Experimental

Compounds

The compounds used were purchased from Tokyo Kasei Co.

NMR Measurements

The spectra were obtained by a JNM-3H-60 spectrometer of Japan Electron Optics Lab. Co. operating at 60 Mcps. Signal integrations were carried out with a JES-1D integrator attached to our NMR spectrometer.

We are greatly indebted to Dr. Waro Nakahara, Director of National Cancer Center Research Institute, and Professor Toshihiko Okamoto of University of Tokyo for their encouragement and useful discussions throughout this work.

Summary

It was demonstrated that the quantitative analysis of various kinds of active hydrogens was conveniently carried out by nuclear magnetic resonance technique. The exchange reactivities of α-hydrogens adjacent to carbonyl functions were compared with each other by this technique.

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193. Sadao Oida, Masaaki Kurabayashi, and Eiji Ohki : Fragmentation Reaction of Azabicyclic Compounds.*1

(*Central Research Laboratory, Sankyo Co., Ltd.**2)

In a recent paper[1] from this laboratory, it was shown that the treatment of 3-methyl-3-azabicyclo[3.3.1]nonan-9-one with phenylmagnesium bromide a 3-methyl-9α-hydroxy-9β-phenyl-3-azabicyclo[3.3.1]nonane (Ia) and its 9β-hydroxy epimer*3 (IIa) and that the former was earily epimerized to the latter on refluxing in 10% aqueous hydrochloric acid. Recently House, *et al.*[2] established the stereochemistry of some 3-azabicyclic compounds including Ia and IIa, as shown below by esterification study and nuclear magnetic resonance (NMR) analysis; they also suggested that as to the transformation process of Ia to IIa the ammonium ion (III) derived from IIa, which is stabilized by an intramolecular hydrogen bond, promotes the Ia~IIa equilibrium to a IIa-rich mixture.

In the course of our recent study on these potential analgesics, interesting observations were made on the chemical nature of 3-azabicyclo-[3.3.1]nonane and -[3.2.1] octane compounds, which form the subject of this paper.

Either the 9α-hydroxy (Ia) or the 9β-hydroxy (IIa) compound was refluxed in methanol, ethanol, or *n*-propanol in place of the aqueous condition in the presence of mineral acid to give the corresponding same ether*3 as a major product. Presumably

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*1 Presented at the Meeting of the Pharmaceutical Society of Japan in Tokyo (May 1966, Tokyo).

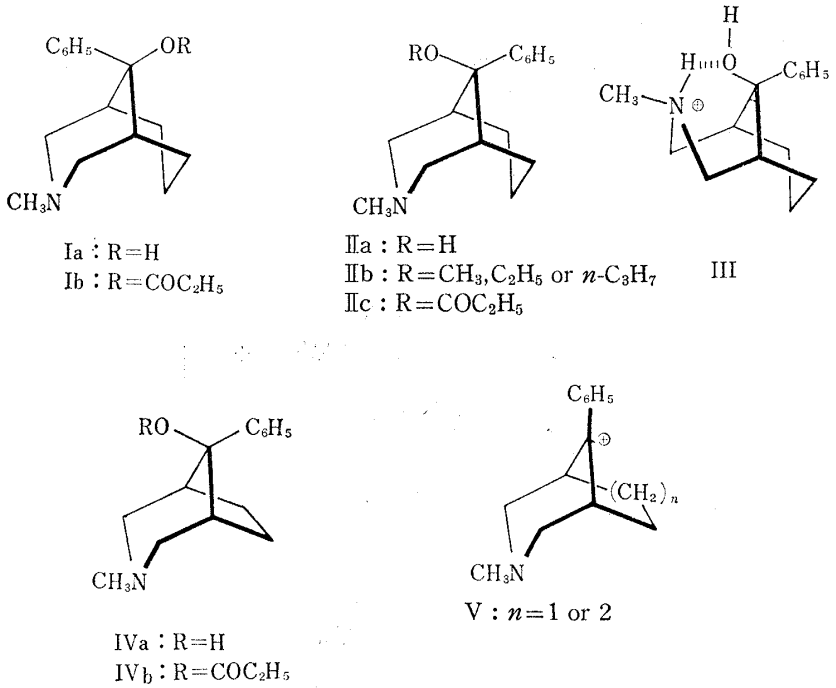
*2 Hiromachi, Shinagawa-ku, Tokyo (老田貞夫, 倉林正明, 大木英二).

*3 These derivatives were found to be promissing as new analgesics; and pharmaceutical study on them will be announced in another paper.

1) I. Iwai, B. Shimizu : Jap. Pat. 18,038 (1964) (March 14, 1961); Cf. Brit. Pat. 952,137 (1964) to Sankyo Co., Ltd. (Chem. Abstr., **61**, 5614 (1964)).

2) H. O. House, W. M. Bryant III : J. Org. Chem., **30**, 3634 (1965).

configuration of IIb corresponded to that of IIa, because the position of the N-methyl signal in the NMR spectra for IIb was constant at 2.2 p.p.m. without any influence of the benzene ring current. On the other hand, it was found that 3-methyl-8 β-hydroxy-8 α-phenyl-3-azabicyclo[3.2.1]octan*4 (IVa), m.p. 130~131°, obtained by treatment of 3-methyl-3-azabicyclo[3.2.1]octan-8-one[2] with phenylmagnesium bromide, was very stable



Ia : R=H
Ib : R=COC_2H_5

IIa : R=H
IIb : R=CH_3, C_2H_5 or n-C_3H_7
IIc : R=COC_2H_5

III

IVa : R=H
IVb : R=COC_2H_5

V : n=1 or 2

Chart 1.

to acids; and it was recovered without any etherification from the reaction mixture obtained in boiling alcoholic hydrochloric acid. These facts suggested that the etherification of these alcohols may be effected through the carbonium ion like V, activation to which needs higher energy in the case of the 8-hydroxyoctane analog (IVa). This also supports the previous illustration of House, *et al.*[2] that the conversion of Ia to IIa is not a kinetically controlled process but includes the Ia~IIa equilibrium controlled by stability of the components.

In the previous paper[1], it was shown that heating of the 9 α- or 9 β-hydroxy compound (Ia or IIa) in propionic anhydride at 100° gave a corresponding propionate (Ib or IIc), while treatment of either Ia or IIa in the anhydride at 160° afforded one and the same product. This product had a strong absorption at 242 mμ in the ultraviolet region, which indicated the presence of a styrene-like compound in it. Fractionation of the reaction mixture gave a styrene-amide (VI), $C_{17}H_{23}ON$, from the neutral part in 60% yield and a styrene amine (VII), $C_{15}H_{21}N$, from the basic part in 5% yield. These structures were conclusively established as VI and VII, respectively, as follows.

The infrared absorption of VI at 1650 cm^{-1} suggested the presence of an amide group; the ultraviolet absorption at 242 mμ (ε 9500) showed the presence of a substituted styrene group. NMR data also indicated these functional groups; one triplet proton with a center at 5.93 p.p.m. (J=3.5 c.p.s.) for vinyl proton, three singlet protons at 2.75 p.p.m. for N-methyl, three triplet protons with a center at 1.00 p.p.m. (J=7 c.p.s.) for

*4 The signal of N-methyl group at 2.28 p.p.m. in the NMR spectrum of IVa indicated that the hydroxyl group also has β-configuration. Synthesis of 8β-hydroxy-3,8α-dimethyl-3-azabicyclo[3. 2. 1]octane and its structural assignment have been reported.[2] In our case 8α-hydroxy epimer could not be isolated in the same way.

methyl of a propionyl group, and five singlet protons at 7.23 p.p.m. for a phenyl group. Reduction of the amide function of VI with lithium aluminum hydride, followed by treatment with methyl iodide gave a methiodide (VIII), $C_{17}H_{28}NI$, m.p. 161~163°. VIII was degraded with aqueous sodium hydroxide to a phenyl-diene (IX) and dimethylpropylamine. The latter was characterized as its picrate, m.p. 109.5~111°, and identified with the authentic sample. Elementary analysis of the phenyl-diene (IX) corresponded to a composition of $C_{14}H_{14}$: and its infrared absorption at 890 cm^{-1} and the increased intensity of the ultraviolet absorption at 242 mμ (ε 15500) indicated the presence of an exocyclic methylene conjugated with the styrene group at the α-position. The structure of IX was also supported by its NMR analysis as shown in the experimental.

In addition, VI resisted hydrolysis; and when refluxed in ethanol in the presence of hydrochloric acid, took up one mole of water to give an amide-phenylcarbinol*5 (X), $C_{17}H_{25}O_2N$, m.p. 102~103°, as shown in Fig. 2. X was reduced with lithium aluminum

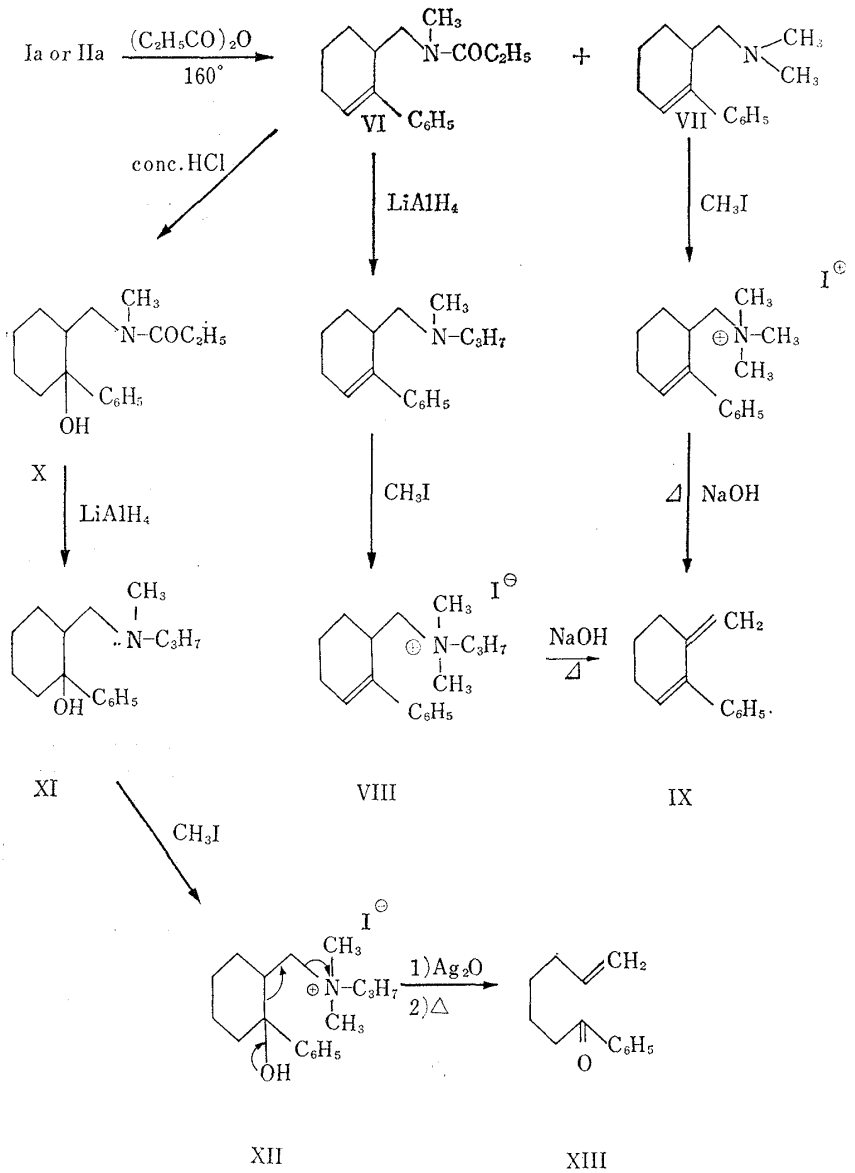


Chart 2.

*5 The infrared or ultraviolet data supported the structure of X; there are, however, some signals not elucidated at lower field of the NMR spectrum of X, as described in the experimental, although XI or XII derived from X gave satisfactory data on their NMR spectra.

hydride to an oily aminocarbinol (XI), $C_{17}H_{27}ON$, which was converted to a crystalline methiodide (XII), $C_{18}H_{30}ONI$, m.p. 150° (decomp.). Hofmann degradation of XII afforded 5-hexenyl phenyl ketone (XIII) which was characterized as its dinitrophnylhydrazone of m.p. 142~143°. As for the structure of XIII, the absorption at 241 mμ (ε 8200) and 279 mμ (ε 850) in the ultraviolet region and at 1686 cm^{-1} in the infrared region showed the presence of a benzoyl group, and absorptions at 989 and 910 cm^{-1} in the infrared field, one vinyl group. The transformation of XII to XIII will be illustrated as a concerted reaction, including the bond fission of α,β-position of the phenyl ring, which is promoted by the initial removal of the hydroxyl proton, preceding release of the β-proton. Based on this sequence of reactions, the styrene-amide was designated as VI.

On the other hand, the styrene-amine (VII) has a dimethylamino group, which was indicated by six singlet protons at 2.11 p.p.m. in its NMR spectrum, in place of the methyl propionylamido group of the amide (VI). Methiodide of VI, m.p. 198~199°, was treated with 20% aqueous sodium hydroxide at 120° to afford trimethylamine and the same phenyl-diene (IX), which was also obtained by the degradation of VI as described above. Based on this fact, we concluded the structure of the styrene-amine as VII.

A plausible path for the formation of VI and VII may be visualized as a kind of fragmentation reaction[3] which was observed in many cases of γ-aminoalkyl halide and its homologs. That either the 9α- or the 9β-hydroxy compound (Ia or IIa) was degraded to the same product without being affected by orientation of the hydroxyl group suggests the initial formation of a carbonium ion (V) following the conversion into the immonium ion (XIV) as shown below. Presumably XIV is solvolized with propionic anhydride to afford the styrene-amide (VI) or converted to the styrene-amine (VII) under hydride ion-transfer, but we have no idea or no plausible proof on the source of hydride ion yet.

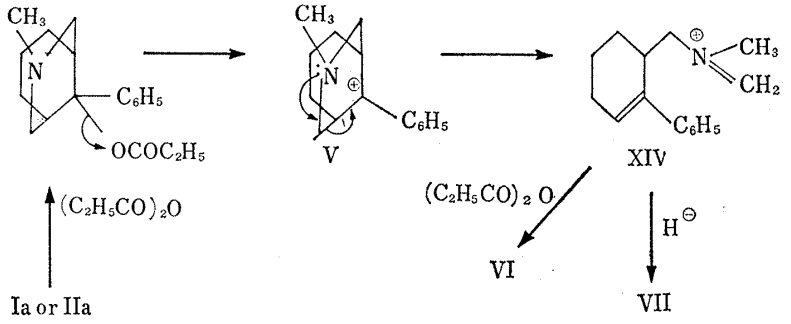


Chart 3.

Moreover, in an acetate buffer solution at pH 5~6 at 100°, the 9α-propionate (Ib) was stable without any conversion, while the 9β-propionate (IIc) was hydrolysed to the 9β-alcohol (IIa), accompanied with a small amount of by-products, in which the same styrene-amine (VII) was detected. Treatment of either the 9α-alcohol (Ia) or the 9β-alcohol (IIa) in the same buffer solution at 160° afforded one and the same complicated reaction mixture, from which VII was also isolated in 20% yield; however, attempts to obtain any possible secondary amine derivative or other transformation product were unsuccessful.*6

On the other hand, treatment of the 8β-alcohol (IVa) with propionic anhydride at 160° did not give any fragmentation product, but gave its propionate (IVb) in a quanti-

*6 A small amount of an amine, $C_{15}H_{21}N$, m.p. 47.5~48.5° was obtained from the reaction mixture, but further study could not be carried out due to the lack of the sample.

3) C. A. Grob: "Theoretical Organic Chemistry," Report on the Kekúle Symposium, 114 (1958), London.

tative yield. This fact is also consistent with the previous observation on the stability of Ⅳa to etherification and it also indicates that there is an unsurmountable obstacle against activation to the carbonium ion, like Ⅴ, due to the rigid skeleton of the bicyclic octane system.

Experimental

Melting points were not corrected. Ultraviolet spectra were determined in 95% EtOH on a Beckman Model DK-2 and infrared spectra on Perkin-Elmer Model 21. Proton magnetic resonance spectra (NMR) were taken in CCl_4 on a Varian A-60 spectrometer with tetramethylsilane as an internal standard. The removal of solvents *in vacuo* was accomplished by a rotating flash evaporator at 20~30 mm. and with the water bath usually at 35~50°. Plates for thin-layer chromatography were prepared with Silica gel G acc. to Stahl (E. Merck AG) or MN Silica gel G/UV 257 (N. Nagel AG). A solvent mixture of hexane-acetone (3:1) was usually used for developing. Visualization of spots was effected by spraying Draggendorff's reagent or irradiation of ultraviolet ray.

3-Methyl-9β-alkoxy-9α-phenyl-3-azabicyclo[3. 3. 1]nonane (Ⅱb)——A solution of 1.45 g. of 3-methyl-9β-hydroxy-9α-phenyl-3-azabicyclo[3. 3. 1]nonane (Ⅱa) in 30 ml. of anhydrous EtOH containing 3 ml. of conc. H_2SO_4 was refluxed for 4 hr. After evaporation of the solvent *in vacuo*, the residue was diluted with ice-water, made basic with conc. NH_4OH and extracted with ether. The extract was dried and evaporated to give 1.55 g. of a colorless oil, which was purified through a picrate of fine yellow leaflets, m.p. 200°(decomp.). *Anal.* Calcd. for $C_{23}H_{28}O_8N_4$: C, 56.55; H, 5.78; N, 11.47. Found: C, 56.30; H, 5.90; N, 11.48.

The oil regenerated from picric acid was distilled to collect Ⅱb ($R=C_2H_5$) as a colorless liquid $b.p_3$ 150~160° (bath temp.). The NMR spectrum exhibited a multiplet signal at 7.2~7.7 (5H, aromatic), a quartet at 2.92 (J=7 c.p.s.) (2H, $-OC\underline{H}_2CH_3$), a singlet at 2.22 (3H, $N-CH_3$), and a triplet at 0.92 p.p.m. with J=7 c.p.s. (3H, $-OCH_2-C\underline{H}_3$).

The 9α-OH compound (Ia) was also refluxed with alcoholic H_2SO_4 to give the same reaction product as obtained from Ⅱa, from which Ⅱb ($R=C_2H_5$) was isolated in the same way. In each case, thin-layer chromatography of the reaction mixture showed two spots in a ratio of 10 : 1. The minor product, unable to be isolated, was assumed to be the possible 9α-ethoxy epimer, because the NMR spectrum of the reaction mixture showed a weak absorption at 2.00 p.p.m., which suggested the higher shift of N-methyl signal affected by the benzene ring current and which disappeared in the spectrum of purified Ⅱb.

The methyl ether (Ⅱb: $R=CH_3$) was also obtained by refluxing of Ia with methanolic H_2SO_4 under the same procedure, as fine leaflets, m.p. 73~74.5°. Analytical sample was recrystallized from MeOH. *Anal.* Calcd. for $C_{16}H_{23}ON$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.38; H, 9.57; N, 5.54. The NMR spectrum showed a multiplet signal at 7.1~7.5 (5H, aromatic), a singlet at 2.68 (3H, $O-CH_3$), and a singlet at 2.18 p.p.m. (3H, $N-CH_3$).

The propyl ether (Ⅱb, $R=n-C_3H_7$) was obtained as a colorless oil, which was characterized as a citrate of m.p. 148°(decomp.). *Anal.* Calcd. for $C_{24}H_{35}O_8N$: C, 61.92; H, 7.58; N, 3.01. Found: C, 61.42; H, 7.48; N, 3.21. The NMR spectrum of the purified oil showed a multiplet signal at 7.2~7.6 (5H, aromatic), a triplet with J=6 c.p.s. at 2.83 (2H, $-O-CH_2-$), a singlet at 2.23 (3H, $N-CH_3$), and a triplet at 0.78 p.p.m. with J=6 c.p.s. (3H, $-O-CH_2-CH_2-C\underline{H}_3$). The NMR spectra of all of these alkoxy derivatives (Ⅱb) exhibited similar absorption in the methine and methylene field.

3-Methyl-8β-hydroxy-8α-phenyl-3-azabicyclo[3. 2. 1]octane (Ⅳa) and Its Propionate (Ⅳb)——To a Grignard solution, prepared by refluxing 4.1 g. of bromobenzene with 0.61 g. of magnesium turnings in 20 ml. of anhydrous ether was added slowly 3.00 g. of 3-methyl-3-azabicyclo[3. 2. 1]octan-8-one in 20 ml. of anhydrous tetrahydrofuran under vigorous stirring. The mixture was allowed to stand at room temperature under stirring for 3 hr. and a saturated NH_4Cl solution was added to the cooled solution. The mixture was diluted with water and extracted twice with 20 ml. of ether. The combined extract was washed with H_2O, dried, and evaporated to give 4.64 g. of a crystalline residue, which was recrystallized from AcOEt to Ⅳa as prisms of m.p. 130~131°. Yield, 2.51 g. IR: ν_{max}^{Nujol} 3250 cm^{-1} (OH). *Anal.* Calcd. for $C_{14}H_{19}ON$: C, 77.38: H, 8.81; N, 6.45. Found: C, 77.00; H, 8.87; N, 6.42. The NMR spectrum showed a multiplet signal at 7.4 (5H, aromatic), a multiplet at 2.25~3.0 (4H, $-N-CH_2-$), a singlet at 2.28 (3H, $N-CH_3$), and a multiplet at 1.1~2.0 p.p.m. (7H, methylene and methine).

A solution of 500 mg. of the amino-alcohol (Ⅳa) in 5 ml. of propionic anhydride was heated at 160~165° for 3 hr. After removal of the anhydride *in vacuo*, the residue was diluted with ice-water, made basic with conc. NH_4OH and extracted with ether. The extract was dried and evaporated to give a colored oil, whose thin-layer chromatography showed one spot, accompanied with a small amount of impurity. The product was distilled to give Ⅳb as a colorless liquid, $b.p_{0.5}$ 150° (bath temp.). Yield, 533 mg. IR: $\nu_{max}^{liq.}$ 1743 cm^{-1} (C=O). *Anal.* Calcd. for $C_{17}H_{23}O_2N$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.21; H, 8.51; N, 5.27.

The NMR spectrum of Ⅳb exhibited absorptions at 7.1～7.6 (5H, multiplet : aromatic), 2.22 (3H, singlet: N-CH_3), 2.13 (2H, quartet with J=7.5 c.p.s.:-$C\underline{H}_2$-CH_3), and 1.00 p.p.m. (3H, triplet with J=7.5 c.p.s.:-CH_2-$C\underline{H}_3$).

Degradation of 3-Methyl-9-hydroxy-9-phenyl-3-azabicyclo[3. 3. 1]nonane (Ia or IIa) to the Styrene-amide (VI) and Styrene-amine (VII)——A solution of 515 mg. of the 9β-alcohol (IIa) in 5 ml. of propionic anhydride was heated at 160～170° for 4 hr. The reaction mixture was evaporated *in vacuo* and diluted with dehyd. EtOH. After warming for a few minutes on water bath, removal of the solvent afforded 668 mg. of a brown residue. The residue was dissolved in 30 ml. of ether and extracted with 20 ml. of dil. HCl to separate (i) basic and (ii) neutral fraction.

(i) The aqueous layer was made basic with conc. NH_4OH and extracted with ether. The extract was washed with saturated NaCl solution and dried over anhydrous $MgSO_4$. Removal of the solvent gave 49 mg. of a basic fraction, which was dissolved in ether and then added with picric acid to give a picrate of Ⅶ as yellow leaflets, m.p. 137～139°. Analytical sample was recrystallized from EtOH-MeOH. *Anal.* Calcd. for $C_{21}H_{24}O_7N_4$: C, 56.75; H, 5.44; N, 12.61. Found : C, 56.35; H, 5.37; N, 12.56. The picrate was dissolved in dil. HCl and washed with ether. The aqueous layer was made basic with conc. NH_4OH and extracted with ether. After drying, evaporation of ether gave an oil which was purified by distillation to give Ⅶ as a colorless liquid, b.p_1 130° (bath temp.). UV λ_{max} 242 mμ (ε 10600). The infrared spectrum was transparent in OH or C=O region. The NMR spectrum showed absorptions at 7.20 (5H, singlet : aromatic), 5.90 (1H, triplet, J=4 and 1 c.p.s. : vinyl proton), 2.6～3.0 (1H, broad : -C$\underline{H}$-C=), 2.11 (6H, singlet : N-methyl), and 1.2～2.5 p.p.m. (8H, multiplet : methylene).

A solution of 0.44 g. of the styrene-amine (Ⅵ) in 10 ml. of ether was refluxed with excess amount of CH_3I for 4 hr. Removal of the solvent afforded 0.74 g. of the methiodide of Ⅶ, which was recrystallized from MeOH-ether to leaflets, m.p. 198～199°. *Anal.* Calcd. for $C_{16}H_{24}NI$: C, 53.79; H, 6.77; N, 3.92. Found : C, 53.62; H, 6.77; N, 3.92. The NMR spectrum in D_2O exhibited absorptions at 7.44 (5H, singlet: aromatic), 6.02 (1H, triplet with J=3.5 c.p.s. : -CH=), 2.99 (3H, singlet : -N-CH_3) 2.8～3.8, and 1.4～2.4 p.p.m. (9H, multiplet : methylene and methine).

(ii) After removal of the basic fraction, the ether layer was washed with H_2O and dried over anhydrous $MgSO_4$. Removal of the solvent afforded 547 mg. of an oil which was chromatographed over a silica gel column. The benzene-$CHCl_3$ eluate was evaporated to give 335 mg. of the styrene-amide (Ⅵ) as a colorless liquid, which was further purified by distillation, b.$p_{0.05}$ 180° (bath temp.). UV λ_{max} 242 mμ (ε 9500). IR $\nu_{max}^{liq.}$ 1650 cm^{-1} (-CO-NR_2). *Anal.* Calcd. for $C_{17}H_{23}ON$: C, 79.33; H, 9.01; N, 5.44. Found : C, 78.14; H, 8.96; N, 5.19. The NMR spectrum showed absorptions at 7.23 (5H, singlet : aromatic), 5.93 (1H, triplet with J=3.5 c.p.s. : -CH=), 3.3～3.8 (1H, multiplet : -C$\underline{H}$-C=), 2.9～3.25 (2H, multiplet, -CH_2-N-), 2.75 (3H, singlet : -N-CH_3), 1.5～2.5 (8H, multiplet), and 1.00 p.p.m. (3H, triplet, J=7 c.p.s. : -CH_2-$C\underline{H}_3$).

The 9α-OH (Ia) was also treated with propionic anhydride at 160～170° to afford the same reaction mixture, which was compared with the above-mentioned mixture obtained from IIa by thin-layer chromatography and gas chromatography.*7

Methiodide (VIII) derived from the Styrene-amide (VI)——To a solution of 294 mg. of the styrene-amide (Ⅵ) in 3 ml. of anhydrous tetrahydrofuran was added 50 mg. of $LiAlH_4$ in small portions under cooling. The mixture was refluxed for 3 hr., poured into ice-water, and extracted twice with ether. After drying, removal of the solvent gave 253 mg. of a pale yellow liquid. Its infrared spectrum was transparent in OH or C=O region. The amine obtained here was dissolved in 5 ml. of ether and added with excess of CH_3I. The mixture was refluxed for 2.5 hr. Removal of the solvent afforded 399 mg. of crude crystals of Ⅷ which was recrystallized from ether-MeOH to Ⅷ as prisms of m.p. 163～165°. Yield, 76% from Ⅵ. *Anal.* Calcd. for $C_{18}H_{28}NI$: C, 56.10; H, 7.32; N, 3.64. Found : C, 55.99; H, 7.28; N, 3.53.

Hofmann Degradation of the Methiodide of VII or VIII——(i) A solution of 0.60 g. of the methiodide of Ⅶ in 2 ml. of 20% aqueous NaOH solution was heated at 120° under refluxing for 0.5 hr. The oily product obtained was extracted with ether. The extract was dried over anhydrous $MgSO_4$ and distilled. To the distillate was added picric acid dissolved in ether to give the picrate of $N(CH_3)_3$, which was recrystallized from MeOH, and 70 mg. of the picrate was obtained as yellow needles, m.p. 218～220° which was identified with the authentic sample by mixing melting point and infrared spectroscopy.

The residue of the extract afforded by distillation a colorless oil of the phenyl-diene (Ⅸ), b.p_{20} 160° (bath temp.). Yield, 0.12 g. IR $\nu_{max}^{liq.}$: 1630 and 1600 cm^{-1} (C=C); UV λ_{max} 242 mμ (ε 15500). *Anal.* Calcd. for $C_{13}H_{14}$: C, 91.71; H, 8.29. Found : C, 91.69; H, 8.47. The NMR spectrum of the diene showed absorptions at 7.20 (5H, singlet: aromatic), 5.73 (1H, triplet with J=4.5 and 1.5 c.p.s. : -CH=), 4.83 and 4.68 (2H, broad singlets: $=CH_2$), 2.1～2.6 (4H, multiplet : methylene), and 1.6～2.09 p.p.m. (2H, multiplet : methylene).

(ii) Under the same condition as described above, 216 mg. of the amine (Ⅷ) was treated with alkali to give 43 mg. of dimethylpropylamine picrate, m.p. 109.5～111° (reported,[4] m.p. 108～109°) and 93 mg. of the same phenyl-diene (Ⅸ) which was identified with the sample obtained from the methiodide of Ⅶ by comparison of infrared spectra.

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*7 A Shimadzu Model GC-IB programmed vapor-phase chromatography, employing a 4 mm. × 2.25 m. stainless steel column packed with 1.5% SE-30 silicone gum on Chromosolv W was used at 200°.

4) W. Hanhart, C. K. Ingold : J. Chem. Soc., **1927**, 1007.

The Amide-phenylcarbinol (X)——A solution of 310 mg. of the styrene-amide (Ⅵ) in 25 ml. of a mixture of MeOH-H_2O-conc. HCl (1:1:1) was refluxed for 3 hr. The mixture was diluted with 50 ml. of H_2O, made alkaline with dil. NaOH solution and extracted with ether. After drying, removal of the solvent gave 310 mg. of an oily residue which partly crystallized on standing. The crude product, collected and washed with cooled ether, was recrystallized from hexane-AcOEt to 30 mg. of the amide-phenylcarbinol (X) as needles, m.p. 102～103°. The ultraviolet spectrum showed no absorption except that of a phenyl group. IR $\nu_{max}^{CHCl_3}$ 1620 (amide) and 3320 cm^{-1} (OH). *Anal.* Calcd. for $C_{17}H_{25}O_2N$: C, 74.14; H, 9.15; N, 5.09. Found: C, 73.95; H, 9.16; N, 4.97. The NMR spectrum showed absorptions at 7.0～7.6 (5H, multiplet, aromatic), 4.52 (1H, singlet, OH, disappeared with addition of acid), 3.7～4.2 (1H, four peaks centering at 3.95), 2.50 (3H, singlet: N-CH_3), 1.0～2.8 (12H, multiplet), and 0.65～1.0 p.p.m. (3H, multiplet).

Amino-phenylcarbinol (XI) and Its Methiodide (XII)——To a solution of 191 mg. of the amide-phenylcarbinol (X) in 2 ml. of anhyd. tetrahydrofuran was added 30 mg. of $LiAlH_4$ in small portions under stirring and the mixture was refluxed for 6 hr. The cooled mixture was processed as usual to give 155 mg. of a colorless liquid, which was distilled to give 128 mg. of the amino-phenylcarbinol (XI), b.$p_{0.05}$ 150° (bath temp.). IR $\nu_{max}^{liq.}$ 3200～3500 cm^{-1} (OH) and no absorption in C=O region. *Anal.* Calcd. for $C_{17}H_{27}ON$: C, 78.11; H, 10.41; N, 5.36. Found: C, 77.81; H, 10.26; N, 5.09. The NMR spectrum showed absorptions at 7.0～7.6 (5H, multiplet: aromatic), 5.1～5.6 (1H, broad: OH), 2.02 (3H, singlet: N-CH_3), 1.0～2.6 (15H, multiplet), and 0.85 (3H, triplet with J=7 c.p.s: -CH_2-$C\underline{H}_3$).

On treatment with CH_3I, the amine (XI) was converted into the methiodide (XII), m.p. 150°(decomp.), which was recrystallized from MeOH-ether as plates. Yield, 77%. IR ν_{max}^{Nujol} 3350 cm^{-1} (OH). *Anal.* Calcd. for $C_{18}H_{30}ONI \cdot \frac{1}{2}H_2O$: C, 52.43; H, 7.58; N, 3.40. Found: C, 52.14; H, 7.65; N, 3.24.

Hofmann Degradation of the Methiodide (XII)——A solution of 304 g. of the methiodide (XII) in 1 ml. of H_2O was stirred with 300 mg. of freshly prepared Ag_2O for 1 hr. After the solid was filtered off, the aqueous solution was evaporated *in vacuo* and finally distilled under thermal decomposition to give 120 mg. of 5-hexenyl phenyl ketone (XIII) as a pale yellow liquid, b.p_7 180～190° (bath temp.). UV λ_{max} 241 mμ (ε 8200) and 279 mμ (ε 850). IR $\nu_{max}^{liq.}$ cm^{-1}: 1686 (benzoyl), 1645, 989 and 910 (vinyl). The NMR spectrum showed absorptions at 5.82 (1H, multiplet) and 4.8～5.2 (2H, multiplet) which also corresponded to a vinyl group. The 2,4-dinitrophenylhydrazone of the oil (XIII) was obtained and recrystallized from EtOH as red needles, m.p. 142～143°. *Anal.* Calcd. for $C_{19}H_{20}O_4N$: C, 61.94; H, 5.47; N, 15.21. Found: C, 62.06; H, 5.52; N, 15.63.

Decomposision of 3-Methyl-9-hydroxy-9-phenyl-3-azabicyclo[3.3.1]nonane (Ia or IIa) in Aqueous Solution——A solution of 2.50 g. of the 9β-OH epimer (IIa), 3.0 g. of AcOH, and 18.0 g. of crystalline NaOAc in 200 ml. of H_2O was heated at 160～170° in an autoclave for 3 hr. The cooled mixture was acidified with dil. HCl to pH 2～3, and washed with ether. The aqueous layer was made basic with conc. NH_4OH and extracted twice with 20 ml. of ether. The combined extract was dried and evaporated to give 1.62 g. of a brown oil which was chromatographed on a silica gel column (30 g.). Removal of the solvent from benzene-$CHCl_3$ (1:1) eluate gave 57 mg. of an amine which was characterized by conversion into a picrate of m.p. 190°(decomp.). *Anal.* Calcd. for $C_{21}H_{24}O_4N_4$: C, 56.75; H, 5.44; N, 12.61. Found: C, 56.50; H, 5.48; N, 12.75.

The crystalline amine regenerated from the picrate was recrystallized from MeOH to leaflets, m.p. 47.5～48.5°. Its infrared spectrum was transparent in OH or C=O region, and the ultraviolet spectrum showed no absorption except that of a phenyl. *Anal.* Calcd. for $C_{12}H_{21}N$: C, 83.66; H, 9.83; N, 6.51. Found: C, 83.53; H, 9.83; N, 6.99.

The combined eluates from $CHCl_3$ and $CHCl_3$ containing 1% of MeOH was evaporated to give 404 mg. of the styrene-amine (Ⅶ) which was identified with the sample obtained earlier by thin-layer chromatography and infrared spectroscopy. The picrate obtained also from Ⅶ was identified with the authentic sample by mixing melting point and infrared spectroscopy.

Under the same condition as described above, the 9α-OH epimer was treated to give the same reaction product which was proved by thin-layer chromatography and gas chromatography.*7

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Summary

Either 3-methyl-9α-hydroxy-9β-phenyl-3-azabicyclo[3.3.1]nonane (Ia) or 9β-hydroxy epimer (IIa) was treated in boiling alcohol in the presence of an acid to yield 9β-alkoxy compound (IIb) as a major product. Ia or IIa was decomposed with propionic anhydride at 160～170° into one and the same reaction product from which styrene derivatives (Ⅵ and Ⅶ) were isolated. These facts illustrated the tendency of the skeleton of 9-phenylazabicyclo[3.3.1]nonane to yield the carbonium ion (V).

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