UDC 547.563.1-422.07 : 576.858.095.18

150. Fumio Ueda : Studies on the Syntheses and Antiviral Effect of 3-Alkylphenoxy- and 3-Alkanoylaminophenoxy-1,2-propanediols.*1

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Antiviral chemotherapeutic drugs have hitherto been studied by T. Ueda, *et al.* and it has been pointed out that the compounds with hydrophobic groups, such as alkyl and alkanoyl, seemed to exert considerable antiviral activity.[1)]

In these studies, several compounds of Mephenesin type, in which methyl group in the aromatic ring has been replaced by higher alkyl or alkanoylamino group, were synthesized and screened for antiviral activity. It is of interest to examine the antiviral activities of these compounds, which are chemically similar to Mephenesin, in their penetrative power into the brain, since it is known that Mephenesin has affinity to the nervous tissues.

This paper describes the syntheses and antiviral activity of the compounds of 3-(*o*-alkylphenoxy)-, 3-(*p*-alkylphenoxy)-, and 3-(*o*-alkanoylaminophenoxy)-1,2-propanediol series.

3-Alkylphenoxy-1,2-propanediols, having lower alkyl groups such as methyl, ethyl, propyl, or butyl in the aromatic ring, were investigated by Berger[2)] and Yale[3)] as muscle relaxants, but higher alkyl derivatives have not hitherto been synthesized yet. 3-Alkylphenoxy-1,2-propanediols having alkyl chains of 6~14 carbon atoms were synthesized according to the general method shown in Chart 1.

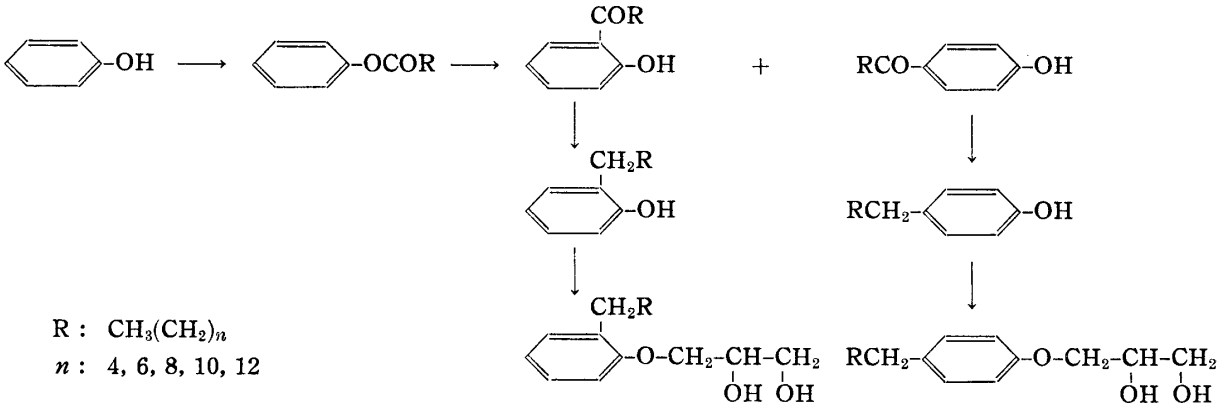

Chart 1.

Fatty acid phenyl esters employed as the starting materials were prepared by the condensation of fatty acid chlorides with phenol in the presence of pyridine.[4)] Fatty acid phenyl esters thus obtained were rearranged by the Fries reaction into alkanoylphenols.[5)] The alkanoylphenols thus obtained were mixture of *o*- and *p*-isomers. The

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*1 This constitutes Part XXIII of a series entitled "Researches on Chemotherapeutic Drugs against Viruses" by Takeo Ueda. Part XXII : This Bulletin, **2**, 429(1954).

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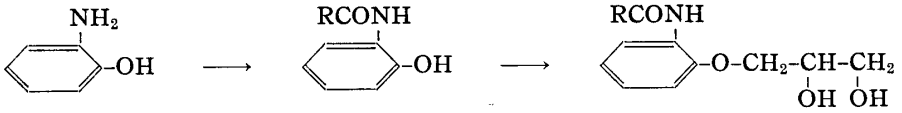
2) F. M. Berger : J. Pharmacol., **1**, 265(1946); J. Pharmacol. Exptl. Therap., **93**, 470(1948); *ibid.*, **96**, 249(1949).
3) H. L. Yale, E. J. Pribyl, W. Braker, F. H. Bergein, W. A. Lott : J. Am. Chem. Soc., **72**, 3710(1950).
4) F. Kraft, J. Bürger : Ber., **17**, 1378(1884).
5) Org. Syntheses, Coll. Vol. II, 543.

isolation was carried out by the method reported by Bell[6] and Ralston[7] in a modified way. The yield of *ortho*- and *para*-isomers was 30~45%, and the total yield was 70~80%. The alkanoylphenols were reduced into the corresponding alkylphenols by Clemmensen reduction with good yield.[8] None of these compounds, except the hexyl and octyl derivatives,[9,10] have been seen in the literature. Among these compounds, the lower alkyl derivatives are colorless oils at room temperature, but the higher ones are obtained as colorless crystals. The *p*-alkylphenols are soluble in alkali solution with formation of alkali salts, but *o*-alkylphenols are insoluble.

The glycerol alkylphenyl ethers have been prepared by various methods, for instance, by the reaction of a phenol and a halohydrin or an epoxide. 3-(*o*-Alkylphenoxy)-1,2-propanediols were prepared by the reaction of *o*-alkylpnenols and 3-chloro-1,2-propanediol with addition of sodium ethoxide in ethanol as hydrogen chloride acceptor. 3-(*p*-Alkylphenoxy)-1,2-propanediols were similarly prepared and 3-(*p*-alkylphenoxy)-1,2-propanediols were prepared by the reaction of *p*-alkylphenols and 3-chloro-1,2-propanediol, employing sodium hydroxide in hydrous ethanol. This method, however, was not suitable for the *ortho* derivatives. The yield was 50~60%. The ethers thus obtained were purified by fractional distillation and recrystallization from petroleum ether. Both 3-(*o*-alkylphenoxy)- and 3-(*p*-alkylphenoxy)-1,2-propanediols came in colorless crystals, sparingly soluble in water but soluble in organic solvents, such as ethanol, methanol, and ether.

3-(*o*-Alkanoylaminophenoxy)-1,2-propanediols were synthesized by the condensation of *o*-alkanoylaminophenols with 3-chloro-1,2-propanediol, employing sodium ethoxide in ethanol as the hydrogen chloride acceptor. *o*-Alkanoylaminophenols were obtained by the respective condensation of *o*-aminophenol with fatty acid chlorides in the presence of pyridine. The whole process of the reaction is shown in Chart 2.



R : $CH_3(CH_2)_n$ n : 6, 8, 10

Chart 2.

Among the *o*-alkanoylaminophenols, dodecanoyl derivative has been reported.[11] 3-(*o*-Alkanoylaminophenoxy)-1,2-propanediols are sparingly soluble in water and petroleum ether, and soluble in ethanol, methanol, and benzene.

The properties of the compounds obtained are summarized in Tables I and II.

The 3-alkylphenoxy- and 3-(*o*-alkanoylaminophenoxy)-1,2-propanediols shown in Table II were examined for antiviral activities *in vivo* on Japanese B encephalitis virus and *in vitro* on poliomyelitis virus according to the method described in the Experimental section. The results are shown in Tables III and IV.

Table III shows that among the compounds of 3-(*o*-alkanoylaminophenoxy)-1,2-propanediol series, 3-(*o*-decanoylaminophenoxy)-1,2-propanediol had antiviral activity against the Nakayama strain, but 3-(*o*-alkylphenoxy)- and 3-(*p*-alkylphenoxy)-1,2-propanediols did not show such a marked effect as was expected.

Table IV shows that the compounds of 3-(*o*-alkylphenoxy)- and 3-(*p*-alkylphenoxy)-

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7) A. W. Ralston, S. T. Baner : J. Org. Chem., **5**, 165(1940); *ibid.*, **5**, 645(1940).
8) Org. Syntheses, **20**, 57.
9) G. Sandulesco, A. Girad : Bull. soc. chim., (**4**)**47**, 1300(1930)(C. A., **25**, 1228(1931)).
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11) E. Bergs, F. Winterwitz : Ann., **332**, 206(1904).

Table I. R-C$_6$H$_4$-OH

Compd. No.	R	b.p. (°C/mm. Hg)	m.p. (°C)
I-1	*o*-$CH_3(CH_2)_5$	128/6[a]	—
I-2	*o*-$CH_3(CH_2)_7$	140/4[b]	—
I-3	*o*-$CH_3(CH_2)_9$	136/2	—
I-4	*o*-$CH_3(CH_2)_{11}$	166/2	38~40
I-5	*o*-$CH_3(CH_2)_{13}$	175/3	49~50
II-1	*p*-$CH_3(CH_2)_5$	130/4[c]	—
II-2	*p*-$CH_3(CH_2)_7$	150/4[d]	41~42[e]
II-3	*p*-$CH_3(CH_2)_9$	167/4	50~51
II-4	*p*-$CH_3(CH_2)_{11}$	175/2	64~65
II-5	*p*-$CH_3(CH_2)_{13}$	195/3	67~68
III-1	*o*-$CH_3(CH_2)_6CONH$	—	71~72
III-2	*o*-$CH_3(CH_2)_8CONH$	—	69~70
III-3	*o*-$CH_3(CH_2)_{10}CONH$	—	74~75[f]

All are colorless plate crystals. Nos. III-1, III-2, and III-3 are light yellow in color.

Reported b.p.[9,10] *a*) 135~136/10, *b*) 160~162/11, *c*) 146~147/10, *d*) 169/10.
Reported m.p.[9,10] *e*) 41~42. Reported m.p.[11] *f*) 68~69.

Table II. R-C$_6$H$_4$-O-CH_2-CH(OH)-CH_2OH

Compd. No.	R	b.p. (°C/mm. Hg)	m.p. (°C)
IV-1	*o*-$CH_3(CH_2)_5$	206/4	44~45
IV-2	*o*-$CH_3(CH_2)_7$	193/4	53~54
IV-3	*o*-$CH_3(CH_2)_9$	194/2	55~56
IV-4	*o*-$CH_3(CH_2)_{11}$	205/2	60~61
IV-5	*o*-$CH_3(CH_2)_{13}$	—	62~63
V-1	*p*-$CH_3(CH_2)_5$	204/4	66~67
V-2	*p*-$CH_3(CH_2)_7$	199/2	69~70
V-3	*p*-$CH_3(CH_2)_9$	—	73~74
V-4	*p*-$CH_3(CH_2)_{11}$	—	78~79
V-5	*p*-$CH_3(CH_2)_{13}$	—	77~78
VI-1	*o*-$CH_3(CH_2)_6CONH$	—	90~91
VI-2	*o*-$CH_3(CH_2)_8CONH$	—	98~99
VI-3	*o*-$CH_3(CH_2)_{10}CONH$	—	102~103

All are colorless plate crystals.

Table III. Antiviral activities against Japanese B Encephalitis Virus

Compd. No.	Dose (mg./kg.)	Treated group[a]	Untreated group[a]	χ^2 [b]
IV-1	60	3/40	3/40	—
IV-2	42	6/40		0.50
IV-3	44	4/40		—
IV-4	150	3/40		—
IV-5	80	3/40		—
V-1	38	4/40		—
V-2	80	4/40		—
V-3	75	3/40		—
V-4	150	3/40		—
V-5	100	5/40		—
VI-1	200	10/40		3.30
VI-2	200	11/40		4.24
VI-3	100	3/40		—

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

Table. IV. Antiviral Activities against Poliomyelitis Virus

Compd. No.	LD_{50} Treated group (Compd. concn.) 500 γ/cc.	200 γ/cc.	Untreated group
IV-1	$10^{-2.0}$	$10^{-3.0}$	$10^{-3.5}$
IV-2	$10^{-2.33}$	$10^{-3.0}$	
IV-3	$10^{-2.4}$	$10^{-3.0}$	
IV-4	$10^{-2.5}$	$10^{-3.0}$	
IV-5	$10^{-2.54}$	$10^{-3.0}$	
V-1	$10^{-2.1}$	$10^{-2.94}$	
V-2	$10^{-2.0}$	$10^{-3.0}$	
V-3	$10^{-2.16}$	$10^{-3.0}$	
V-4	$10^{-2.16}$	$10^{-2.8}$	
V-5	$10^{-2.35}$	$10^{-2.87}$	
VI-1	$10^{-2.7}$	$10^{-3.0}$	
VI-2	$10^{-2.8}$	$10^{-3.0}$	
VI-3	$10^{-2.9}$	$10^{-3.0}$	

1,2-propanediol series are active against the Lansing strain in concentration of 500 γ/cc. and the activity of 3-(*o*-alkanoylaminophenoxy)-1,2-propanediols is weak. Further, 3-(*p*-alkylphenoxy)-1,2-propanediols were active in concentration of 200 γ/cc.

At the present stage, it is difficult to explain why these compounds are active against the Lansing strain, but it is of interest that there are compounds among the series of alkylphenoxy compounds active against the poliomyelitis virus.

Experimental

General Procedure for the Reduction of Alkanoylphenol into Alkylphenol—To a suspension of 100 g. of amalgamated mossy Zn[12] in a mixture of 100 cc. of water and 100 cc. of conc. HCl was added a solution of 0.1 mole of alkanoylphenol in 50 cc. of EtOH. The mixture was agitated vigorously and refluxed for 20~24 hr. to complete the reduction. After the reaction, the oily product was extracted with toluene, the toluene solution was washed with water, and the suspended matter filtered off. Toluene was evaporated and the residue was distilled *in vacuo*. The analytical data are given in Table V.

Table V.

Compd. No.	Mol. formula	C (%) Calcd.	C (%) Found	H (%) Calcd.	H (%) Found
I-1	$C_{12}H_{18}O$	80.85	80.52	10.18	10.11
I-2	$C_{14}H_{22}O$	81.50	81.64	10.75	10.87
I-3	$C_{16}H_{26}O$	81.99	82.29	11.18	11.29
I-4	$C_{18}H_{30}O$	82.38	82.75	11.52	11.76
I-5	$C_{20}H_{34}O$	82.69	82.55	11.80	11.68
II-1	$C_{12}H_{18}O$	80.85	80.83	10.18	10.24
II-2	$C_{14}H_{22}O$	81.50	81.51	10.75	10.83
II-3	$C_{16}H_{26}O$	81.99	81.53	11.18	10.95
II-4	$C_{18}H_{30}O$	82.38	82.85	11.52	11.52
II-5	$C_{20}H_{34}O$	82.69	82.72	11.80	11.90

General Method of Synthesis for 3-Alkylphenoxy-1,2-propanediol—a) To a solution of EtONa from 0.3 g. (0.012 mole) of metallic Na and 8 cc. of EtOH, 0.012 mole of alkylphenol was added and then 1.5 g. (0.014 mole) of 3-chloro-1,2-propanediol. After stirring on a steam bath for 6 hr., EtOH was distilled off, the residue was treated with water, and extracted with ether. The ether extract was washed with water and dried over Na_2SO_4. After removal of ether, the residue, obtained as

12) E.L. Martin : Org. Reactions, **1**, 155.

oil, was distilled under reduced pressure and the distillate was recrystallized from petr. ether. The residue, if solid, was collected by filtration and recrystallized from petr. ether.

b) To a solution of 1.0 g. (0.025 mole) of NaOH in 5 cc. of water, a solution of 0.02 mole of *p*-alkylphenol and 2.7 g. (0.024 mole) of 3-chloro-1,2-propanediol in 20 cc. of EtOH were added. The mixture was warmed on a steam bath for 3 hr. with stirring. After removal of EtOH, the residue was poured into 20 cc. of water and extracted with ether. The ether extracts were treated as in procedure (a). The analytical data are given in Table VI.

Table VI.

Compd. No.	Mol. formula	C (%)		H (%)	
		Calcd.	Found	Calcd.	Found
IV-1	$C_{15}H_{24}O_3$	71.39	71.00	9.59	9.48
IV-2	$C_{17}H_{28}O_3$	72.82	72.81	10.06	10.13
IV-3	$C_{19}H_{32}O_3$	73.98	74.14	10.46	10.19
IV-4	$C_{21}H_{36}O_3$	74.95	74.86	10.78	10.81
IV-5	$C_{23}H_{40}O_3$	75.77	76.16	11.06	11.16
V-1	$C_{15}H_{24}O_3$	71.39	71.31	9.59	9.58
V-2	$C_{17}H_{28}O_3$	72.82	72.60	10.06	10.28
V-3	$C_{19}H_{32}O_3$	73.98	73.77	10.46	10.54
V-4	$C_{21}H_{36}O_3$	74.95	74.76	10.78	10.70
V-5	$C_{23}H_{40}O_3$	75.77	75.61	11.06	11.10

General Method of Synthesis for *o*-Alkanoylaminophenol—To a solution of 6.0 g. (0.055 mole) of *o*-aminophenol in 10 cc. of pyridine, 0.06 mole of fatty acid chloride was added dropwise, with stirring. After stirring for 30 min. on a steam bath, pyridine was distilled off *in vacuo*, and the precipitate, produced by adding 50 cc. of 5% HCl, was extracted with ether. The ether extract was washed with water and dried over Na_2SO_4. After removal of ether, the residue was recrystallized from a mixture of ether and petr. ether. The yield was 60~70%. The analytical data are given in Table VII.

Table VII.

Compd. No.	Mol. formula	N (%)	
		Calcd.	Found
III-1	$C_{14}H_{21}O_2N$	5.95	6.12
III-2	$C_{16}H_{25}O_2N$	5.32	5.42
III-3	$C_{18}H_{29}O_2N$	4.81	4.79

General Method of Synthesis of 3-(*o*-Alkanoylaminophenoxy)-1,2-propanediol—To a solution of EtONa from 0.3 g. (0.012 mole) of metallic Na and 5 cc. of EtOH, was added 0.012 mole of *o*-alkanoylaminophenol and then 1.5 g. (0.014 mole) of 3-chloro-1,2-propandiol. After stirring on a steam bath for 6 hr., EtOH was distilled off and the oily substance, separated by adding 30 cc. of water, was extracted with ether. The ether extract was washed with water and dried over Na_2SO_4. After removal of ether, the residue was recrystallized from a mixture of ether and petr. ether. The yield was 50~60%. The analytical data are given in Table VIII.

Table VIII.

Compd. No.	Mol. formula	C (%)		H (%)		N (%)	
		Calcd.	Found	Calcd.	Found	Calcd.	Found
VI-1	$C_{17}H_{27}O_4N$	—	—	—	—	4.53	4.38
VI-2	$C_{19}H_{31}O_4N$	67.62	67.55	9.26	9.64	4.15	4.00
VI-3	$C_{21}H_{35}O_4N$	—	—	—	—	3.83	3.85

Method of Screening Test for Antiviral Activity

(I) **Japanese B Encephalitis Virus**—The Nakayama strain of Japanese B encephalitis virus*3

*3 The strains were given to the author by Dr. K. Ando, the retired Director of the National Institute of Health, Tokyo.

was employed. This strain had been kept by serial passages through mice. The D. M. K. strain of mice, 8~10 g. in body weight, was used for the experiments.

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

(**II**) **Poliomyelitis Virus**—The Lansing strain of poliomyelitis virus (Type II)*[3] was employed. The D. M. K. strain of mice, 7~9 g. in body weight, was used for the experiments.

Various viral dilutions of the Lansing strain were prepared. Each 0.1 cc. of the dilution was placed in a test tube containing 0.1 cc. of a sterilized solution of a compound and 0.8 cc. of Lush's solution. After incubation at 37° for 1 hr., 0.03 cc. each of this mixture was inoculated intracerebrally into mice. After daily observation for 3 weeks, LD_{50} of the treated and untreated groups was calculated by the method of Reed and Munch.

Summary

Under the assumption that compounds with hydrophobic group would have antiviral activity, the compounds of 3-(*o*-alkylphenoxy)-, 3-(*p*-alkylphenoxy)-, and 3-(*o*-alkanoylaminophenoxy)-1,2-propanediol series were synthesized and examined for antiviral activities.

3-Alkylphenoxy-1,2-propanediols were prepared from fatty acid phenyl esters by their Fries rearrangement to *o*- and *p*-alkanoylphenols, Clemmensen reduction to *o*- and *p*-alkylphenols, and condensation with 3-chloro-1,2-propanediol in the presence of sodium ethoxide in ethanol to 3-(*o*-alkylphenoxy)- and 3-(*p*-alkylphenoxy)-1,2-propanediols having alkyl chains of 6~14 carbon atoms.

3-(*o*-Alkanoylaminophenoxy)-1,2-propanediols having alkanoyl chains of 8~12 carbon atoms were prepared by the condensation of *o*-alkanoylaminophenols with 3-chloro-1,2-propanediol in the presence of sodium ethoxide in ethanol.

3-(*o*-Decanoylaminophenoxy)-1,2-propanediol had antiviral activity against the Nakayama strain of Japanese B encephalitis virus *in vivo*. Several compounds of 3-(*p*-alkylphenoxy)- and 3-(*o*-alkylphenoxy)-1,2-propanediol series had antiviral activity against the Lansing strain of poliomyelits virus *in vitro*.

(Received April 21, 1959)