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35. Takeo Ueda, Kiyoshi Takahashi, Masako Muraoka, and Keiko Ohki: Studies on the Syntheses of Ring Substituted *p*-Alkylephedrines and *p*-Alkylnorephedrines

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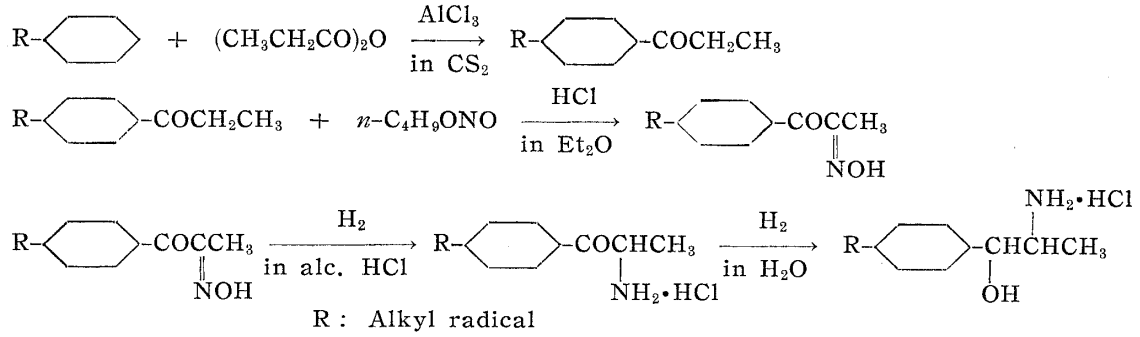
As previously reported,[1] N-alkylephedrines and their ammonium salts were synthesized and their pharmacological activities examined by the present authors. As a next stage, in order to study the relationship between the effect of alkyl chains attached to the N-atom and that of alkyl chains introduced into the benzene ring upon the activity of ephedrine, attempt was made to introduce a normal alkyl chain in the benzene ring of ephedrine and norephedrine, instead of putting it on the nitrogen atom in the side chain of ephedrines. This paper describes only the syntheses of *p*-alkylephedrines and *p*-alkylnorephedrines, and the pharmacological studies of these compounds here obtained will be reported in the near future.

Alkylbenzenes, employed as the starting materials, were prepared by the Wurz-Fittig reaction from alkyl bromides and bromobenzenes,[2] or by the method of Gilman and Heck from benzylmagnesium chlorides and alkyl *p*-toluenesulfonates.[3] Alkylbenzenes thus obtained were condensed with propionic anhydride in the presence of aluminum chloride into *p*-alkylpropiophenones. These ketones were then converted into *p*-alkyl-α-isonitrosopropiophenones by treatment with butyl nitrite.[4] When the isonitrosoketones were obtained as an oily substance, it was extracted with benzene and, after drying the extract, the solvent was removed by evaporation. The residue was submitted to successive reduction without further purification.

According to the finding of Hartung and Munch,[4] these isonitrosoketones should be reduced directly into the corresponding amino alcohols by catalytic hydrogenation in the presence of palladium-carbon catalyst. It appeared, however, that the reducible tendency of the isonitrosoketone decreased with increasing number of carbon in the alkyl chain. Therefore, stepwise catalytic hydrogenation was adopted here, and this procedure was used in all the compounds. *p*-Alkyl-α-isonitrosopropiophenones were first reduced into amino ketones in dehydrated ethanol containing hydrogen chloride in the presence of palladium-carbon catalyst. *p*-Alkyl-α-aminopropiophenone hydrochlorides were derived to amino alcohols in water by the aid of the same kind of catalyst. The whole process is shown below.



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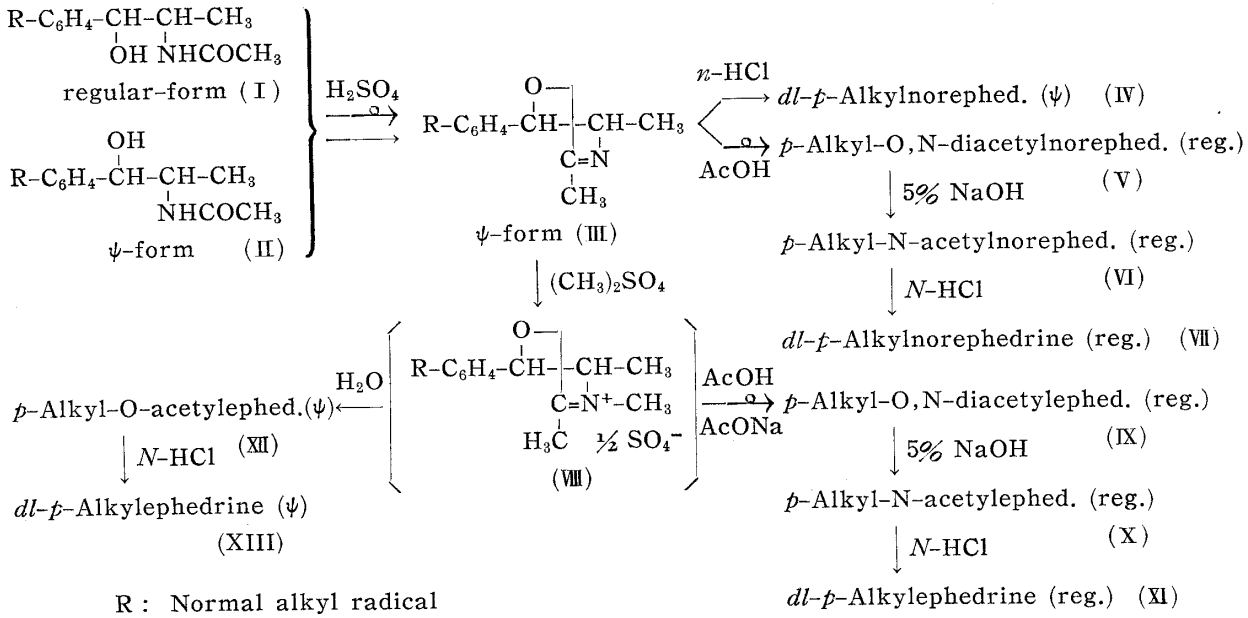
1) T. Ueda, S. Toyoshima, K. Takahashi, M. Muraoka: This Bulletin, **3**, 465(1955).
2) Org. Syntheses, **25**, 11(1945).
3) *Ibid.*, **10**, 4(1930).
4) W. H. Hartung, J. C. Munch: J. Am. Chem. Soc., **51**, 2262(1929).

The α-(p-alkylphenyl)-β-aminopropanol thus obtained, viz., p-alkylnorephedrine, might probably be a mixture of compounds of regular- and pseudo-forms. Then, in order to isolate each of them separately from the mixture, the elaborate method of Taguchi *et al.*[5] was applied in a modified form, and satisfactory results were obtained as shown in the following chart :



R : Normal alkyl radical

After acetylation of the amino group in p-alkylnorephedrine, a mixture of regular- and ψ-form[6](I, II), followed by ring closure by dehydration with conc. sulfuric acid uniformly afforded *dl*-ψ-2,4-dimethyl-5-(p-alkylphenyl)oxazoline (III). The oxazoline (III) was converted by refluxing with N hydrochloric acid into *dl*-ψ-p-alkylnorephedrine (IV) (retention). On the other hand, by treating the oxazoline (III) with dehydrated acetic acid, inversion into a compound of regular-form took place in this case, which was boiled with 5% alkali and then with N hydrochloric acid to give, via the N-acetyl compound (VI), regular *dl*-p-alkylnorephedrine (VII).

In order to obtain the compounds of p-alkylephedrine series, above-mentioned oxazoline (III) was methylated with dimethyl sulfate to N-methyloxazoline (VIII). This underwent inversion, on being treated with a mixture of dehyd. acetic acid and anhydrous sodium acetate, under moisture-free conditions, into O,N-diacetyl compound of the regular-form (IX). The compound (IX) was boiled with 5% alkali and then with N hydrochloric acid to afford, through the N-acetyl compound (X), regular *dl*-p-alkylephedrine (XI). In addition, *dl*-ψ-p-alkylephedrine (XIII) was also obtained by refluxing N-methyloxazoline (VIII) with N hydrochloric acid.

By these methods, p-methyl-, p-ethyl-, p-propyl-, p-butyl-, p-amyl-, p-hexyl-, p-heptyl-, p-octyl-, p-decyl-, p-dodecyl-ephedrines and the corresponding norephedrines were easily obtained. In addition, these ring substituted ephedrines and norephedrines were separated into the regular- and pseudo-series. None of these compounds, except the p-methyl derivative, have been seen in the literatures.

Accoring to the findings with pharmacological experiments by Toyoshima *et al.*, it is of interest that these compounds show not only actions characteristic of ephedrine and its analogs, but also antimicrobial actions, especially antiviral effects. The

5) T. Taguchi, M. Kojima : J. Pharm. Soc. Japan, **74**, 1293(1954).
6) S. Kanao : *Ibid*, **57**, 1072(1927).

works on these problems will be described in medical journals in the near future.

The authors wish to express their gratitude to the members of the Central Analysis Room in University of Kyoto for carrying out the elementary analyses of these compounds.

Experimental

1) General Procedure of Synthesis of *p*-Alkylpropiophenone from Alkylbenzene and Propionic Anhydride—One-half mole of propionic anhydride was added slowly with rapid stirring to a mixture of 0.5 mole of alkylbenzenes and 1.1 moles of powdered anhyd. $AlCl_3$ in 200 cc. of CS_2. The mixture was then warmed on a water bath and stirring was continued until no more HCl was evolved. After cooling, the reaction mixture was poured into crushed ice and extracted with ether. The CS_2-ethereal layer was washed with water, with 10% NaOH, and finally with water, and dried over $CaCl_2$. After the solvent was removed by evaporation, the residue was distilled *in vacuo*.

***p*-Methylpropiophenone**—Prepared from toluene and propionic anhydride. b.$p_{5.5}$ 97~98°. Semicarbazone: Colorless needles, m.p. 190~192°. *Anal.* Calcd. for $C_{11}H_{15}ON_3$: N, 20.47. Found: N, 20.20.

***p*-Ethylpropiophenone**—Prepared from ethylbenzene and propionic anhydride. b.$p_{3.5}$ 101~106°. Semicarbazone: Colorless needles, m.p. 146~149°. *Anal.* Calcd. for $C_{12}H_{17}ON_3$: N, 19.16. Found: N, 19.56.

***p*-Propylpropiophenone**—Prepared from propylbenzene and propionic anhydride. b.p_4 114~116°. Semicarbazone: Colorless needles, m.p. 138~141°. *Anal.* Calcd. for $C_{13}H_{19}ON_3$: N, 18.01. Found: N, 18.14.

***p*-Butylpropiophenone**—Prepared from butylbenzene and propionic anhydride. b.$p_{3\sim4}$ 122~124°. Semicarbazone: Colorless needles, m.p. 132~135°. *Anal.* Calcd. for $C_{14}H_{21}ON_3$: N, 17.00. Found: N, 16.76.

***p*-Amylpropiophenone**—Prepared from amylbenzene and propionic anhydride. b.$p_{4.5}$ 142~148°. Semicarbazone: Colorless plates, m.p. 130~132°. *Anal.* Calcd. for $C_{15}H_{23}ON_3$: N, 16.08. Found: N, 15.92.

***p*-Hexylpropiophenone**—Prepared from hexylbenzene and propionic anhydride. b.$p_{2.5\sim3}$ 140~146°. Semicarbazone: Colorless plates, m.p. 135~137°. *Anal.* Calcd. for $C_{16}H_{25}ON_3$: N, 15.26. Found: N, 15.15.

***p*-Heptylpropiophenone**—Prepared from heptylbenzene and propionic anhydride. b.$p_{1.5}$ 128~130°. Semicarbazone: Colorless plates, m.p. 124~127°. *Anal.* Calcd. for $C_{17}H_{27}ON_3$: N, 14.52. Found: N, 14.83.

***p*-Octylpropiophenone**—Prepared from octylbenzene and propionic anhydride. b.p_1 153~157°. Semicarbazone: Colorless needles, m.p. 120~122°. *Anal.* Calcd. for $C_{18}H_{29}ON_3$: N, 13.85. Found: N, 14.00.

***p*-Decylpropiophenone**—Prepared from decylbenzene and propionic anhydride. b.p_2 181~187°. Semicarbazone: Colorless plates, m.p. 124~127° *Anal.* Calcd. for $C_{20}H_{33}ON_3$: N, 12.68. Found: N, 12.59.

***p*-Dodecylpropiophenone**—Prepared from dodecylbenzene and propionic anhydride. Recrystallized from 95% EtOH to colorless needles, m.p. 33~35°. Semicarbazone: Colorless plates, m.p. 115~116°. *Anal.* Calcd. for $C_{22}H_{37}ON_3$: N, 11.69. Found: N, 11.40.

2) General Procedure of Preparation of *p*-Alkyl-α-isonitrosopropiophenone—0.3 mole of freshly distilled butyl nitrite was added in 2~3 cc. portions with stirring to a solution of 0.3 mole of *p*-alkylpropiophenone in 200 cc. of anhyd. ether, while HCl was passed through the reaction mixture. Stirring and bubbling of HCl were continued for the total time required for the addition of the nitrite. After the addition of the nitrite, the same procedure was continued for 15 mins. and the mixture was then allowed to stand overnight. The mixture was slowly stirred into dil. NaOH solution containing pieces of ice and the ethereal layer was repeatedly extracted with cold alkali until no more product was obtained. The alkaline extracts were slowly stirred into conc. HCl containing sufficient ice to keep the reaction mixture cold. In this manner, the isonitrosoketone was obtained as an oily or a solid substance. The former was extracted with benzene and dried over $CaCl_2$. On evaporation of the benzene, the residue was submitted to subsequent reduction without further purification. The latter was collected by filtration and recrystallized from benzene.

3) General Procedure for the Reduction of *p*-Alkyl-α-isonitrosopropiophenone into *p*-Alkyl-α-aminopropiophenone Hydrochloride—A solution of 0.06 mole of *p*-alkyl-α-isonitrosopropiophenone in 150 cc. of dehyd. EtOH containing 7 g. of dried HCl was shaken in H_2 atmosphere in the presence of Pd-C catalyst at a room temp., until calculated amount of H_2 was absorbed. The catalyst was filtered off and the solid mass that appeared on cooling or on concentration was collected by filtration and recrystallized from EtOH.

***p*-Methyl-α-aminopropiophenone Hydrochloride (A-I)**—Prepared from *p*-methyl-α-isonitroso-

propiophenone. Colorless plates, m.p. 215~218°. *Anal.* Calcd. for $C_{10}H_{13}ON \cdot HCl$: N, 7.05. Found: N, 7.20.

p-**Ethyl-α-aminopropiophenone Hydrochloride** (**A-II**)—Prepared from *p*-ethyl-α-isonitrosopropiophenone. Colorless plates, m.p. 228~232°. *Anal.* Calcd. for $C_{11}H_{15}ON \cdot HCl$: N, 6.56. Found: N, 6.51.

p-**Propyl-α-aminopropiophenone Hydrochloride** (**A-III**)—Prepared from *p*-propyl-α-isonitrosopropiophenone. Colorless plates, m.p. 216~220°. *Anal.* Calcd. for $C_{12}H_{17}ON \cdot HCl$: N, 6.15. Found: N, 6.20.

p-**Butyl-α-aminopropiophenone Hydrochloride** (**A-IV**)—Prepared from *p*-butyl-α-isonitrosopropiophenone. Colorless plates, m.p. 215~218°. *Anal.* Calcd. for $C_{13}H_{19}ON \cdot HCl$: N, 5.79. Found: N, 5.82.

p-**Amyl-α-aminopropiophenone Hydrochloride** (**A-V**)—Prepared from *p*-amyl-α-isonitrosopropiophenone. Colorless plates, m.p. 220~222°. *Anal.* Calcd. for $C_{14}H_{21}ON \cdot HCl$: N, 5.48. Found: N, 5.61.

p-**Hexyl-α-aminopropiophenone Hydrochloride** (**A-VI**)—Prepared from *p*-hexyl-α-isonitrosopropiophenone. Colorless plates, m.p. 214~218°. *Anal.* Calcd. for $C_{15}H_{23}ON \cdot HCl$: N, 5.20. Found: N, 5.27.

p-**Heptyl-α-aminopropiophenone Hydrochloride** (**A-VII**)—Prepared from *p*-heptyl-α-isonitrosopropiophenone. Colorless plates, m.p. 208~212°. *Anal.* Calcd. for $C_{16}H_{25}ON \cdot HCl$: N, 4.94. Found : N, 4.85.

p-**Octyl-α-aminopropiophenone Hydrochloride** (**A-VIII**)—Prepared from *p*-octyl-α-isonitrosopropiophenone. Colorless plates, m.p. 203~207°. *Anal.* Calcd. for $C_{17}H_{27}ON$:HCl : N, 4.70. Found : N, 4.74.

p-**Decyl-α-aminopropiophenone Hydrochloride** (**A-X**)—Prepared from *p*-decyl-α-isonitrosopropiophenone. Colorless plates, m.p. 207~212°. *Anal.* Calcd. for $C_{19}H_{31}ON \cdot HCl$: N, 4.30. Found: N, 4.38.

p-**Dodecyl-α-aminopropiophenone Hydrochloride**(**A-XII**)—Prepared from *p*-dode cyl-α-isonitrosopropiophenone. Colorless plates, m.p. 208~212°. *Anal.* Calcd. for $C_{21}H_{35}ON \cdot HCl$: N, 4.10. Found: N, 4.05.

4) General Procedure for the Reduction of *p*-Alkyl-α-aminopropiophenone Hydrochloride into α-(*p*-Alkylphenyl)-β-aminopropanol Hydrochloride—A solution of *p*-alkyl-α-aminopropiophenone hydrochloride in water was shaken in H_2 atmosphere in the presence of Pd-C catalyst at room temp., until calculated amount of H_2 was absorbed. The catalyst was removed by filtration, the filtrate was concentrated under a reduced pressure, and the residual product was reprecipitated from a solution in dehyd. EtOH with dried ether.

α-(*p*-**Methylphenyl**)-β-**aminopropanol Hydrochloride** (**B-I**)—Prepared from (A-I). Colorless plates, m.p. 197~202°. *Anal.* Calcd. for $C_{10}H_{15}ON$:HCl : N, 6.95. Found : N, 6.95.

α-(*p*-**Ethylphenyl**)-β-**aminopropanol Hydrochloride** (**B-II**)—Prepared from (A-II). Colorless plates, m.p. 211~215°. *Anal.* Calcd. for $C_{11}H_{17}ON \cdot HCl$: N, 6.49. Found : N, 6.43.

α-(*p*-**Propylphenyl**)-β-**aminopropanol Hydrochloride** (**B-III**)—Prepared from (A-III). Colorless plates, m.p. 205~210°. *Anal.* Calcd. for $C_{12}H_{19}ON \cdot HCl$: N, 6.10. Found : N, 6.03.

α-(*p*-**Butylphenyl**)-β-**aminopropanol Hydrochloride** (**B-IV**)—Prepared from (A-IV). Colorless plates, m.p. 215~218°. *Anal.* Calcd. for $C_{13}H_{21}ON \cdot HCl$: N, 5.75. Found : N, 5.77.

α-(*p*-**Amylphenyl**)-β-**aminopropanol Hydrochloride** (**B-V**)—Prepared from (A-V). Colorless plates, m.p. 214~217°. *Anal.* Calcd. for $C_{14}H_{23}ON \cdot HCl$: N, 5.44. Found : N, 5.36.

α-(*p*-**Hexylphenyl**)-β-**aminopropanol Hydrochloride** (**B-VI**)—Prepared from (A-VI). Colorless plates, m.p. 209~213°. *Anal.* Calcd. for $C_{15}H_{25}ON \cdot HCl$: N, 5.16. Found : N, 5.20.

α-(*p*-**Heptylphenyl**)-β-**aminopropanol Hydrochloride** (**B-VII**)—Prepared from (A-VII). Colorless plates, m.p. 211~214°. *Anal.* Calcd. for $C_{16}H_{27}ON \cdot HCl$: N, 4.89. Found : N, 4.93.

α-(*p*-**Octylphenyl**)-β-**aminopropanol Hydrochloride** (**B-VIII**)—Prepared from (A-VIII). Colorless plates, m.p. 206~208°. *Anal.* Calcd. for $C_{17}H_{29}ON \cdot HCl$: N, 4.67. Found : N, 4.65.

α-(*p*-**Decylphenyl**)-β-**aminopropanol Hydrochloride** (**B-X**)—Prepared from (A-X). Colorless plates, m.p. 220~222°. *Anal.* Calcd. for $C_{19}H_{33}ON \cdot HCl$: N, 4.27. Found : N, 4.32.

α-(*p*-**Dodecylphenyl**)-β-**aminopropanol Hydrochloride**(**B-XII**)—Prepared from (A-XII). Colorless plates, m.p. 202~206°. *Anal.* Calcd. for $C_{21}H_{37}ON \cdot HCl$: N, 3.94. Found : N, 3.98.

5) General Procedure of *p*-Alkyl-N-acetylnorephedrine—The Kanao's method[6] was applied to acetylation of amino group of *p*-alkylnorephedrines, which consisted of regular and pseudo forms.

p-**Methyl-N-acetylnorephedrine** (**C-I**)—Prepared from (B-I). Colorless needles, m.p. 218~221°. *Anal.* Calcd. for $C_{12}H_{17}O_2N$: N, 6.76. Found : N, 6.86.

p-**Ethyl-N-acetylnorephedrine** (**C-II**)—Prepared from (B-II). Colorless needles, m.p. 138~141°. *Anal.* Calcd. for $C_{13}H_{19}O_2N$: N, 6.33. Found : N, 6.40.

p-**Propyl-N-acetylnorephedrine** (**C-III**)—Prepared from (B-III). Colorless needles, m.p. 128~131°. *Anal.* Calcd. for $C_{14}H_{21}O_2N$: N, 5.95. Found : N, 5.94.

***p*-Butyl-N-acetylnorephedrine (C-IV)**—Prepared from (B-IV). Colorless needles, m.p. 112~115°. *Anal.* Calcd. for $C_{15}H_{23}O_2N$: N, 5.62. Found: N, 5.56.

***p*-Amyl-N-acetylnorephedrine (C-V)**—Prepared from (B-V). Colorless needles, m.p. 96~99°. *Anal.* Calcd. for $C_{16}H_{25}O_2N$: N, 5.32. Found: N, 5.34.

***p*-Hexyl-N-acetylnorephedrine (C-VI)**—Prepared from (B-VI). Colorless needles, m.p. 104~107°. *Anal.* Calcd. for $C_{17}H_{27}O_2N$: N, 5.05. Found: N, 5.09.

***p*-Heptyl-N-acetylnorephedrine (C-VII)**—Prepared from (B-VII). Colorless needles, m.p. 55~58°. *Anal.* Calcd. for $C_{18}H_{29}O_2N$: N, 4.81. Found: N, 4.89.

***p*-Octyl-N-acetylnorephedrine (C-VIII)**—Prepared from (B-VIII). Colorless needles, m.p. 98~100°. *Anal.* Calcd. for $C_{19}H_{31}O_2N$: N, 4.59. Found: N, 4.51.

***p*-Decyl-N-acetylnorephedrine (C-X)**—Prepared from (B-X). Colorless needles, m.p. 103~107°. *Anal.* Calcd. for $C_{21}H_{35}O_2N$: N, 4.20. Found: N, 4.11.

***p*-Dodecyl-N-acetylnorephedrine (C-XII)**—Prepared from (B-XII). Colorless needles, m.p. 92~95°. *Anal.* Calcd. for $C_{23}H_{39}O_2N$: N, 3.87. Found: N, 3.72.

6) General Procedure of 2,4-Dimethyl-5-(*p*-alkylphenyl)-ψ-oxazoline—Conc. H_2SO_4 was gradually added into *p*-alkyl-N-acetylnorephedrine to complete dissolution. The mixture was poured onto crushed ice and neutralized with K_2CO_3. The oxazoline, which was obtained as an oily or a solid substance, was extracted with ether, washed with water, and dried over Na_2SO_4. After removal of ether, the residue, if oily, was distilled under a reduced pressure. The residue, if solid, was collected by filtration and recrystallized from petr. ether.

2,4-Dimethyl-5-(*p*-methylphenyl)-ψ-oxazoline (D-I)—Prepared from (C-I). $b.p_5$ 116~118°.

2,4-Dimethyl-5-(*p*-ethylphenyl)-ψ-oxazoline (D-II)—Prepared from (C-II). $b.p_{3.5\sim4}$ 114°.

2,4-Dimethyl-5-(*p*-propylphenyl)-ψ-oxazoline (D-III)—Prepared from (C-III) $b.p_{3.5\sim4}$ 125~129°.

2,4-Dimethyl-5-(*p*-butylphenyl)-ψ-oxazoline (D-IV)—Prepared from (C-IV). $b.p_{2\sim3}$ 117°.

2,4-Dimethyl-5-(*p*-amylphenyl)-ψ-oxazoline (D-V)—Prepared from (C-V). $b.p_{2\sim3}$ 134~144°.

2,4-Dimethyl-5-(*p*-hexylphenyl)-ψ-oxazoline (D-VI)—Prepared from (C-VI). $b.p_3$ 158~159°. Colorless needles, m.p. 68~72°. *Anal.* Calcd. for $C_{17}H_{25}ON$: N, 5.40. Found: N, 5.41.

2,4-Dimethyl-5-(*p*-heptylphenyl)-ψ-oxazoline (D-VII)—Prepared from (C-VII). $b.p_3$ 165~170°. Colorless plates, m.p. 50~54°. *Anal.* Calcd. for $C_{18}H_{27}ON$: N, 5.12. Found: N, 5.19.

2,4-Dimethyl-5-(*p*-octylphenyl)-ψ-oxazoline (D-VIII)—Prepared from (C-VIII). $b.p_3$ 168~174°. Colorless needles, m.p. 61~66°. *Anal.* Calcd. for $C_{19}H_{29}ON$: N, 4.87. Found: N, 4.91.

2,4-Dimethyl-5-(*p*-decylphenyl)-ψ-oxazoline (D-X)—Prepared from (C-X). Colorless plates, m.p. 65~68°. *Anal.* Calcd. for $C_{21}H_{33}ON$: N, 4.44. Found: N, 4.57.

2,4-Dimethyl-5-(*p*-dodecylphenyl)-ψ-oxazoline (D-XII)—Prepared from (C-XII). Colorless needles, m.p. 76~79°. *Anal.* Calcd. for $C_{23}H_{37}ON$: N, 4.08. Found: N, 4.15.

7) General Procedure for Regular *dl*-*p*-Alkylnorephedrine—A mixture of ca. 0.004 mole of the oxazoline and dehyd. AcOH, which was prepared by refluxing 5 g. of AcOH and 0.5 g. of Ac_2O for 10 mins., was refluxed in an oil bath for 3 hrs. with exclusion of moisture. The mixture was then poured into 100 cc. of water and neutralized with $NaHCO_3$. The separated oily substance was extracted with ether, washed with water, and dried over Na_2SO_4. On evaporation of the ether, the residue (regular *dl*-*p*-alkyl-O,N-diacetylnorephedrine) was added to 60 cc. of 5% NaOH and warmed on a water bath for 5 hrs. After cooling, the reaction mixture was extracted with ether. After removal of the ether, the residue (regular *dl*-*p*-alkyl-N-acetylnorephedrine) was added to 100 cc. of *N*-HCl and boiled for 2 hrs. The reaction mixture was poured onto crushed ice, saturated with K_2CO_3, and extracted with ether. The extract was washed with water and dried over Na_2SO_4. On removal of the ether, regular *dl*-*p*-alkylnorephedrine was obtained as an oily or a solid substance. It was purified by distillation under a reduced pressure or recrystallization from ether.

Regular *dl*-*p*-Methylnorephedrine—Prepared from (D-I). Colorless plates, m.p. 55~58°, $b.p_5$ 128~139°. *Anal.* Calcd. for $C_{10}H_{15}ON$: C, 72.69; H, 9.15; N, 8.48. Found: C, 73.12; H, 9.21; N, 8.56. Hydrochloride: Colorless needles, m.p. 178~180°. *Anal.* Calcd. for $C_{10}H_{15}ON \cdot HCl$: N, 6.95. Found: N, 6.94.

Regular *dl*-*p*-Ethylnorephedrine—Prepared from (D-II). Colorless plates, m.p. 54~57°, $b.p_2$ 98~105°. *Anal.* Calcd. for $C_{11}H_{17}ON$: N, 7.81. Found: N, 7.93. Hydrochloride: Colorless needles, m.p. 180~184°. *Anal.* Calcd. for $C_{11}H_{17}ON \cdot HCl$: N, 6.49. Found: N, 6.61.

Regular *dl*-*p*-Propylnorephedrine—Prepared from (D-III). Colorless plates, m.p. 84~87°, $b.p_{4\sim5}$ 144~147°. *Anal.* Calcd. for $C_{12}H_{19}ON$: N, 7.25. Found: N, 6.98. Hydrochloride: Colorless plates, m.p. 178~182°. *Anal.* Calcd. for $C_{12}H_{19}ON \cdot HCl$: N, 6.10. Found: N, 5.89.

Regular *dl*-*p*-Butylnorephedrine—Prepared from (D-IV). Colorless plates, m.p. 68~73°, $b.p_{3\sim4}$ 144~152°. *Anal.* Calcd. for $C_{13}H_{21}ON$: N, 6.76. Found: N, 6.87. Hydrochloride: Colorless plates, m.p. 171~175°. *Anal.* Calcd. for $C_{13}H_{21}ON \cdot HCl$: N, 5.75. Found: N, 5.56.

Regular *dl*-*p*-Amylnorephedrine—Prepared from (D-V). Colorless needles, m.p. 85~89°, $b.p_{2\sim2.5}$ 150~156°. *Anal.* Calcd. for $C_{14}H_{23}ON$: N, 6.27. Found: N, 6.15.

Regular *dl-p*-Hexylnorephedrine—Prepared from (D-VI). Colorless needles, m.p. 72~75°, b.$p_{3.5}$ 154~161°. *Anal.* Calcd. for $C_{15}H_{25}ON$: N, 5.95. Found: N, 5.67.

Regular *dl-p*-Heptylnorephedrine—Prepared from (D-VII). Colorless plates, m.p. 42~46°, b.p_3 163°. *Anal.* Calcd. for $C_{16}H_{27}ON$: N, 5.62. Found: N, 5.76.

Regular *dl-p*-Octylnorephedrine—Prepared from (D-VIII). Colorless plates, m.p. 78~83°, b.p_3 179°. *Anal.* Calcd. for $C_{17}H_{29}ON$: N, 5.33. Found: N, 5.23.

Regular *dl-p*-Decylnorephedrine—Prepared from (D-X). Colorless plates, m.p. 69~73°. *Anal.* Calcd. for $C_{19}H_{33}ON$: N, 4.81. Found: N, 4.95.

Regular *dl-p*-Dodecylnorephedrine—Prepared from (D-XII). Colorless needles, m.p. 75~78°. *Anal.* Calcd. for $C_{21}H_{37}ON$: N, 4.38. Found: N, 4.26.

8) **General Procedure for *dl-ψ-p*-Alkylnorephedrine**—A mixture of 1 g. of the oxazoline and 20 cc. of *N*-HCl was boiled for 2 hrs. The mixture was then poured onto crushed ice and saturated with K_2CO_3. The separated oily or solid substance was extracted with ether, washed with water, and dried over Na_2SO_4. On evaporation of the ether, the residue was purified by distillation under a reduced pressure or recrystallization from ether.

dl-ψ-p-**Methylnorephedrine**—Prepared from (D-I). Colorless needles, m.p. 75~78°. *Anal.* Calcd. for $C_{10}H_{15}ON$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.85; H, 9.26; N, 8.41.

dl-ψ-p-**Ethylnorephedrine**—Prepared from (D-II). Colorless needles, m.p. 71~75°. *Anal.* Calcd. for $C_{11}H_{17}ON$: N, 7.81. Found: N, 7.68.

dl-ψ-p-**Propylnorephedrine**—Prepared from (D-III). Colorless plates, m.p. 55~57°, b.p_2 131~134°. *Anal.* Calcd. for $C_{12}H_{19}ON$: N, 7.25. Found: N, 7.11.

dl-ψ-p-**Butylnorephedrine**—Prepared from (D-IV). Colorless needles, m.p. 66~68°. *Anal.* Calcd. for $C_{13}H_{21}ON$: N, 6.76. Found: N, 6.61.

dl-ψ-p-**Amylnorephedrine**—Prepared from (D-V). Colorless needles, m.p. 54~57°, b.p_4 140~145°. *Anal.* Calcd. for $C_{14}H_{23}ON$: N, 6.27. Found: N, 6.19.

dl-ψ-p-**Hexylnorephedrine**—Prepared from (D-VI). Colorless plates, m.p. 61~64°, b.$p_{4.5\sim5.5}$ 169~174°. *Anal.* Calcd. for $C_{15}H_{25}ON$: N, 5.95. Found: N, 5.88.

dl-ψ-p-**Heptylnorephedrine**—Prepared from (D-VII). Colorless plates, m.p.57~61°. *Anal.* Calcd. for $C_{16}H_{27}ON$: N, 5.62. Found: N, 5.71.

dl-ψ-p-**Octylnorephedrine**—Prepared from (D-VIII). Colorless plates, m.p. 62~65°. *Anal.* Calcd. for $C_{17}H_{29}ON$: N, 5.33. Found: N, 5.24.

dl-ψ-p-**Decylnorephedrine**—Prepared from (D-X). Colorless plates, m.p. 78~81°. *Anal.* Calcd. for $C_{19}H_{33}ON$: N, 4.81. Found: N, 4.78.

dl-ψ-p-**Dodecylnorephedrine**—Prepared from (D-XII). Colorless plates, m.p. 79~82°. *Anal.* Calcd. for $C_{21}H_{37}ON$: N, 4.38. Found: N, 4.31.

9) **General Procedure for Regular *dl-p*-Alkylephedrine**—A mixture of ca. 0.015 mole of the oxazoline and 2.8 g. of Me_2SO_4 in 15 cc. of dehyd. benzene was warmed on a water bath for 20 mins. with exclusion of moisture. After removal of the benzene, a solution, prepared by refluxing 14 cc. of dehyd. AcOH, 0.6 cc. of Ac_2O, and 3 g. of fused AcONa for 10 mins., was immediately added to the residue. The mixture was refluxed for 3 hrs. and then poured into crushed ice. The treatments after this reaction were the same as for regular *p*-alkylnorephedrine.

Regular *dl-p*-Methylephedrine—Prepared from (D-I). Colorless needles, m.p. 98~102°, b.$p_{1.5}$ 95~110°. *Anal.* Calcd. for $C_{11}H_{17}ON$: C, 73.70; H, 9.56; N, 7.81. Found: C, 74.03; H, 9.75; N, 7.75. Hydrochloride: Colorless needles, m.p. 196~198°. *Anal.* Calcd. for $C_{11}H_{17}ON\cdot HCl$: N, 6.50. Found: N, 6.34.

Regular *dl-p*-Ethylephedrine—Prepared from (D-II). Colorless needles, m.p. 113~117°, b.p_3 100~103°. *Anal.* Calcd. for $C_{12}H_{19}OC$: N, 7.25. Found: N, 7.20. Hydrochloride: Colorless needles, m.p. 95~98°. *Anal.* Calcd. for $C_{12}H_{19}ON\cdot HCl$: N, 6.10. Found: N, 6.07.

Regular *dl-p*-Propylephedrine—Prepared from (D-III). Colorless needles, m.p. 79~83°, b.p_2 132~134°. *Anal.* Calcd. for $C_{13}H_{21}ON$: N, 6.76. Found: N, 6.69. Hydrochloride: Colorless plates, m.p. 94~97°. *Anal.* Calcd. for $C_{13}H_{21}ON\cdot HCl$: N, 5.74. Found: N, 5.75.

Regular *dl-p*-Butylephedrine—Prepared from (D-IV). Colorless needles, m.p. 94~97°, b.$p_{1\sim2}$ 125~130°. *Anal.* Calcd. for $C_{14}H_{23}ON$: N, 6.33. Found: N, 6.23. Hydrochloride: Colorless needles, m.p. 91~95°. *Anal.* Calcd. for $C_{14}H_{23}ON\cdot HCl$: N, 5.43. Found: N, 5.39.

Regular *dl-p*-Amylephedrine—Prepared from (D-V). Colorless plates, m.p. 94~97°, b.p_2 147~153°. *Anal.* Calcd. for $C_{15}H_{25}ON$: N, 5.95. Found: N, 5.78.

Regular *dl-p*-Hexylephedrine—Prepared from (D-VI). Colorless plates, m.p. 66~68°, b.$p_{3.5}$ 158~161°. *Anal.* Calcd. for $C_{16}H_{27}ON$: N, 5.62. Found: N, 5.56.

Regular *dl-p*-Heptylephedrine—Prepared from (D-VII). Colorless plates, m.p. 56~60°. *Anal.* Calcd. for $C_{17}H_{29}ON$: N, 5.33. Found: N, 5.25.

Regular *dl-p*-Octylephedrine—Prepared from (D-VIII). Colorless needles, m.p. 85~88°, b.p_4 205~210°. *Anal.* Calcd. for $C_{18}H_{31}ON$: N, 5.05. Found: N, 5.02.

Regular *dl*-*p*-**Decylephedrine**—Prepared from (D-X). Colorless plates, m.p. 75~78°. *Anal.* Calcd. for $C_{20}H_{35}ON$: N, 4.59. Found: N, 4.55.

Regular *dl*-*p*-**Dodecylephedrine**—Prepared from (D-XII). Colorless plates, m.p. 72~76°. *Anal.* Calcd. for $C_{22}H_{39}ON$: N, 4.20. Found: N, 4.15.

10) General Procedure for *dl*-*ψ*-*p*-**Alkylephedrine**—A mixture of ca. 0.005 mole of the oxazoline and 1 g. of Me_2SO_4 in 3 cc. of dehyd. benzene was warmed on a water bath for 20 mins. After removal of benzene, the treatments after this reaction were the same as for *dl*-*ψ*-*p*-alkylnorephedrine.

dl-*ψ*-*p*-**Methylephedrine**—Prepared from (D-I). Colorless needles, m.p. 116~120°. *Anal.* Calcd. for $C_{11}H_{17}ON$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.28; H, 9.51; N, 7.73.

dl-*ψ*-*p*-**Ethylephedrine**—Prepared from (D-II). Colorless needles, m.p. 102~106°. *Anal.* Calcd. for $C_{12}H_{19}ON$: N, 7.25. Found: N, 7.19.

dl-*ψ*-*p*-**Propylephedrine**—Prepared from (D-III). Colorless needles, m.p. 88~92°. *Anal.* Calcd. for $C_{13}H_{21}ON$: N, 6.76. Found: N, 6.73.

dl-*ψ*-*p*-**Butylephedrine**—Prepared from (D-IV). Colorless needles, m.p. 91~94°, $b.p_{6\sim7}$ 145~150°. *Anal.* Calcd. for $C_{14}H_{23}ON$: N, 6.33. Found: N, 6.24.

dl-*ψ*-*p*-**Amylephedrine**—Prepared from (D-V). Colorless needles, m.p. 92~95°, $b.p_4$ 145~147°. *Anal.* Calcd. for $C_{15}H_{25}ON$: N, 5.95. Found: N, 5.80.

dl-*ψ*-*p*-**Hexylephedrine**—Prepared from (D-VI). Colorless needles, m.p. 85~88°, $b.p_3$ 150~154°. *Anal.* Calcd. for $C_{16}H_{27}ON$: N, 5.62. Found: 5.55.

dl-*ψ*-*p*-**Heptylephedrine**—Prepared from (D-VII). Colorless needles, m.p. 47~51°, $b.p_{2.5}$ 146~156°. *Anal.* Calcd. for $C_{17}H_{29}ON$: N, 5.33. Found: N, 5.25.

dl-*ψ*-*p*-**Octylephedrine**—Prepared from (D-VIII). Colorless needles, m.p. 84~87°. *Anal.* Calcd. for $C_{18}H_{31}ON$: N, 5.05. Found: N, 4.97.

dl-*ψ*-*p*-**Decylephedrine**—Prepared from (D-X). Colorless needles, m.p. 68~73°. *Anal.* Calcd. for $C_{20}H_{35}ON$: N, 4.59. Found: N, 4.71.

dl-*ψ*-*p*-**Dodecylephedrine**—Prepared from (D-XII). Colorless needles, m.p. 78~82°. *Anal.* Calcd. for $C_{22}H_{39}ON$: N, 4.20. Found: N, 4.28.

Summary

Alkylbenzenes were condensed with propionic anhydride in the presence of aluminum chloride into *p*-alkylpropiophenones, which were converted into *p*-alkyl-*α*-isonitrosopropiophenones by treatment with butyl nitrite. These isonitrosoketones were first reduced into aminoketones in dehyd. ethanol containing hydrogen chloride in the presence of palladium-carbon catalyst, and the *p*-alkyl-*α*-aminopropiophenone hydrochlorides were converted into amino alcohols in water by the aid of the same kind of catalyst. *α*-(*p*-Alkylphenyl)-*β*-aminopropanols, or *p*-alkylnorephedrines, thereby obtained are probably a mixture of compounds of regular and pseudo forms. In order to obtain each of them separately from the mixture, the elaborate method of Taguchi *et al.* was applied in a modified form. By these mothods, *p*-methyl-, *p*-ethyl-, *p*-propyl-, *p*-butyl-, *p*-amyl-, *p*-hexyl-, *p*-heptyl-, *p*-octyl-, *p*-decyl-, and *p*-dodecyl-ephedrines and the corresponding norephedrines were obtained. In addition, these ring-substituted ephedrines and norephedrines were divided into the regular- and pseudo-series.

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