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141. Mitsuru Furukawa and Takeo Ueda: Studies on Syntheses of Dimethylated Ephedrine Derivatives.

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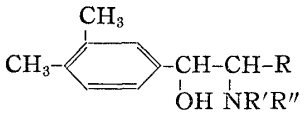
As described in the previous reports,[1,2] compounds of alkylephedrine having monoalkyl group in its benzene ring were synthesized by T. Ueda, *et al.* and some of them were found to be effective on Japanese B encephalitis virus. These findings suggested that the alkyl group in benzene ring is essential for the development of antiviral effect of alkylephedrines, because the effectiveness of ring-substituted alkylephedrine was found superior to that of N-alkylephedrine derivatives. However, the following problems remain to be solved: (1) Effect on antiviral effect of the number of alkyl groups and the number of carbon atoms in the alkyl group attached to the benzene ring and (2) effect of the number of carbon atoms in the side chain on the antiviral effect.

To clarify these points, ring-substituted dimethylephedrine and its related compounds, as shown by the following general formula, were synthesized, in which R, R′, and R″ stand for hydrogen atom or alkyl group.



Although there are many position isomers in ring-substituted dimethylephedrine, this paper describes only the syntheses of ring-substituted 3,4-dimethylephedrine and its related derivatives.

In order to prepare 1-(3,4-dimethylphenyl)-2-amino-1-propanol, *o*-xylene was employed as the starting material, from which 3,4-dimethylphenyl ethyl ketone was obtained by the Friedel-Crafts reaction. By treating 3,4-dimethylphenyl ethyl ketone with methyl nitrite, 3,4-dimethylphenyl α-isonitrosoethyl ketone was prepared, which was converted into the corresponding amino alcohol by catalytic hydrogenation.

There should be two diastereoisomers, i.e. *erythro* and *threo* forms, of 1-(3,4-dimethylphenyl)-2-amino-1-propanol. The configuration of 1-(3,4-dimethylphenyl)-2-amino-1-propanol obtained by catalytic hydrogenation agreed with the *erythro* form, which was prepared in a pure state through oxazoline described by Taguchi, *et al.*[3]

After acetylation of the amino group in both forms of 1-(3,4-dimethylphenyl)-2-amino-1-propanol, the acetyl compound afforded *threo*-2,4-dimethyl-5-(3,4-dimethylphenyl)oxazoline by ring closure with conc. sulfuric acid. When the ring cleavage of the oxazoline was carried out with mineral acids, the configuration of the resulting 1-(3,4-dimethylphenyl)-2-amino-1-propanol was not converted, but inverted with dry acetic acid. Accordingly, it is evident that the *threo* form of 1-(3,4-dimethylphenyl)-2-amino-1-propanol could be prepared from the *erythro* form by way of oxazoline formation.

Next, 1-(3,4-dimethylphenyl)-2-methylamino-1-propanol was prepared from 3,4-dimethylphenyl 1-methylaminoethyl ketone by catalytic hydrogenation. The configuration of 1-(3,4-dimethylphenyl)-2-methylamino-1-propanol thus obtained was found to be the *erythro* form by comparison with the *erythro* form prepared via oxazoline formation.

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1) T. Ueda, K. Takahashi, M. Muraoka, K. Ohki: This Bulletin, **4**, 182(1956).
2) T. Ueda, S. Toyoshima, K. Takahashi, M. Muraoka: Keio J. Med., **8**, 199(1959).
3) T. Taguchi, M. Kojima: Yakugaku Zasshi, **74**, 1293(1954).

As shown in the case of methylation of norephedrine,[4] it was found difficult to prepare 1-(3,4-dimethylphenyl)-2-methylamino-1-propanol from 1-(3,4-dimethylphenyl)-2-amino-1-propanol by methylation with methyl iodide. In this reaction, trimethyl-[2-(3,4-dimethylphenyl)-2-hydroxyisopropyl]ammonium iodide was found as a product. Therefore, 1-(3,4-dimethylphenyl)-2-dimethylamino-1-propanol was obtained from 3,4-dimethylphenyl 1-dimethylaminoethyl ketone by catalytic hydrogenation. The configuration of 1-(3,4-dimethylphenyl)-2-dimethylamino-1-propanol thus obtained was assumed to be *erythro* form, by inference from the case of 1-(3,4-dimethylphenyl)-2-aminopropanol and 1-(3,4-dimethylphenyl)-2-methylamino-1-propanol. By studies on the infrared spectra of ephedrine and its related compounds, it was found by Kanzawa[5] that the wave length difference of the two characteristic absorption bands observed in 3 μ region was larger for the *threo* forms than for the *erythro* ones. Between the absorptions of the assumed *erythro* form and *threo* form of 1-(3,4-dimethylphenyl)-2-dimethylamino-1-propanol, i.e. there is a relationship similar to that between ephedrine and ψ-ephedrine, as can be seen from the experimental result.

The inverted isomer was obtained by inversion of the *erythro* compound with alkali hydroxide after treating with thionyl chloride. Though this reaction product was found mixed with diastereoisomers, the two forms were obtained separately by recrystallization of the mixture from ethanol.

The process of the synthesis of 1-(3,4-dimethylphenyl)-2-dimethylamino-1-propanol is shown in Chart 1.

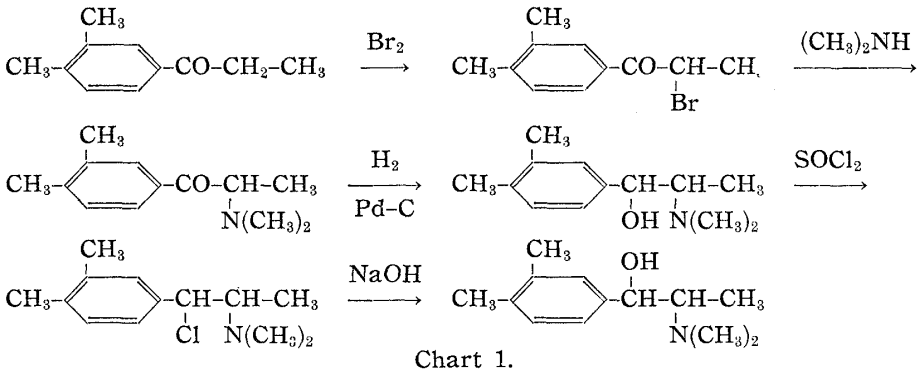


Chart 1.

Finally, the synthesis of 1-(3,4-dimethylphenyl)-2-aminoethanol was carried out according to the method for synthesis of 1-phenyl-2-aminoethanol.[6,7] As shown in Chart 2, *o*-xylene as the starting material was condensed with acetic anhydride in the presence of anhydrous aluminium chloride and by the reaction of the resulting product, 3,4-dimethylphenyl methyl ketone, with butyl nitrite, 3,4-dimethylphenyl isonitrosomethyl ketone was prepared, which was converted into 1-(3,4-dimethylphenyl)-2-aminoethanol by catalytic hydrogenation. The process of the synthesis is shown in Chart 2 and the compounds synthesized are summarized in Table I.

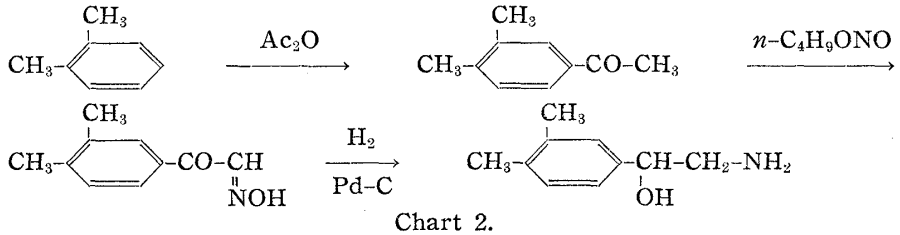
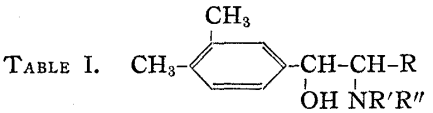


Chart 2.

4) G. Ehrhart: Metallbörse, **20**, 1800(1930)(C. A., **24**, 5755(1930)).
5) T. Kanzawa: This Bulletin, **3**, 71(1955).
6) W. K. Slater: J. Chem. Soc., **1920**, 589.
7) W. H. Hartung: J. Am. Chem. Soc., **50**, 3370(1928).

TABLE I. 

R	R′	R″	Form	m.p. (°C)	Hydrochloride m.p. (°C)	Mol. formula	N (%) Calcd.	N (%) Found
H	H	H	—	—	213～215	$C_{10}H_{16}ONCl$	6.90	7.09
CH_3	H	H	*erythro*	90	150～151	$C_{11}H_{17}ON$	7.81	7.64
CH_3	H	H	*threo*	62～65	195～198	$C_{11}H_{17}ON$	7.81	7.89
CH_3	CH_3	H	*erythro*	55～57	211	$C_{12}H_{20}ONCl$	6.09	5.98
CH_3	CH_3	H	*threo*	107～108	171～173	$C_{12}H_{20}ONCl$	6.09	6.08
CH_3	CH_3	CH_3	*erythro*	76	203～204	$C_{13}H_{22}ONCl$	5.74	5.89
CH_3	CH_3	CH_3	*threo*	75	202～203	$C_{13}H_{22}ONCl$	5.74	5.68
CH_3	CH_3	CH_3	*erythro* methiodide	234～235	—	$C_{14}H_{24}ONI$	4.02	3.97
CH_3	CH_3	CH_3	*threo* methiodide	227	—	$C_{14}H_{24}ONI$	4.02	4.16

As described above, nine compounds were synthesized to screen their pharmacological activities. However, problems still remain to resolve optical isomers from the racemic dimethylated ephedrine derivatives. The work on these problems will be published in the near future.

Experimental

Most of these compounds were prepared in accordance with the synthetic method for *p*-alkylephedrines and only the experimental method not mentioned in the preceding report[1] will be given here.

3,4-Dimethylphenyl Methyl Ketone—Prepared from *o*-xylene and Ac_2O, b.p_{10} 113～114°. Yield, 72%. Thiosemicarbazone : Colorless plates, m.p. 190°. *Anal.* Calcd. for $C_{11}H_{15}N_3S$: N, 18.98. Found: N, 19.06.

3,4-Dimethylphenyl Ethyl Ketone—Prepared from *o*-xylene and propionic anhydride, b.p_5 114°. Yield, 85%. Thiosemicarbazone : Colorless plates, m.p. 153°. *Anal.* Calcd. for $C_{12}H_{17}N_3S$: N, 17.85. Found : N, 17.94.

3,4-Dimethylphenyl 1-Bromoethyl Ketone—Into a solution of 16 g. of 3,4-dimethylphenyl ethyl ketone in 75 cc. of benzene, 16 g. of Br_2 was added dropwise with stirring. After the addition, the reaction mixture was allowed to stand for 1 hr., washed with 10% Na_2CO_3 solution, and dried over anhyd. Na_2SO_4. Removal of the solvent and distillation of the residue gave 20 g. (83%) of 3,4-dimethylphenyl 1-bromoethyl ketone as colorless plates, m.p. 62°; b.p_5 141°.

3,4-Dimethylphenyl Isonitrosomethyl Ketone—Prepared from 3,4-dimethylphenyl methyl ketone and butyl nitrite. Colorless columns, m.p. 117～118°. *Anal.* Calcd. for $C_{10}H_{11}O_2N$: N, 7.91. Found: N, 8.09.

3,4-Dimethylphenyl 1-Isonitrosoethyl Ketone—Methyl nitrite (evolved by dropping a mixture of 9 cc. of conc. HCl and 18 cc. of water into the mixture of 16 g. of 95% $NaNO_2$, 10.5 cc. MeOH, and 10 cc. of water) was introduced into the stirred solution of 34 g. of 3,4-dimethylphenyl ethyl ketone in 150 cc. of Et_2O, while dry HCl was passed through the reaction mixture, the rate of evolution of the nitrite was adjusted to a gentle bubbling. After the reaction mixture was allowed to stand overnight, it was extracted repeatedly with cold NaOH solution. This extract was poured slowly, with stirring, into conc. HCl containing ice. The precipitate thereby obtained was collected on a filter, washed with petr. ether for decolorization, and recrystallized from benzene to 31 g. (81%) of colorless columns, m.p. 109°. *Anal.* Calcd. for $C_{11}H_{13}O_2N$: N, 7.33. Found : N, 7.43.

3,4-Dimethylphenyl 1-Aminoethyl Ketone Hydrochloride—Colorless needles, m.p. 211～212°(decomp.), from EtOH. *Anal.* Calcd. for $C_{11}H_{16}ONCl$: N, 6.55. Found : N, 6.34.

3,4-Dimethylphenyl 1-Methylaminoethyl Ketone Hydrochloride—Excess of 30% solution of $MeNH_2$ in EtOH was added dropwise with cooling and stirring into 5 g. of 3,4-dimethylphenyl 1-bromoethyl ketone in 50 cc. of dehyd. EtOH. The reaction mixture was allowed to stand overnight, poured into water, and the separated oil was extracted with Et_2O. The extract was washed with water and dried over anhyd. Na_2SO_4. The solvent was removed by evaporation in vacuum and the residue was dissolved in EtOH. After introducing dry HCl into the solution, the solution was concentrated. 3,4-Dimethylphenyl 1-methylaminoethyl ketone hydrochloride (1.7 g.) was obtained as colorless needles, m.p. 207～208°, from EtOH. *Anal.* Calcd. for $C_{12}H_{18}ONCl$: N, 6.17. Found : N, 6.00.

3,4-Dimethylphenyl 1-Dimethylaminoethyl Ketone Hydrochloride—Prepared from 3,4-dimethylphenyl α-bromoethyl ketone and excess Me_2NH by the same method as for 3,4-dimethylphenyl 1-methylaminoethyl ketone hydrochloride. Colorless needles from EtOH, m.p. 186～187°. Yield, 76%.

Anal. Calcd. for $C_{13}H_{20}ONCl$: N, 5.79. Found : N, 5.97.

1-(3,4-Dimethylphenyl)-2-aminoethanol Hydrochloride—Colorless needles, m.p. 213~215°, from EtOH. *Anal.* Calcd. for $C_{10}H_{16}ONCl$: N, 6.90. Found : N, 7.06.

***dl-erythro*-1-(3,4-Dimethylphenyl)-2-acetamido-1-propanol**—Colorless needles, m.p. 134~135°, from Et_2O. Yield, 91%. *Anal.* Calcd. for $C_{13}H_{19}O_2N$: N, 6.33. Found : N, 6.48.

***dl-threo*-1-(3,4-Dimethylphenyl)-2-acetamido-1-propanol**—Colorless prisms, m.p. 135~136°, from hydr. EtOH. Yield, 94%. *Anal.* Calcd. for $C_{13}H_{19}O_2N$: N, 6.33. Found : N, 6.14.

***threo*-2,4-Dimethyl-5-(3,4-dimethylphenyl)oxazoline**—Colorless liquid, $b.p_5$ 125°. Yield, 63%. Picrate : Yellow prisms, m.p. 157°, from EtOH. *Anal.* Calcd. for $C_{19}H_{20}O_8N_4$: N, 12.96. Found : N, 12.99.

***dl-erythro*-1-(3,4-Dimethylphenyl)-2-amino-1-propanol**—Colorless columns, m.p. 90°, from hydr. EtOH. IR ν_{max}^{Nujol} cm^{-1} : 3621, 3359, 3300. Yield, 56%. Hydrochloride : Colorless needles, m.p. 150~151°, from the mixed solvent of EtOH and AcOEt.

***dl-erythro*-1-(3,4-Dimethylphenyl)-2-methylamino-1-propanol**—Colorless needles, m.p. 55~57°. IR ν_{max}^{Nujol} cm^{-1} : 3616, 3417, 3360. Yield, 72%. Hydrochloride : Colorless needles, m.p. 211°, from EtOH. *Anal.* Calcd. for $C_{12}H_{20}ONCl$: N, 6.09. Found : N, 5.98.

Other Preparations : With a catalyst prepared from 0.1 g. of $PdCl_2$ and 0.6 g. of charcoal, 2.7 g. of 3,4-dimethylphenyl 1-methylaminoethyl ketone hydrochloride in 20 cc. of water was reduced at room temperature until calculated amount of H_2 was absorbed. The catalyst was filtered off and the filtrate was concentrated. After recrystallization of 2.0 g. (75%) of isolated hydrochloride from EtOH, the salt melted at 211°.

***dl-erythro*-1-(3,4-Dimethylphenyl)-2-dimethylamino-1-propanol**—Prepared from 3,4-dimethylphenyl 1-dimethylaminoethyl ketone by catalytic hydrogenation in the presence of $PdCl_2$; m.p. 76° (from hydr. EtOH). IR ν_{max}^{Nujol} cm^{-1} : 3615, 3332. Hydrochloride : Colorless needles, m.p. 203~204°, from EtOH. *Anal.* Calcd. for $C_{13}H_{22}ONCl$: N, 5.74. Found : N, 5.89.

***dl-erythro*-N,N,N-Trimethyl-[2-(3,4-dimethylphenyl)-2-hydroxyisopropyl]ammonium Iodide**—To a solution of 1 g. of *erythro*-1-(3,4-dimethylphenyl)-2-amino-1-propanol hydrochloride in 10 cc. of water, an excess MeI and NaOH were added and the mixture was heated for 5 hr. on a steam bath. When cool, isolated solid was recrystallized from water to colorless prisms, m.p. 234~235°. *Anal.* Calcd. for $C_{14}H_{24}ONI$: N, 4.02. Found : N, 3.97.

***dl-threo*-1-(3,4-Dimethylphenyl)-2-amino-1-propanol**—Colorless needles, m.p. 62~65°; $b.p_8$ 148. IR ν_{max}^{Nujol} cm^{-1} : 3623, 3352, 3288. Yield, 54%. *Anal.* Calcd. for $C_{11}H_{17}ON$: N, 7.81. Found : N, 7.89. Hydrochloride : Colorless prisms, m.p. 195~198°, from EtOH.

***dl-threo*-1-(3,4-Dimethylphenyl)-2-methylamino-1-propanol**—Colorless needles, m.p. 107~108°; $b.p_6$ 139°. IR ν_{max}^{Nujol} cm^{-1}: 3621, 3321. Yield, 93%. *Anal.* Calcd. for $C_{12}H_{18}ON$: N, 7.25. Found : N, 7.47. Hydrochloride : Colorless needles, m.p. 171~173°, from EtOH. *Anal.* Calcd. for $C_{12}H_{20}ONCl$: N, 6.09. Found : N, 6.08.

***dl-threo*-1-(3,4-Dimethylphenyl)-2-dimethylamino-1-propanol**—To 2 g. of *erythro*-1-(3,4-dimethylphenyl)-2-methylamino-1-propanol hydrochloride, 4 cc. of $SOCl_2$ was added. After allowing to stand for 3 hr. at room temp., the reaction mixture was refluxed for 1.5 hr. on a boiling water bath and excess $SOCl_2$ was evaporated under a reduced pressure. The residue with 50 cc. of 5% NaOH added, was heated at 60° for 3 hr. and extracted with Et_2O. After washing with water and drying over anhyd. Na_2SO_4, the solvent was removed by evaporation and the residue was distilled. Dry HCl was passed through the distillate in EtOH and concentrated. Recrystallization from EtOH gave colorless prisms, m.p. 202~203°. Yield, 60% (1.2 g.). *Anal.* Calcd. for $C_{13}H_{22}ONCl$: N, 5.74. Found : N, 5.68. Free base : m.p. 75°. IR ν_{max}^{Nujol} cm^{-1} : 3619, 3324.

***dl-threo*-N,N,N-Trimethyl-[2-(3,4-dimethylphenyl)-2-hydroxyisopropyl]ammonium Iodide**—Prepared from *threo*-1-(3,4-dimethylphenyl)-2-aminopropanol and excess MeI. Colorless columns, m.p. 227°, from water. *Anal.* Calcd. for $C_{14}H_{24}ONI$: N, 4.02. Found : N, 4.16.

Summary

dl-1-(3,4-Dimethylphenyl)-2-aminopropanol derivatives and *dl*-1-(3,4-dimethylphenyl)-2-aminoethanol were prepared from the corresponding amino ketones by catalytic hydrogenation in the presence of palladium-carbon catalyst. Though 3,4-dimethylphenyl 1-methylaminoethyl ketone and 3,4-dimethylphenyl 1-dimethylaminoethyl ketone were obtained by treatment with the corresponding bromo ketone and methylamine or dimethylamine, 3,4-dimethylphenyl 1-aminoethyl ketone was prepared from isonitroso ketone, which was synthesized from 3,4-dimethylphenyl ethyl ketone and methyl nitrite, by catalytic hydrogenation in the presence of palladium-carbon catalyst. *dl*-1-(3,4-Dimethylphenyl)-2-amino-1-propanol derivatives obtained by such a method were found to be the *erythro* form. The inverted isomers of these compounds were prepared by applying the method of Taguchi, *et al.* or by treatment with thionyl chloride.

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