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124. Kiyoshi Takahashi, Keiko Ohki, Toyoharu Mizuma, and Shigeshi Toyoshima: Researches on Chemotherapeutic Drugs against Viruses. XXVI.*1 Syntheses and Antiviral Activity of N,N-Dimethyl-2-(*p*-alkylbenzhydrylthio)ethylamine and N,N-Dimethyl-2-(*p*-alkylthiobenzhydrylthio)ethylamine.

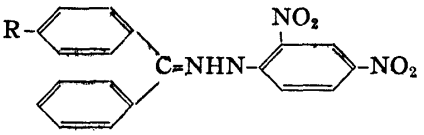
(*Pharmaceutical Institute, Keio-Gijuku University**2)

As described in the previous paper,[1] several alkyl derivatives of synthetic neurotropic compounds were found by this research group to have antiviral activity against some of pathogenic viruses. In accordance with these findings, plans were made to introduce an alkyl group into the structure of N,N-dimethyl-2-(benzhydrylthio)ethylamime related to Diphenhydramine. Thus, the compounds of N,N-dimethyl-2-(*p*-alkylbenzhydrylthio)-ethylamine and N,N-dimethyl-2-(*p*-alkylthiobenzhydrylthio)ethylamine were synthesized and their effect on the Nakayama strain of Japanese B encephalitis virus was examined.

This paper is concerned with the syntheses of N,N-dimethyl-2-(*p*-alkylbenzhydrylthio)ethylamine and N,N-dimethyl-2-(*p*-alkylthiobenzhydrylthio)ethylamine, and their antiviral activity.

Although N,N-dimethyl-2-(benzhydrylthio)ethylamine and N,N-dimethyl-2-(*p*-methylbenzhydrylthio)ethylamine were already synthesized by Hughes, *et al.*[2] and by Fukuda,[3] the derivatives substituted with longer carbon chain of alkyl group have not been prepared yet.

TABLE I.



R	m.p. (°C)	Mol. formula	N (%) Calcd.	N (%) Found
CH_3	218~220	$C_{20}H_{16}O_4N_4$	14.88	14.93
C_2H_5	165~168	$C_{21}H_{18}O_4N_4$	14.35	14.33
C_3H_7	150~153	$C_{22}H_{20}O_4N_4$	13.86	13.86
C_4H_9	141~143	$C_{23}H_{22}O_4N_4$	13.39	13.33
C_5H_{11}	135~137	$C_{24}H_{24}O_4N_4$	12.95	12.85
C_6H_{13}	122~124	$C_{25}H_{26}O_4N_4$	12.55	12.43
C_8H_{17}	112~116	$C_{27}H_{30}O_4N_4$	11.81	11.70
$C_{10}H_{21}$	102~107	$C_{29}H_{34}O_4N_4$	11.15	11.05
$C_{12}H_{25}$	104~108	$C_{30}H_{38}O_4N_4$	10.56	10.46

All the compounds are orange plates.

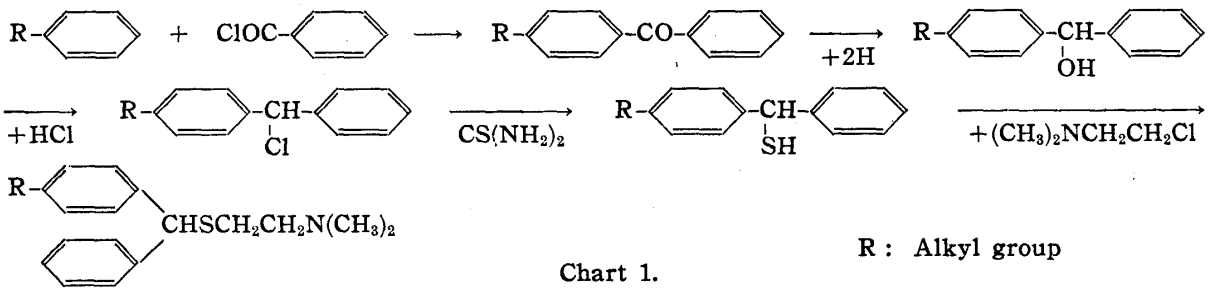
*1 This paper constitutes part of a series entitled "Researches on Chemotherapeutic Drugs against Viruses" by Takeo Ueda. Part XXV: This Bulletin, **7**, 843(1959).

*2 Shinano-machi, Shinjuku-ku, Tokyo (高橋 廉, 大木恵子, 水間豊治, 豊島 滋).

1) T. Ueda, S. Toyoshima, K. Takahashi, M. Muraoka: Keio J. Med., **8**, 199(1959).
2) E. D. Hughes, *et al.*: J. Chem. Soc., **1940**, 949.
3) H. Fukuda: Yakugaku Zasshi, **72**, 1472(1952).

Synthesis of N,N-Dimethyl-2-(*p*-alkylbenzhydrylthio)ethylamine

As the starting material, *p*-alkylbenzophenone was employed, which was prepared from alkylbenzene and benzoyl chloride by the Friedel-Crafts condensation. The resulting ketones were identified as their 2,4-dinitrophenylhydrazones, as shown in Table I. *p*-Alkylbenzophenone was reduced to the corresponding *p*-alkylbenzhydrol with aluminium isopropoxide by the Meerwein-Ponndorf-Verley reduction. By introducing hydrogen chloride gas into the ether solution of *p*-alkylbenzhydrol, *p*-alkylbenzhydryl chloride was formed, which was then converted into *p*-alkylthiobenzhydrol with thiourea. N,N-Dimethyl-2-(*p*-alkylbenzhydrylthio)ethylamine was prepared by condensation of the resulting *p*-alkylthiobenzhydrol with 2-dimethylaminoethyl chloride hydrochloride in the presence of sodium ethoxide. The whole synthetic processes described above are shown in Chart 1.



R : Alkyl group

Chart 1.

Thus, nine compounds of N,N-dimethyl-2-(*p*-alkylbenzhydrylthio)ethylamine hydrochloride were obtained and these compounds are listed in Table II.

Table II. R-C6H4-CHSCH2CH2N(CH3)2·HCl

R	m.p. (°C)	Mol. formula	N (%) Calcd.	N (%) Found
CH_3	151~152	$C_{18}H_{24}NClS$	4.35	4.30
C_2H_5	141~143	$C_{19}H_{26}NClS$	4.15	4.12
C_3H_7	131~133	$C_{20}H_{28}NClS$	4.00	3.96
C_4H_9	132~134	$C_{21}H_{30}NClS$	3.86	3.82
C_5H_{11}	124~126	$C_{22}H_{32}NClS$	3.70	3.75
C_6H_{13}	117~118	$C_{23}H_{34}NClS$	3.57	3.54
C_8H_{17}	122~123	$C_{25}H_{38}NClS$	3.33	3.26
$C_{10}H_{21}$	123~124	$C_{27}H_{42}NClS$	3.12	3.15
$C_{12}H_{25}$	123~125	$C_{29}H_{46}NClS$	2.94	2.91

Synthesis of N,N-Dimethyl-2-(*p*-alkylthiobenzhydrylthio)ethylamine

Among the compounds of N,N-dimethyl-2-(*p*-alkylthiobenzhydrylthio)ethylamine series, those having alkyl chain of C_1 to C_8 were already reported by Weidmann and Peterson,[4] who referred to their pharmacological properties, but synthetic method for the eight compounds is not found in any literature.

As the first step of syntheses of these compounds, *p*-alkylthiobenzhydrol was prepared by the sequence of reactions shown in Chart 2. In the reaction of the last step, however, magnesium was not easily digested and so, on addition of benzaldehyde, the yield of *p*-alkylthiobezhydrol was very poor.

Therefore, method similar to the synthesis of N,N-dimethyl-2-(*p*-alkylbenzhydryl-

4) H. Weidmann, P. V. Peterson : J. Pharmacol. Exptl. Therap., **108**, 201(1953).

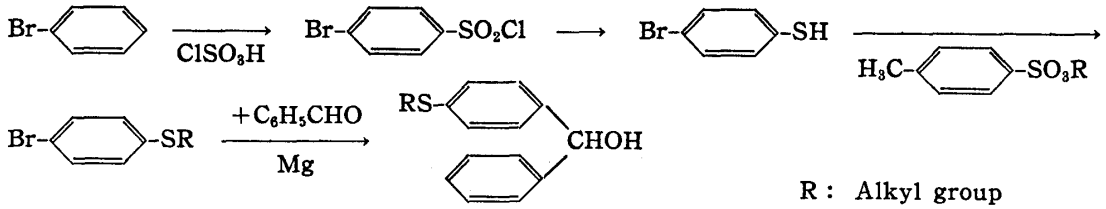


Chart 2.

thio)ethylamine was employed with success, and alkylthiobenzene, prepared from thiophenol and alkyl bromide, was condensed with benzoyl chloride in the presence of aluminium chloride. The data for alkylthiobenzene, *p*-alkylthiobenzophenone, and their 2,4-dinitrophenylhydrazones are listed in Tables III and IV. After reduction of the

Table III. R-S-

R	b.p. (°C/mm. Hg)	R	b.p. (°C/mm. Hg)
C_3H_7	218~219/760	C_9H_{19}	153~155/3
C_4H_9	113~114/13	$C_{10}H_{21}$	162~163/7
C_5H_{11}	125~127/13	$C_{11}H_{23}$	(plates)
C_6H_{13}	133~140/15	$C_{12}H_{25}$	(〃)
C_7H_{15}	118~121/2	$C_{14}H_{29}$	(〃)
C_8H_{17}	155~157/11	$C_{16}H_{33}$	(〃)

Table IV. R-S-C=NNH-(NO2)-NO2

R	m.p. (°C)	Mol. formula	N (%)		S (%)	
			Calcd.	Found	Calcd.	Found
C_3H_7	131~133	$C_{22}H_{20}O_4N_4S$	12.84	12.76	7.33	7.38
C_4H_9	118~120	$C_{23}H_{22}O_4N_4S$	12.44	12.45	7.10	7.05
C_5H_{11}	116~117	$C_{24}H_{24}O_4N_4S$	12.06	12.11	6.89	6.97
C_6H_{13}	111~113	$C_{25}H_{26}O_4N_4S$	11.71	11.59	6.69	6.65
C_7H_{15}	101~103	$C_{26}H_{28}O_4N_4S$	11.38	11.45	6.50	6.38
C_8H_{17}	97~99	$C_{27}H_{30}O_4N_4S$	11.06	10.98	6.32	6.24
C_9H_{19}	81~84	$C_{28}H_{32}O_4N_4S$	10.76	10.66	6.13	6.11
$C_{10}H_{21}$	83~85	$C_{29}H_{34}O_4N_4S$	10.48	10.38	5.99	5.92
$C_{11}H_{23}$	94~95	$C_{30}H_{36}O_4N_4S$	10.21	10.15	5.83	5.74
$C_{12}H_{25}$	93~94	$C_{31}H_{38}O_4N_4S$	9.96	9.95	5.69	5.61
$C_{14}H_{29}$	84~87	$C_{33}H_{42}O_4N_4S$	9.49	9.36	5.42	5.43
$C_{16}H_{33}$	89~91	$C_{35}H_{46}O_4N_4S$	9.06	8.98	5.17	5.08

ketone to the corresponding benzhydrol with aluminium isopropoxide, the resulting benzhydrol was converted into benzhydryl chloride with hydrogen chloride gas. The chloride was converted to mercaptan with thiourea. Further, N,N-dimethyl-2-(*p*-alkylthiobenzhydrylthio)ethylamine was synthesized by condensation of the mercaptan thus formed with 2-dimethylaminoethyl chloride hydrochloride in the presence of sodium ethoxide. The sequence of reactions described above is shown in Chart 3.

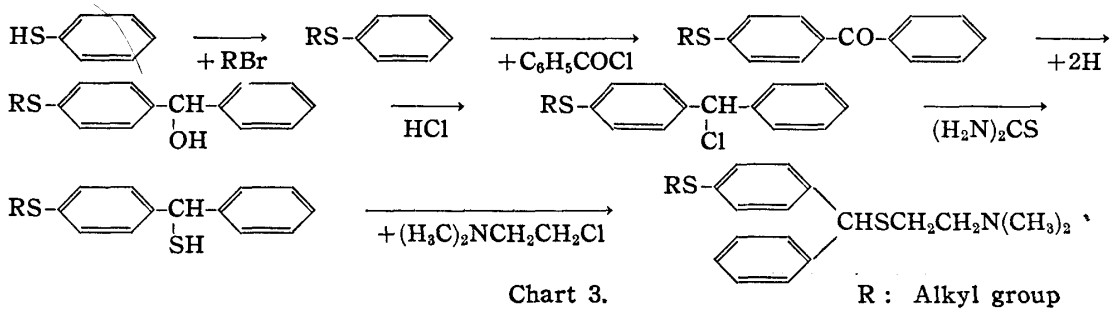
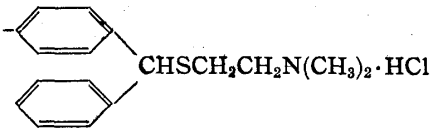


Chart 3.

Thus, twelve compounds of N,N-dimethyl-2-(*p*-alkylthiobenzhydrylthio)ethylamine hydrochloride series were obtained and data of these compounds are listed in Table V.

TABLE V.



R	m.p. (°C)	Mol. formula	N (%) Calcd.	N (%) Found
C_3H_7	132~133	$C_{20}H_{26}NClS_2$	3.66	3.58
C_4H_9	128~130	$C_{21}H_{30}NClS_2$	3.55	3.62
C_5H_{11}	131~133	$C_{22}H_{32}NClS_2$	3.41	3.36
C_6H_{13}	129~130	$C_{23}H_{34}NClS_2$	3.30	3.30
C_7H_{15}	127~129	$C_{24}H_{36}NClS_2$	3.19	3.24
C_8H_{17}	125~126	$C_{25}H_{38}NClS_2$	3.09	2.99
C_9H_{19}	124~126	$C_{26}H_{40}NClS_2$	3.00	2.93
$C_{10}H_{21}$	125~126	$C_{27}H_{42}NClS_2$	2.91	2.88
$C_{11}H_{23}$	124~126	$C_{28}H_{44}NClS_2$	2.81	2.76
$C_{12}H_{25}$	127~128	$C_{29}H_{46}NClS_2$	2.75	2.74
$C_{14}H_{29}$	128~129	$C_{31}H_{50}NClS_2$	2.61	2.64
$C_{16}H_{33}$	124~126	$C_{33}H_{54}NClS_2$	2.47	2.53

All the compounds are colorless needles.

Screening Test with N,N-Dimethyl-2-(*p*-alkylbenzhydrylthio)ethylamine and N,N-Dimethyl-2-(*p*-alkylthiobenzhydrylthio)ethylamine

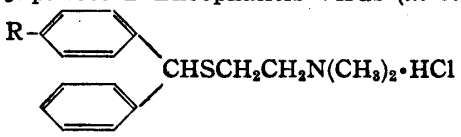
The *in vivo* and *in vitro* effects of the compounds synthesized were examined on the Nakayama strain of Japanese B encephalitis virus. Experimental procedures were the same as described in the preceding paper[5] and experimental results are shown in Table VI.

None of the compounds showed *in vitro* effect against the Nakayama strain. On the other hand, as can be seen in Table VI, several compounds of N,N-dimethyl-2-(*p*-alkylthiobenzhydrylthio)ethylamine hydrochloride series were found to possess fairly good *in vivo* effect on the virus, while none of the compounds of N,N-dimethyl-2-(*p*-alkylbenzhydrylthio)ethylamine series were effective. When the skeletal structure of N,N-dimethyl-2-(*p*-alkylbenzhydrylthio)ethylamine is compared with that of N,N-dimethyl-2-(*p*-alkylthiobenzhydrylthio)ethylamine, a different point is noticed. The former has an alkyl group directly bonded to the benzene ring, while the alkyl group of the latter is bound to the benzene ring through a sulfur-bridge. It might be partly due to this structural difference that certain compounds of the latter series showed *in vivo* effect on the virus while none of the compounds of the former series were effective. The effective compounds of N,N-dimethyl-2-(*p*-alkylthiobenzhydrylthio)ethylamine series may be able to exert neurotropic activity, invade the host cells on account of the alkyl group, and there interfere with enzymes which are essential for viral multiplication.

Based on the idea that N,N-dimethyl-2-(*p*-alkylthiobenzhydrylthio)ethylamine, known as a sedative, might be cerebrotropic, alkyl derivatives of this compound were synthesized and several of these compounds were found to be effective on the Nakayama strain in *in vivo* experiments.

5) Part XXIII: This Bulletin, 7, 823(1959).

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



R	Dose (mg./kg.)	Treated group[a)]	Untreated group[a)]
CH_3	22	5/55	4/50
	17	6/49	
C_2H_5	30	4/45	4/50
	20	3/45	
C_3H_7	30	6/41	4/50
	20	6/47	
C_4H_9	30	8/50	4/50
	20	5/50	
C_5H_{11}	25	1/43	4/50
	20	4/47	
C_6H_{13}	30	5/50	2/50
	20	3/51	
C_8H_{17}	45	4/50	2/50
	30	1/49	
$C_{10}H_{21}$	75	2/50	2/50
	50	7/50	
$C_{12}H_{25}$	30	4/49	2/50
	20	1/46	
C_3H_7S	22	12/48	6/48
	15	*19/48	
C_4H_9S	30	*17/50	6/48
	20	9/48	
$C_7H_{15}S$	45	11/49	6/48
	30	*18/49	
$C_9H_{19}S$	30	10/44	6/48
	20	*23/46	
$C_{10}H_{21}S$	60	9/42	6/48
	40	7/47	
$C_{11}H_{23}S$	50	*11/32	6/48
	35	*17/47	
$C_{12}H_{25}S$	30	5/40	4/50
	20	7/43	
$C_{14}H_{29}S$	40	4/38	4/50
	30	3/41	
$C_{16}H_{33}S$	40	3/44	4/50
	30	5/44	

a) The numerator represents the number of mice that survived, and the denominator, number treated.
* shows a significant value by the calculation of χ^2.

Experimental

General Procedure of Synthesis of N,N-Dimethyl-2-(*p*-alkylbenzhydrylthio)ethylamine Hydrochloride

a) ***p*-Alkylbenzophenone**—0.2 mole of BzCl was added dropwise under rapid stirring to a cold mixture of 0.2 mole of anhyd. $AlCl_3$ and 0.17 mole of alkylbenzene in 60 cc. of CS_2. Stirring was continued at a room temperature until no more HCl gas evolved. Then the reaction mixture was poured on crushed ice and extracted with Et_2O. The Et_2O extract was washed with 10% NaOH and water, and dried over anhyd. Na_2SO_4. The Et_2O residue was purified by distillation and identified as 2,4-dinitrophenylhydrazone.

b) ***p*-Alkylbenzhydrol**—A mixture of 0.05 mole of *p*-alkylbenzophenone and 0.05 mole of Al(iso-PrO)$_3$ in 50 cc. of iso-PrOH was refluxed on a water bath at such a rate that 5~10 drops of the distillate was collected per min. When the Me_2CO test became negative, most of the excess iso-PrOH was removed under a slightly reduced pressure. The cooled residue was hydrolyzed with dil. HCl (prepared from 17.5 cc. of conc. HCl and 88 cc. of water) and dissolved in Et_2O. The Et_2O solution

was washed with dil. HCl and water, and dried over anhyd. Na_2SO_4.

c) ***p*-Alkylbenzhydryl Chloride**—Into the Et_2O solution obtained as above, a stream of HCl gas was introduced during 2 hr. and $CaCl_2$ was added to remove the water formed. The same treatment was repeated with the decanted Et_2O solution. The resulting solution was concentrated, shaken with anhyd. Na_2CO_3, and submitted to subsequent reaction without purification.

d) ***p*-Alkylthiobenzhydrol**—A mixture of 0.125 mole of the chloride and 0.127 mole of thiourea in 50 cc. of 95% EtOH was refluxed for 1 hr. After cool, a solution of 7.6 g. of NaOH in 50 cc. of water was added and warmed on a water bath for 2 hr. The reaction mixture was acidified with 10% H_2SO_4, extracted with benzene, and the benzene extract was dried over anhyd. Na_2SO_4. After evaporation of benzene, the residue was submitted to the next reaction without further purification.

e) **N,N-Dimethyl-2-(*p*-alkylbenzhydrylthio)ethylamine Hydrochloride**—A mixture of 0.02 mole of the thiobenzhydrol and 0.5 g. of metallic Na in 25 cc. of dehyd. EtOH was refluxed with agitation for 1 hr. When cool, 0.6 g. of metallic Na and 3.4 g. of 2-dimethylaminoethyl chloride hydrochloride were added and the whole was refluxed for further 2 hr. After the precipitated NaCl was filtered off and EtOH removed, the residue was taken up successively with Et_2O and 10% HCl. HCl solution was washed with Et_2O and the free amine, liberated with 10% NaOH, was extracted with Et_2O. The Et_2O residue was once converted to the oxalate with oxalic acid in iso-PrOH. The oxalate was converted again to the free base with 10% NaOH and taken up in Et_2O. By introducing HCl gas into the resulting Et_2O solution, hydrochloride of the amine was prepared and purified by recrystallization from AcOEt.

General Procedure for Synthesis of N,N-Dimethyl-2-(*p*-alkylthiobenzhydrylthio)ethylamine Hydrochloride

Alkylthiobenzene—To a mixture of 0.2 mole of thiophenol and 0.2 mole of KOH in 50 cc. of 95% EtOH, 0.2 mole of alkyl bromide was added in small portions at 60~70°. After the mixture was refluxed on a water bath for 30 min. and water added, the separated oil was taken up with Et_2O. The Et_2O layer was washed with 10% NaOH and water, and dried over anhyd. Na_2CO_3. After evaporation of the solvent, the residue was purified by distillation *in vacuo* (C_3~C_{10}) or recrystallization from EtOH (C_{11}~C_{16}).

***p*-Alkylthiobenzophenone**—Prepared from the corresponding alkylthiobenzene and BzCl by the same procedure as (a). Purified by recrystallization from EtOH, instead of distillation as in (a).

***p*-Alkylthiobenzhydrol**—Prepared from the corresponding *p*-alkylthiobenzophenone by the same procedure as (b).

***p*-Alkylthiobenzhydryl Chloride**—Prepared from the corresponding *p*-alkylthiobenzhydrol by the same procedure as (c).

***p*-Alkylthio-thiobenzhydrol**—Prepared from the corresponding *p*-alkylthiobenzhydryl chloride and thiourea by the same procedure as (d).

N,N-Dimethyl-2-(*p*-alkylthiobenzhydrylthio)ethylamine Hydrochloride—Prepared from the corresponding *p*-alkylthio-thiobenzhydrol and 2-dimethylaminoethyl chloride hydrochloride by the same procedure as (e).

Summary

Nine compounds of N,N-dimethyl-2-(*p*-alkylbenzhydrylthio)ethylamine hydrochloride series and twelve compounds of N,N-dimethyl-2-(*p*-alkylthiobenzhydrylthio)ethylamine hydrochloride series were synthesized. Several compounds of the latter series were found to possess fairly good *in vivo* effect on the Nakayama strain of Japanese B encephalitis virus, while none of the compounds synthesized showed *in vitro* effect against the virus.

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