after an administration of EHB and completed within 24 hrs. (100 or 200 mg./kg.) or 48 hrs. (400 mg./kg.). About 32% of 3-keto-EHB administered was rapidly excreted but the fate of the remainder was undetectable.

Partial hepatectomy prolonged the period of excretion of 3-keto-EHB and decreased the quantity of that. Unchanged EHB was detected in partially hepatectomized rats.

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91. Takeo Ueda, Shigeshi Toyoshima, Kiyoshi Takahashi, and Masako Muraoka: Studies on Syntheses and Pharmacological Effects of N-Alkylephedrines and their Ammonium Salt Derivatives.[1]

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Ephedrine, as is well known, is one of the most interesting as a sympathomimetic in regard not only to toxicity (tachycardia, hypertension, anxiety, etc.), but also to its effectiveness. Many attempts have hitherto been made to improve ephedrine by decreasing toxicity and increasing the pharmacological effect, but according to the authors' view, it might be said that drugs which are reliably superior to ephedrine on the balance of effect and toxicity have not been found in any clinical trials.

For the purpose of finding improved substitutes for ephedrine, N-alkyl derivatives of ephedrine and their ammonium salts were taken up by the present authors.

It was reported by Misawa[2] that N-methylephedrine might possess an effect twice as strong as that of ephedrine regardless of its optical isomerism. However, it was shown by Shimamoto[3] that difference was found between the effects of three optical isomers of N-methylephedrine and that *l*-N-methylephedrine showed an effect only one-third as strong as that of *l*-ephedrine in the dog's bronchial preparation by the method of Konzett. Therefore, there remain many questions to be solved regarding pharmacological properties of N-alkylated ephedrine.

Misawa's work is of interest as indicating one direction of the improvements of ephedrine. Thus, in an attempt to remove the defects of ephedrine, N-alkyl derivatives of ephedrine were taken up by the present authors, since they have not been systematically studied with the exception of N-methylephedrine.

This paper describes the syntheses and pharmacological effects of N-alkylephedrines and their quaternary ammonium salts. Nitrogen atom in the side-chain in ephedrine was alkylated and the N-alkylephedrines thus obtained were converted into ammonium salt with methyl iodide (or ethyl iodide), because of the utility of ammonium salts of some kind of drugs.

Alkyl bromide to be employed as the alkylating agents were prepared in the usual manner. N-alkylation was effected by heating a mixture of ephedrine base and alkyl bromide at 140~170° for 3~5 hours under pressure, when the reaction proceeded with decreasing yield of the desired substance as the number of carbons in

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1) T. Ueda, K. Takahashi, M. Muraoka: Papers read before the Annual Meeting of the Pharmaceutical Society of Japan (1955).
2) K. Misawa: Tokyo Med. J., **68**, No.3, 3 (1951); **71**, 439 (1954).
3) Shimamoto: Japan. J. Pharm. & Chem. **27**, 460 (1955).

alkyl bromide increased, and there was, in the end, no yield at C_5, viz. amyl bromide. Several trials with modification of reaction conditions (temperature, molar ratio of the reactants, reaction time,) were fruitless. Nevertheless, with alkyl bromide of higher moleculer weight than amyl, the alkylation was successfully carried out when equimolar amount of pulverized potassium hydroxide was added to the mixture of the reactants. Thus, N-alkylephedrines, N-amyl to N-decyl, were prepared by the latter modified method.

N-Alkylephedrines were very easily affected by methyl or ethyl iodide to afford the corresponding ammonium salts, most of which, however, remained as a viscous oily substance without solidification, and all the endeavour to make them solid was in vain. This report describes only the compounds obtained in a solid state.

Though ephedrine base liberated from ephedrine hydrochloride J.P. VI was employed as the starting material, it might be subjected to the inversion of steric configuration in the course of reactions. Therefore, the stereochemical problem of ephedrine derivatives obtained in the present comes into the question. Every effort has been made to solve this problem, which will be discussed in the future.

The pharmacological effect of the compounds synthesized was examined by the Magnus method and these effects were compared with that of *l*-ephedrine, as described in the experimental part. Among these compounds, N-butyl-, N-hexyl-, N-heptyl-ephedrine, and dimethylbutyl-(*β*-phenyl-*β*-hydroxyisopropyl)ammonium iodide were found to have pharmacological effects almost equal to that of *l*-ephedrine, in the balance of inhibitory effect on tonic contractions by acetylcholine, histamine, and barium chloride. All the other compounds except the above four were considered inferior to *l*-ephedrine in the balance of the inhibitory effects. However, questions still remain regarding the stereoisomerism of the above compounds. Works on this problem is in progress.

Experimental

1-Phenyl-2-(methylethylamino)propanol-(1) Hydrochloride (E-1)—A mixture of 11.7 g. of ephedrine and 11.1 g. of EtI was warmed for 0.5 hr. on a water bath. The reaction mixture was diluted with water, acidified with 10% HCl, and washed with ether to remove the unchanged substance and impurities. The aqueous layer was basified with 15% NaOH, and the liberated amine was extracted with ether and dried over KOH. On evaporation of ether, the residue was distilled under diminished pressure to afford N-ethylephedrine, $b.p_{15.5}$ 143~144.5°. Yield, 7.3 g. (53%). By passing dried HCl gas through the ethereal solution of the distillate, the hydrochloride was obtained, which was purified by two reprecipitations from a solution in a small amount of abs. EtOH with dried ether to colorless fine needles, m.p. 175~177°. *Anal.* Calcd. for $C_{12}H_{19}ON \cdot HCl$: N, 6.10. Found: N, 6.25.

1-Phenyl-2-(methylpropylamino)propanol-(1) Hydrochloride (E-2)—6.7 g. of ephedrine was heated with 6.2 g. of PrBr in an autoclave for 3 hrs. at 130° (oil-bath temp.). The treatments after reaction were the same as for (E-1). The yield of N-propylephedrine, $b.p_7$ 130~135°, was 5.5 g. (66%). Hydrochloride: Colorless needles, m.p. 141~144°. *Anal.* Calcd. for $C_{13}H_{21}ON \cdot HCl$: N, 5.75. Found: N, 5.58.

1-Phenyl-2-(methylbutylamino)propanol-(1) Hydrochloride (E-3)—9.5 g. of ephedrine was heated with 7.9 g. of BuBr in an autoclave for 3 hrs. at 130° (oil-bath temp.). The treatments after reaction were the same as for (E-1). The yield of N-butylephedrine, $b.p_{7\sim8}$ 140~148°, was 8 g. (63%). Hydrochloride: Colorless needles, m.p. 95~97°. *Anal.* Calcd. for $C_{14}H_{23}ON \cdot HCl$: N, 5.44. Found: N, 5.42.

General Procedure for Alkylation of Ephedrine with Alkyl Halide of C_5~C_{10}—A mixture (1:1:1) of ephedrine, alkyl halide, and pulverized KOH was heated in an autoclave for 3~5 hrs. at 140~170° (oil-bath temp.). The treatment after the reaction was the same as for (E-1). When decyl bromide was employed, the extracted base, without purification by distillation, was directly converted into the corresponding hydrochloride.

1-Phenyl-2-(methylamylamino)propanol-(1) Hydrochloride (E-4)—A mixture of 8 g. ephed-

rine, 8.2 g. AmBr, and 4.1 g. pulverized KOH was heated for 5 hrs. at 140~150° (oil-bath temp.). 8 g. (71%) of N-amylephedrine, $b.p_7$ 150~154°, was obtained. Hydrochloride: Colorless needles, m.p. 177~183°. *Anal.* Calcd. for $C_{15}H_{25}ON \cdot HCl$: N, 5.16. Found: N, 5.29.

1-Phenyl-2-(methylhexylamino)propanol-(1) Hydrochloride (E-5)—A mixture of 15 g. ephedrine, 15 g. hexyl bromide, and pulverized KOH was heated for 5 hrs. at 140~150° (oil-bath temp.). 16.5 g. (70%) of N-hexylephedrine, b.p. 125~133°, was obtained. Hydrochloride: Colorless plates, m.p. 121~124°. *Anal.* Calcd. for $C_{16}H_{27}ON \cdot HCl$: N, 4.90. Found: N, 4.88.

1-Phenyl-2-(methylheptylamino)propanol-(1) Hydrochloride (E-6)—A mixture of 15.5 g. ephedrine, 20.2 g. heptyl bromide, and 7.4 g. pulverized KOH was heated for 5 hrs. at 150~160° (oil-bath temp.). 18 g. (72%) of N-heptylephedrine, $b.p_1$ 144~149°, was obtained. Hydrochloride: Colorless needles, m.p. 135~140°. *Anal.* Calcd. for $C_{17}H_{29}ON \cdot HCl$: N, 4.67. Found: N, 4.75.

1-Phenyl-2-(methyloctylamino)propanol-(1) Hydrochloride (E-7)—A mixture of 12.5 g. ephedrine, 15 g. octyl bromide, and 15 g. pulverized KOH was heated for 5 hrs. at 150~160° (oil-bath temp.). 14.3 g. (69%) of N-octylephedrine, $b.p_5$ 182~186°, was obtained. Hydrochloride: Colorless needles, m.p. 120~123°. *Anal.* Calcd. for $C_{18}H_{31}ON \cdot HCl$: N, 4.47. Found: N, 4.28.

1-Phenyl-2-(methylnonylamino)propanol-(1) Hydrochloride (E-8)—A mixture of 12.3 g. ephedrine, 18.6 g. nonyl bromide, and 5.9 g. pulverized KOH was heated for 5 hrs. at 160~170° (oil-bath temp.). 17 g. (78%) of N-nonylephedrine, $b.p_1$ 170~174°, was obtained. Hydrochloride: Colorless plates, m.p. 99~103°. *Anal.* Calcd. for $C_{19}H_{33}ON \cdot HCl$: N, 4.27. Found: N, 4.28.

1-Phenyl-2-(methyldecylamino)propanol-(1) Hydrochloride (E-9)—A mixture of 6.7 g. ephedrine, 10.8 g. decyl bromide, and 32 g. pulverized KOH was heated for 5 hrs. at 160~170° (oil-bath temp.). This substance could not be purified by distillation. Hydrochloride: Colorless plates, m.p. 102~108°. *Anal.* Calcd. for $C_{20}H_{35}ON \cdot HCl$: N, 4.10. Found: N, 4.06.

Syntheses of Trialkyl-(β-hydroxy-β-phenylisopropyl)ammonium Iodide—A mixture of 1 mole of N-alkylephedrine and 1.2 mole MeI or EtI was refluxed on a water bath for 30 mins. (1 hr., when EtI was employed). The excess of MeI or EtI was removed *in vacuo* and the residue was washed with AcOEt, if necessary, and recrystallized several times from a suitable solvent.

Trimethyl-(β-hydroxy-β-phenylisopropyl)ammonium Iodide (S-1)—Prepared by Kanao's procedure.[4] After reprecipitation from a solution in abs. EtOH with dried ether, the precipitate was recrystallized from water to colorless pillars, m.p. 210~212°. *Anal.* Calcd. for $C_{12}H_{20}ONI$: N, 4.36. Found: N, 4.32.

Dimethylethyl-(β-hydroxy-β-phenylisopropyl)ammonium Iodide (S-2)—Prepared by the treatment of N-ethylephedrine with MeI and recrystallized twice from water to colorless plates, m,p. 180~182°. *Anal.* Calcd. for $C_{13}H_{22}ONI$: N, 4.18. Found: N, 4.32.

Dimethylpropyl-(β-hydroxy-β-phenylisopropyl)ammonium Iodide (S-3)—Prerared by the treatment of N-propylephedrine with MeI and recrystallized from water to colorless plates, m.p. 152~155°. *Anal.* Calcd. for $C_{14}H_{24}ONI$: N, 4.02. Found: N, 4.08.

Dimethylbutyl-(β-hydroxy-β-phenylisopropyl)ammonium Iodide (S-4)—Prepared by the treatment of N-butylephedrine with MeI, washed with AcOEt, and recrystallized twice from water to colorless plates, m.p. 151~153°. *Anal.* Calcd. for $C_{15}H_{26}ONI$: N, 3.87. Found: N, 3.91.

Dimethylamyl-(β-hydroxy-β-phenylisopropyl)ammonium Iodide (S-5)—Prepared by the treatment of N-amylephedrine with MeI, reprecipitated twice from a solution in abs. EtOH with dried ether, and recrystallized from water to colorless needles, m.p. 125~127°. *Anal.* Calcd. for $C_{16}H_{28}ONI$: N, 3.71. Found: N, 3.68.

Dimethylhexyl-(β-hydroxy-β-phenylisopropyl)ammonium Iodide (S-6)—Prepared by the treatment of N-hexylephedrine with MeI and recrystallized from water to colorless needles, m.p. 95~102°. *Anal.* Calcd. for $C_{17}H_{30}ONI$: N, 3.58. Found: N, 3.68.

Methyldiethyl-(β-hydroxy-β-phenylisopropyl)ammonium Iodide (S-7)—Prepared by the treatment of N-ethylephedrine with EtI and recrystallized twice from water to colorless plates, m.p. 168~170°. *Anal.* Calcd. for $C_{14}H_{24}ONI$: N, 4.01. Found: N, 3.93.

Methylethylpropyl-(β-hydroxy-β-phenylisopropyl)ammonium Iodide (S-8)—Prepared by the treatment of N-propylephedrine with EtI, washed with AcOEt, and recrystallized twice from water to colorless plates, m.p. 192~196°. *Anal.* Calcd. for $C_{15}H_{26}ONI$: N, 3.86. Found: N, 3.93.

Methylethylbutyl-(β-hydroxy-β-phenylisopropyl)ammonium Iodide(S-9)—Prepared by the treatment of N-butylephedrine with EtI, washed with ether, reprecipitated from a solution in abs. EtOH with dried ether, and recrystallized twice from water to colorless needles, m.p. 137~141°. *Anal.* Calcd. for $C_{16}H_{28}ONI$: N, 3.71. Found: N, 3.70.

Biological Procedures

The pharmacological effect of the compounds synthesized were examined by the Magnus Method.

4) S. Kanao: J. Pharm. Soc. Japan, **540**, 113 (1927).

Toxicity—Six mice of about 12 g. body weight were used in one group. Solutions of the compounds were injected into groups of mice through the tail vein, and the solutions were made with two-fold dilution and injected until survival ratios became zero. From these data, LD_{50} was calculated by the method of Behrens and Kärber.

Efficacy (Magnus Method)—Intestines (ileum) were excised from guinea pigs and suspended horizontally in a thermostatic bath containing ca. 12.5 cc. of well-oxygenated Tyrode solution at 37°. The tonic contractions by the action of acetylcholine, histamine, or barium chloride on the ileum were recorded on a kymograph. After getting the maximum contraction (30~60 secs.), each concentration of the compounds to be examined was added and then the inhibitory effect of the chemicals on tonic contraction was observed. As the control, *l*-ephedrine was used. The results are shown in Table I, in which effectiveness of the compounds is represented by the effective coefficient and the toxicity by LD_{50}. Ratio of C/T to Cs/Ts was calculated, as efficacy coefficient, where C and Cs represent the respective minimum molar concentration of the compounds and *l*-ephedrine, and T and Ts are the toxicity of the compound and of *l*-ephedrine, respectively.

TABLE I.

Sample No.	Toxicity LD_{50} (mg./kg.)	Inhibitory Coefficients against Acetylcholine	Histamine	$BaCl_2$
K	140.6	1.0	1.0	1.0
E-1	60.0	0.5	2.5	0.5
E-2	70.0	0.2	2.2	0.4
E-3	30.0	0.6	1.1	1.1
E-4	46.7	3.2	6.4	0.3
E-5	27.5	1.2	1.2	0.6
E-6	32.3	0.6	1.2	0.6
E-7	14.0	1.4	2.8	1.4
E-8	8.3	5.1	5.1	2.5
E-9	27.5	0.2	7.7	7.7
S-1	40.0	0.1	1.0	5.1
S-2	30.0	0.14	1.4	14.2
S-3	30.0	0.8	1.5	0.8
S-4	13.7	0.3	1.7	16.8
S-5	14.0	0.3	3.2	1.6
S-6	7.7	3.2	6.4	32.4
S-7	27.5	0.1	1.6	8·4
S-8	12.7	0.4	1.8	18.1
S-9	5.3	4.6	46.0	46.7

K: Ephedrine Hydrochloride (J.P. VI) as the control. The sample numbers correspond to those in the experimental part.

Summary

N-Alkylephedrines were synthesized by heating a mixture of ephedrine and alkyl bromide under pressure. The alkylation proceeded with decreasing yield of the desired substance as the number of carbons of alkyl bromide increased, and there was, in the end, no yield at C_5, viz., amyl bromide. With alkyl bromides of higher moleculer weight than amyl, the alkylation was successfully carried out by the addition of equimolar amount of pulverized KOH. The N-alkylephedrines thus obtained were converted to the ammonium salts with methyl or ethyl iodide.

The pharmacological effects of the compounds synthesized were examined by the Magnus method and these effects were compared with that of *l*-ephedrine. Among these compounds, N-butyl-, N-hexyl-, N-heptylephedrines, and dimethylbutyl-(β-phenyl-β-hydroxyisopropyl)ammonium iodide were found to have pharmacological effects almost equal to that of *l*-ephedrine, in the balance of inhibitory effect on tonic contractions by acetylcholine, histamine, and barium chloride.

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