Colorless needles	53.3	EtOH	$C_{22}H_{30}ONClS$	67.40	67.17	7.71	7.77	3.57	3.31
C_4H_9	188～189	Colorless plates	19.3	EtOH-AcOEt	$C_{24}H_{34}ONClS$	68.03	67.86	7.94	8.01	3.45	3.52
C_6H_{13}	182～183	〃	32.6	〃	$C_{26}H_{38}ONClS$	69.69	69.73	8.55	8.47	3.13	3.32
C_8H_{17}	173～174	〃	46.2	Me_2CO	$C_{28}H_{42}ONClS$	70.63	70.35	8.89	8.91	2.94	2.94

General Procedure for Synthesis of 1-Alkyl-1-alkylphenyl-3-(1-piperidyl)-1-propanol Hydrochloride——Prepared from 3-(1-piperidyl)-4′-alkylpropiophenone hydrochloride and appropriate alkylmagnesium halide by the same procedure as (b). Data are given in Table IX.

TABLE IX. 

R_1	R_2	m.p. (°C)	Yield (%)	Recrystn. solvent	Formula	Analysis (%) C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
CH_3	⬭	258	43.5	EtOH	$C_{21}H_{35}ONCl$	71.45	71.64	9.98	9.82	3.97	3.72
CH_3	C_6H_{13}	193	10.1	EtOH-Me_2CO	$C_{21}H_{36}ONCl$	71.44	71.56	10.25	10.35	3.97	3.84
CH_3	C_8H_{17}	187～188	13.2	〃	$C_{23}H_{40}ONCl$	72.30	72.41	10.55	10.58	3.66	3.34
CH_3	$C_{12}H_{25}$	185～186	22.5	〃	$C_{27}H_{48}ONCl$	73.99	73.93	11.04	10.96	3.11	3.14
C_2H_5	⬭	245	9.6	〃	$C_{22}H_{37}ONCl$	72.00	72.42	10.16	10.21	3.81	3.57
C_2H_5	$C_{12}H_{25}$	183	11.8	〃	$C_{28}H_{50}ONCl$	74.35	74.69	11.14	11.44	3.10	2.90
$C_{10}H_{21}$	⬭	198～199	20.2	Me_2CO	$C_{30}H_{53}ONCl$	75.19	75.48	11.15	11.05	2.92	2.86

All compounds are colorless needles.

Summary

Eight compounds of 1-(*p*-alkylphenyl)-1-phenyl-3-(1-piperidyl)-1-propanol series, seven compounds of 1-(*p*-alkylphenyl)-1-phenyl-3-dimethylamino-1-propanol series, five compounds of 3-(1-piperidyl)-4′-alkylthiopropiophenone series, four compounds of 1-(*p*-alkylthiophenyl)-1-phenyl-3-(1-piperidyl)-1-propanol series, and seven compounds of 1-alkyl-1-(*p*-alkylphenyl)-3-(1-piperidyl)-1-propanol series were synthesized and their antiviral activities were tested. Several compounds of these series were found to be effective on the PR-8 strain of influenza A virus in chorioallantoic membrane, especially, 3-(1-piperidyl)-4′-octylthiopropiophenone and 1-cyclohexyl-1-(*p*-tolyl)-3-(1-piperidyl)-1-propanol. Several compounds of these series showed *in vivo* effect on the Nakayama strain of Japanese B encephalitis virus.

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141. Mitsuru Furukawa, Yoshiko Seto, and Shigeshi Toyoshima : Syntheses of Compounds related to Guanidine and their Inhibitory Action on Growth of HeLa Cells.*1

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It was reported[1] by this research group that 2-imino-4,6-dimethylhexahydrotriazine was inhibitory on multiplication of some of pathogenic viruses, while 2-oxo- and 2-thioxo-4,6-dimethyl-hexahydrotriazines are inactive among compounds of hexahydrotriazines. This finding suggests that the partial structure of $HN{=}C\langle^{NH-}_{NH-}$ in the hexahydrotriazine ring might have better effect on the generation of antiviral activity than $O{=}C\langle^{NH-}_{NH-}$ or

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

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1) Papers read before the Kanto Local Meeting of the Pharmaceutical Society of Japan (June, 1959).