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Studies on Structure-Activity Relationship of Analgetics. X.[1] Syntheses of 11-Amino-2,3-benzobicyclo[3.3.1]nonane and 3-Phenyl-9-amino-bicyclo[3.3.1]nonane Derivatives[2]

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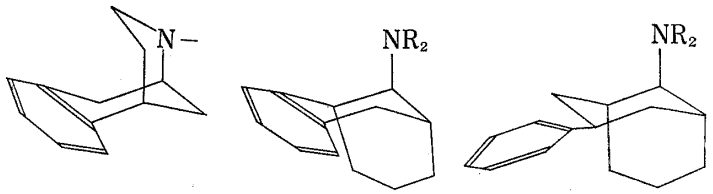
Some derivatives of 11-amino-2,3-benzobicyclo[3.3.1]nonane and 3-phenyl-9-amino-bicyclo[3.3.1]nonane were synthesized from β-tetralon and 4-phenylcyclohexanone, respectively, through an enamine cyclization. Configuration and conformation of these bicyclic compounds were elucidated by nuclear magnetic resonance spectral analysis.

A peculiar property, resembling to Sommelet reaction, of the amino group attached to bridged methylene in bicyclic system is presented.

The mass spectra of the amino derivatives of bicyclo[3.3.1]nonane system are discussed.

For the systematic studies on the relationship between chemical structure and pharmacological activity of analgetics, we had already reported the syntheses of some diazabenzobicyclo[3.3.1]nonane and azabenzobicycloalkane systems[1] possessing a frame-work comparable with that of 6,7-benzomorphan. Now, in this paper we report the syntheses and mass spectrometry of some derivatives of 11-amino-2,3-benzobicyclo[3.3.1]-nonane (**A**) and 3-phenyl-9-amino-bicyclo[3.3.1]nonane (**B**) in which the spacial arrangement of aromatic ring and nitrogen atom similar to that in morphine is retained, and a peculiar property, resembling to Sommelet reaction, of the primary amino group attached to bridged methylene in the bicyclic system.



benzomorphan A B

Chart 1

Though some feasible routes were considered, the route involving an enamine cyclization with acrolein[4] was chosen for the synthetic purpose because it was expected that the sequence would be straightforward and simple to perform.

Thus, pyrrolidine enamine (II)[5] of 3,4-dihydronaphthalen-2(1*H*)-one (I) was treated with acrolein in benzene to afford 4-pyrrolidino-2,3-benzobicyclo[3.3.1]nonan-11-one (III). After ketalization of III with ethylene glycol, the product was treated with hydrogen peroxide to give the corresponding N-oxide (IV). The N-oxide ketal was pyrolized at 150—220° under reduced pressure[4a,6] followed by hydrolysis of the ketal to yield an unsaturated ketone

1) Part IX: K. Mitsuhashi, S. Shiotani, R. Oh-uchi and K. Shiraki, *Chem. Pharm. Bull.* (Tokyo), **17**, 434 (1969).
2) This work was presented at the Annual Meeting of Pharmaceutical Society of Japan, April, 1969, Nagoya.
3) Location: *a*) *Gofuku, Toyama*; *b*) *Hongo, Toyama.*
4) *a*) C.S. Foote and R.B. Woodward, *Tetrahedron*, **20**, 689 (1964); *b*) G. Stork, *J. Am. Chem. Soc.*, **78**, 5129 (1956); *c*) R.N. Schut and T.M.H. Liu, *J. Org. Chem.*, **30**, 2845 (1965); *d*) R.D. Allan, B.G. Gordiner and R.J. Wells, *Tetrahedron Letters*, **1968**, 6055.
5) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).
6) A.C. Cope, T.T. Foster and P.H. Towle, *J. Am. Chem. Soc.*, **71**, 3929 (1949).

(V). For the purification the crude ketone was chromatographed on silica gel column and thus V was afforded as a colorless oil boiling at 125—135°/1.5 mm, which showed one peak in gas chromatography. The over-all yield of V from I was about 10%. In the nuclear magnetic resonance (NMR) spectrum V showed a multiplet of aromaitc protons at 2.95 τ (4H), a multiplet of olefin protons at 4.19—4.62 τ (2H) and a complex multiplet of aliphatic protons at 6.35—7.70 τ (6H).

Catalytic reduction of V over palladium–charcoal in ethanol gave a saturated ketone (VI) contaminated with considerable amounts of its diethyl ketal (VI'). The ketone (VI), bp 130—135°/1.5 mm (mp 49.5—52°), exhibited $\nu_{C=O}$ absorption at 1720 cm^{-1} in the infrared (IR) spectrum and no olefinic proton signal in NMR spectrum, and the elemental analysis was in accord with the calculated values. The oxime (VII) of VI was reduced over Adams catalyst to give an oily basic product which showed two peaks in gas chromatography (ratio, *ca.* 1:1). The two components were separated by preparative gas chromatography and confirmed to be epimers of 11-amino-2,3-benzobicylo[3.3.1]nonane (VIII) by the following facts. In the IR spectrum both showed ν_{NH} absorption at 3400 and 3280 cm^{-1} and δ_{NH} at 1580 cm^{-1} characteristic of primary amino group. The mass spectra of them exhibited parent peak at *m/e* 187 with abundant fragment peaks at *m/e* 170, 142, 141, 129, 128 and 115, respectively.

The amino derivative (VIII) was converted to 11-(N,N-dimethylamino)-2,3-benzobicyclo[3.3.1]nonane (IX) by catalytic reduction of a mixture of VIII and formalin over palladium–charcoal. The N,N-dimethyl derivative was also composed of two epimers (IXa and IXb), which were separated by preparative gas chromatography (ratio, *ca.* 1:1). Mass spectra of the both isomers exhibited parent peak at *m/e* 215 and abundant fragments at *m/e* 172, 171, 170, 142, 141, 129, 128 and 115, respectively. In the NMR spectrum the isomer of the shorter retention time (IXa) showed a singlet of N-methyl protons at 7.87 τ (6H) and the other (IXb) at 7.73 τ (6H). The 0.14 ppm difference in the N-methyl chemical shift between IXa and IXb would be the result of a change in environment of the N-methyl from a position above the aromatic ring to one away from the aromatic ring. In the former case ring current

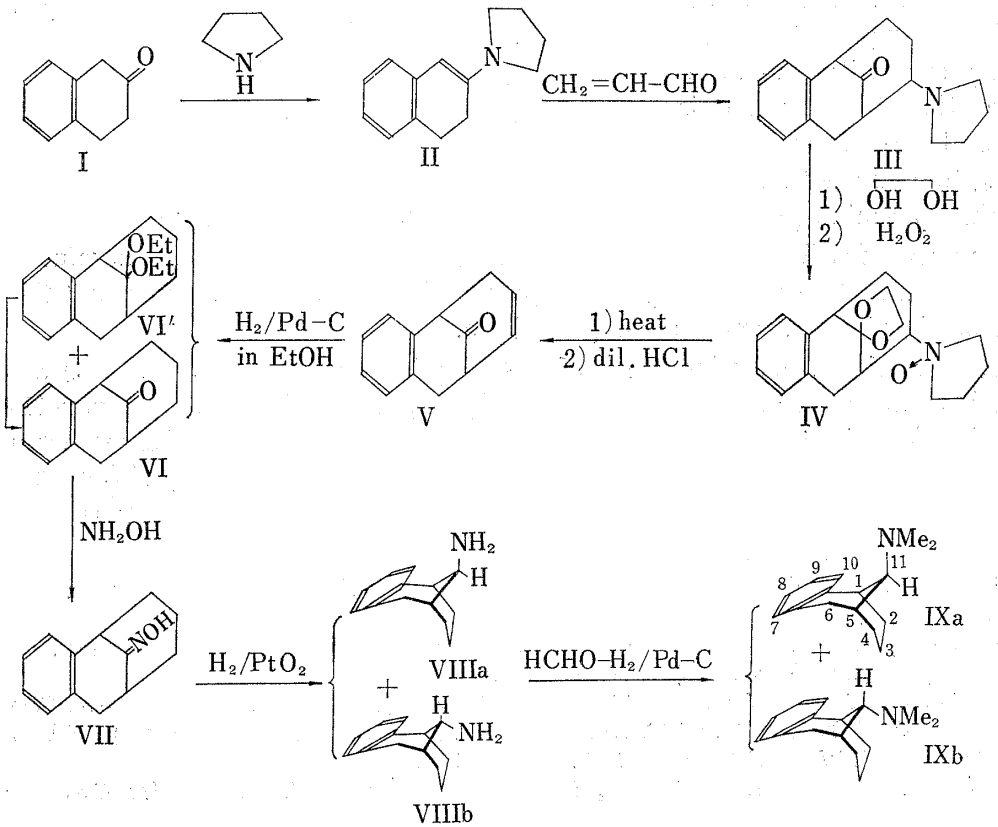


Chart 2

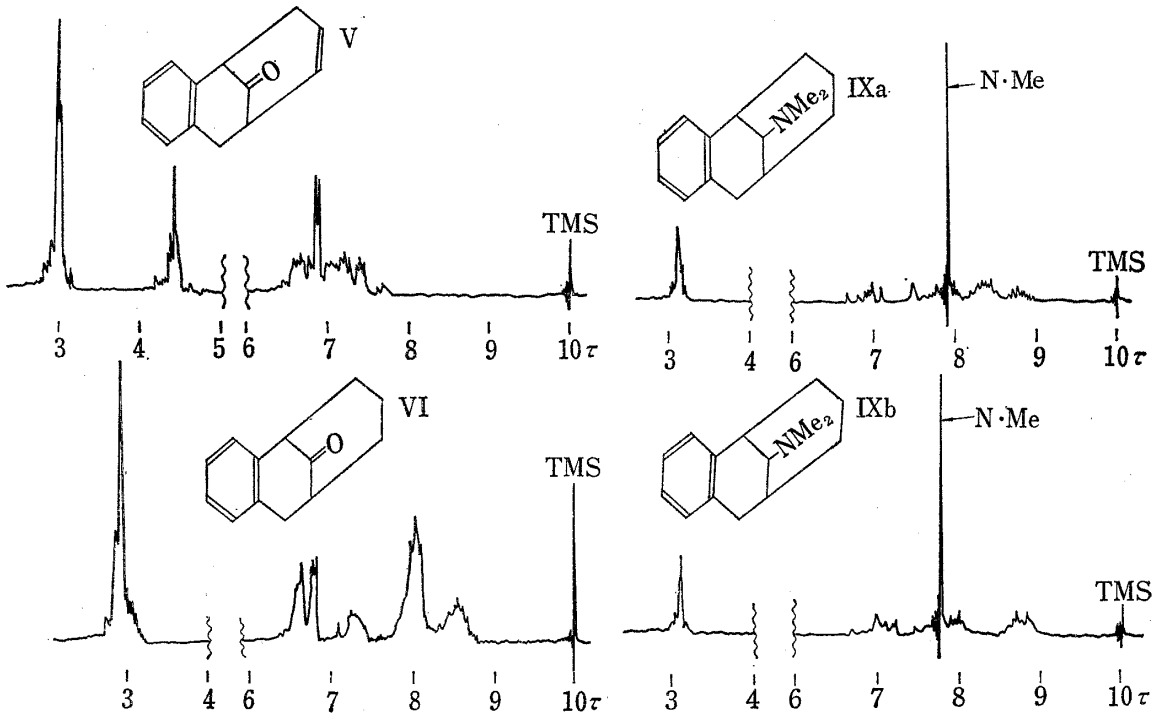


Fig. 1. NMR Spectra of V, VI, IXa and IXb

effect would produce a upfield shift. Thus, the configuration of the amino group in IXa would be confirmed to be close to the aromatic ring and that in IXb apart from the aromatic ring.

In a similar manner as above, morpholine enamine (XI) of 4-phenylcyclohexanone (X)[7] was condensed with acrolein to give 2-morpholino-7-phenylbicyclo[3.31]nonan-9-one (XII). After N-oxidation of the ethylene ketal of XII, the N-oxide ketal (XIII) was pyrolyzed at 155—205° under reduced pressure to give Δ^2-7-phenylbicyclo[3.3.1]nonen-9-one (XIV) as colorless needles, mp 134—135°. The over-all yield of XIV from the enamine (XI) was about 21%. The NMR spectrum of XIV exhibited a multiplet signal of olefinic protons at 3.90—4.51 τ (2H, $J_{2,3}$=10.0 cps, $J_{1,2}$=5.5 cps, $J_{3,4}$=3.0 cps, $J_{2,4}$=1.5 cps) and a multiplet signal of C_7-proton at 6.58 τ (1H, $J_{6ax,7}=J_{7,8ax}$=9.5 cps, $J_{6eq,7}=J_{7,8eq}$=8.4 cps). The unsaturated ketone (XIV) was catalytically reduced over palladium–charcoal in methanol, followed by hydrolysis of the contaminating dimethyl ketal (XV'), to afford 3-phenylbicyclo-[3.3.1]nonane-9-one (XV) which was purified as the oxime (XVI) of colorless plates melting at 209—211°. When the oxime was reduced over Adams catalyst, an amino derivative (XVII) was obtained, which showed ill-splitted two peaks in gas chromatography suggesting the presence of epimers.

The amino derivative (XVII) was derived to the N,N-dimethylamino derivative (XVIII) by catalytic reduction of a mixture of XVII and formalin over palladium-charcoal. The two epimers of XVIII (ratio, *ca.* 1:1) were separated by preparative gas chromatography. The isomer of the shorter retention time (XVIIIa) showed an N-methyl signal at 6.78 τ (6H) in NMR sepctrum and ν_{C-H} of N-methyl at 2800 and 2765 cm^{-1} in IR spectrum, and the other (XVIIIb) at 6.81 τ (6H) and 2800, 2760 cm^{-1}.

Conformations and configurations of these phenyl–bicyclic compounds were elaborated by examination of their NMR spectra. In NMR spectrum, XIV, XV, XVIIIa and XVIIIb exhibited multiplet signal of similar pattern at 6.57 τ ($J_{6ax,7}=J_{7,8ax}$=9.5 cps, $J_{6eq,7}=J_{7,8eq}$ =8.4 cps), 6.28 τ ($J_{6ax,7}=J_{7,8ax}$=10.5 cps, $J_{6eq,7}=J_{7,8eq}$=8.2 cps), 6.77 τ ($J_{6ax,7}=J_{7,8ax}$=13.0

7) H.E. Ungnade, *J. Org. Chem.*, **13**, 361 (1948).

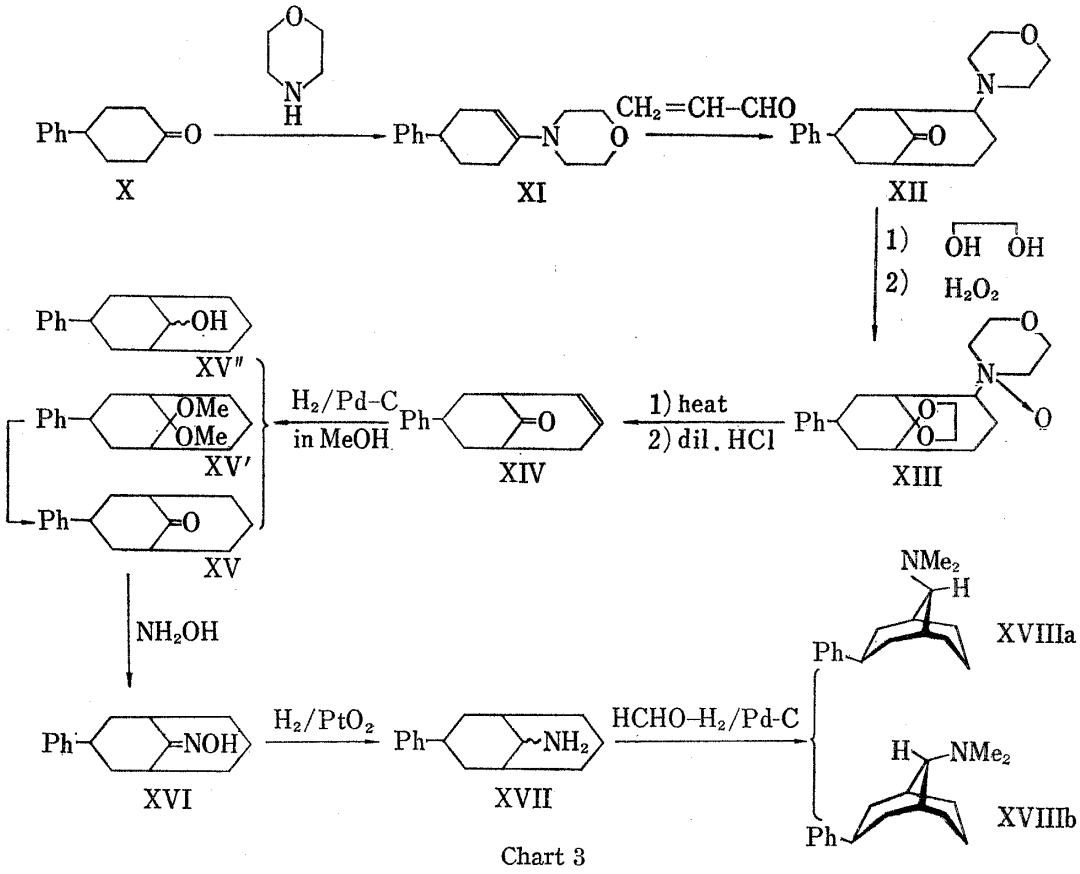


Chart 3

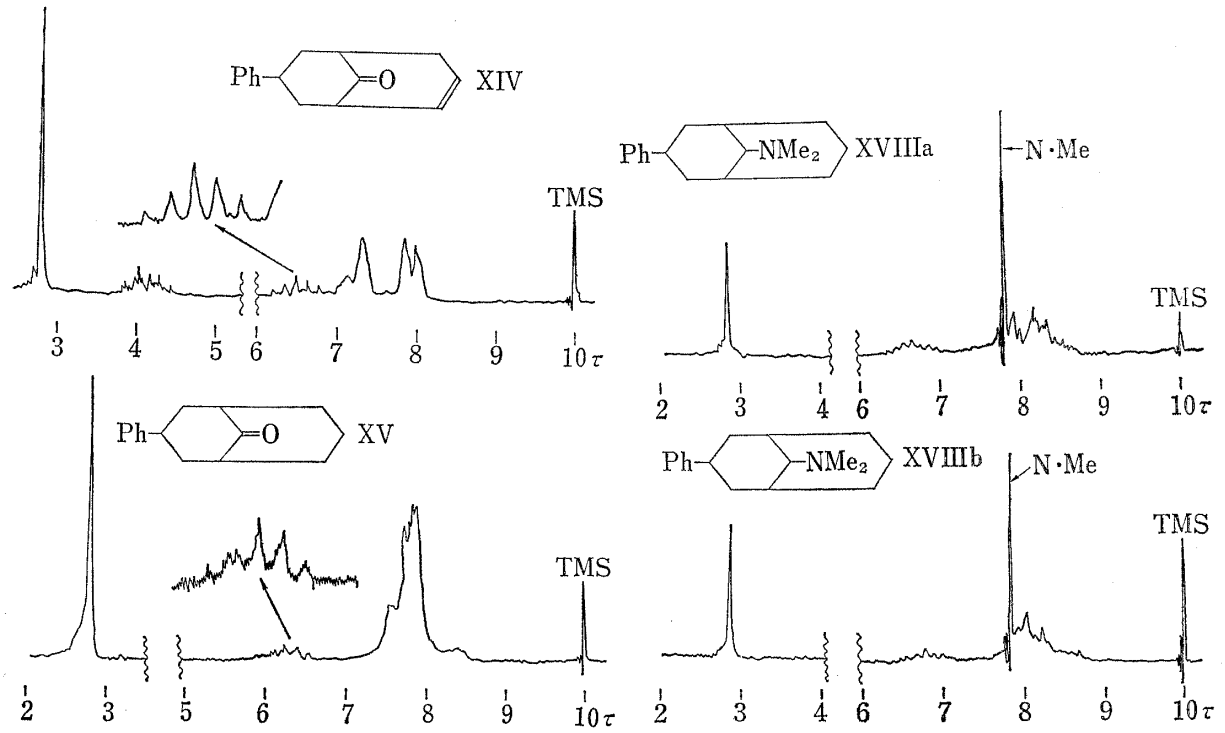


Fig. 2. NMR Spectra of XIV, XV, XVIIIa and XVIIIb

cps, $J_{6eq,7}=J_{7,8eq}=6.0$ cps) and 6.65 τ ($J_{6ax,7}=J_{7,8ax}=13.0$ cps, $J_{6eq,7}=J_{7,8eq}=6.0$ cps), respectively, which were ascribable to C_7-proton in each compound. The coupling constants would be related to the dihedral angles between C_7–H—C_6–H and C_7–H—C_8–H, consequently, the phenyl orientation in these compounds were assumed to be equatorial in chair conforma-

tion of the phenyl substituted ring (**a**) or equatorial in boat (**b**) as shown in Fig. 3.

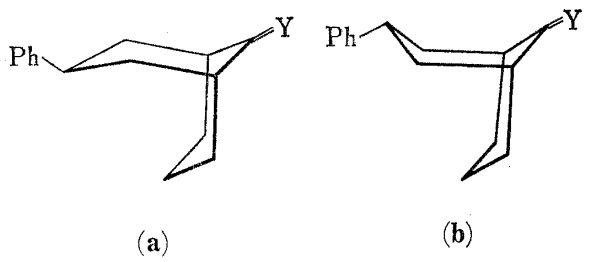


Fig. 3

As shown by the Dreiding models, the difference (0.29 ppm) in chemical shift of C_7–H between XIV and XV would be due to the paramagnetic effect of carbon–carbon double bond which influences to the C_7–H only when the phenyl substituted ring has chair conformation; moreover, the difference (0.49 or 0.37 ppm) between XV and XVIIIa or XVIIIb would be the result of diamagnetic effect of the carbonyl group to the C_7–H in chair conformation of the ring. On the other hand, the stereochemical preference of the alkylation of enamine would be similar to that of enol or enolate anion,[8] and the phenyl orientation in enamine (XI) would be equatorial in half-chair conformation; therefore, the cyclization would proceed through parallel attack of acrolein on the enamine to give the product having *trans* configuration of the phenyl group to the newly created ring. From these considerations and reports on the conformation of bicyclo[3.3.1]nonane,[9] it may be concluded that the compounds XV, XVIIIa and XVIIIb have twin–chair conformation (chair–half chair for XIV) and the phenyl orientation is equatorial.

The configurations of amino group in XVIIIa and XVIIIb could not be determined by NMR examination because of the too small difference (0.04 ppm) in chemical shift of N-methyl signals.[10] However, if may be assumed that the isomer of the shorter retention time (XVIIIa) should have *cis* orientation to the phenyl group and that of the longer (XVIIIb) the *trans*, respectively, from the comparison of the stereochemiacal structure and the retention time of XVIIIa and XVIIIb with those of IXa and IXb whose dimethylamino orientations were elucidated in the above, and from the general relation that the retention time of the compounds having an axial substituent tend to be shorter than that of the compounds with equatorial group.[11]

When the primary amine (VIII) was submitted to Eschweiler–Clarke reaction, considerable amounts of ketone (VI) was obtained along with the intended N,N-dimethyl derivative, and this result led us to inquire as to the reason why such a reaction occurred. As it was proved that the ketone could not be formed by air oxidation of VIII, a reaction of VIII with formalin in methanol containing a small amount of acetic acid was tried; and from the reaction mixture ketone (VI) and 11-methylamino-2,3-benzobicyclo[3.3.1]nonane (XIX) were obtained. In the NMR spectrum, XIX exhibited signals due to N-methyl protons at 7.56 τ (3/2H, singlet) and 7.67 τ (3/2H, singlet), and NH proton at 9.11 τ (1H, singlet, disappeared by treating with D_2O).

The same reactions with 9-amino-3-phenylbicyclo[3.3.1]nonane (XVII) and 9-aminobicyclo[3.3.1]nonane (XXIII) also afforded 3-phenylbicyclo[3.3.1]nonan-9-one (XV) and 9-methylamino-3-phenylbicyclo[3.3.1]nonane (XXIV), and bicyclo[3.3.1]nonan-9-one (XXI) and 9-methylaminobicyclo[3.3.1]nonane (XXV), respectively. Compound XXIV showed N-methyl signals at 7.58 τ (3/2H, singlet) and 7.61 τ (3/2H, singlet) and NH signal at 8.90 τ

8) *a*) E.L. Eliel, N.L. Allinger, S.J. Angyal and G.A. Morrison, "Conformational Analysis," John Wiley and Sons. Inc., New York, 1965, p. 307; *b*) Z. Horii, T. Imanishi and S-W. Kim, *Chem. Pharm. Bull.* (Tokyo), **16**, 1918 (1968).

9) *a*) N.L. Allinger, J.A. Hirsch, M.A. Miller, I.J. Tyminski and F.A. Van-Catledge, *J. Am. Chem. Soc.*, **90**, 1199 (1968); *b*) W.A.C. Brown, J. Martin and G.A. Sim, *J. Chem. Soc.*, **1965**, 1844.

10) It is reasonable that the internal free rotation of the phenyl and the N,N-dimethylamino groups reduced the ring current effect of phenyl group to the *cis* N-methyl protons.

11) I. Matsuo, K. Sugimoto and S. Ohki, *Chem. Pharm. Bull.* (Tokyo), **16**, 1680 (1968).

(1H, singlet, disappeared by treating with D_2O) in the NMR spectrum, and ν_{C-H} band of N-methyl at 2760 cm^{-1} in the IR spectrum. Compound XXV showed in the NMR spectrum N-methyl signal at 7.65 τ (3H, singlet) and NH signal at 9.35 τ (1H, singlet, disappeared by treating with D_2O), and in the IR spectrum ν_{C-H} band of N-methyl at 2780 cm^{-1}. Elemental analyses of both XXIV and XXV were in accord with the calculated values, respectively. From these facts the structures of XXIV and XXV were confirmed.

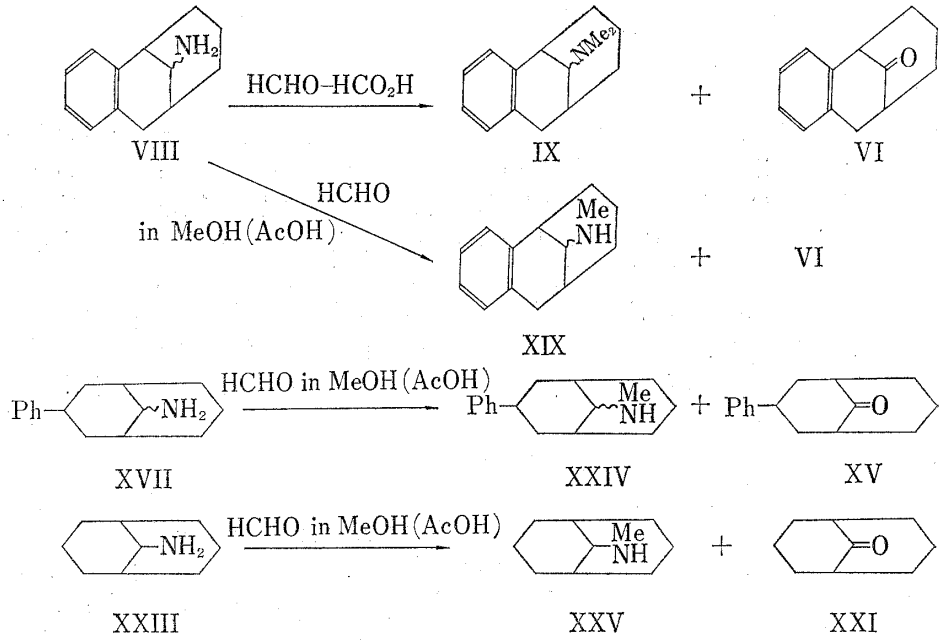


Chart 4

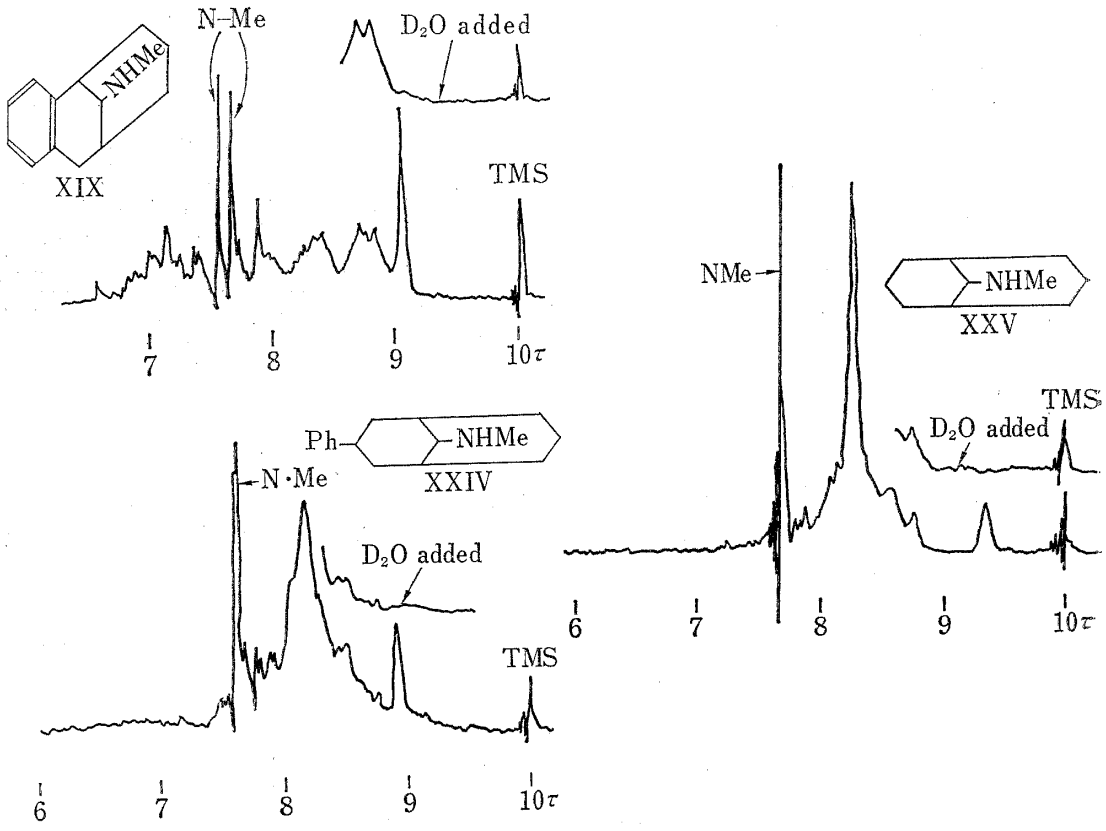
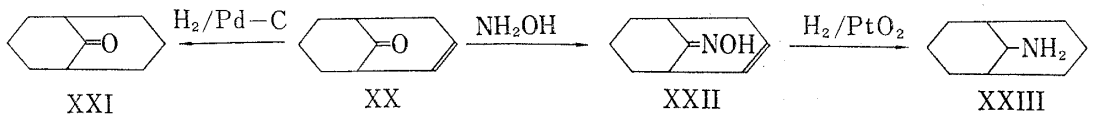


Fig. 4. NMR Spectra of XIX, XXIV and XXV

9-Aminobicyclo[3.3.1]nonane (XXIII) used for the above disproportionation reaction was prepared from Δ^2-bicyclo[3.3.1]nonen-9-one (XX)[4a] by oximation, followed by catalytic reduction of C=C bond and hydroximino group.



XXI XX XXII XXIII

Chart 5

These results suggested that ketones (VI, XV and XXI) were produced not by a simple oxidation but through an oxidation–reduction process mechanistically resembling to Sommelet reaction,[12] and such a behavior would be characteristic of primary amino group attached to bridged methylene in bicyclic system. A mechanism for this reaction may be postulated: the conjugated acid (**b**′) of an azomethine (**b**) formed by condensation of amine (**a**) with formaldehyde dehydrogenates the amine (**a**) to afford imine (**c**), which is then hydrolyzed to ketone (Chart 6).

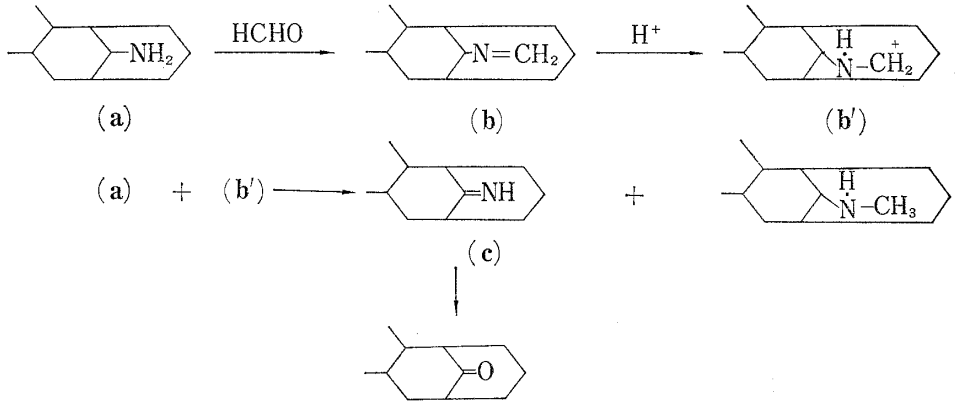


Chart 6

Mass Spectra

In order to see if any feature concerning to the structure of the little-known amino derivatives of bicyclo[3.3.1]nonane system could be found in the fragmentation processes, we examined the mass spectra of VIII, IX, XVIII, XXIV and XXV.

The results indicate that in the benzobicyclo[3.3.1]nonane derivatives, elimination of HNR_2 is the major primary decomposition process, while in the phenyl substituted and unsubstituted bicyclo[3.3.1]nonanes, entirely different processes from that of benzo-system take place.

The 75 eV spectra are shown in Fig. 5. In VIII and IX the ion at *m/e* 170 (**b** or **b**′) is one of the most intense peak, which was confirmed to be $C_{13}H_{14}$ by high resolution mass spectrum (hrms), and the fragmentation process for the formation of the ion was supported by the presence of metastable ion at *m/e* 154.6 (Calcd. 154.6) for VIII and at *m/e* 134.5 (Calcd. 134.4) for IX. This fragment ($M-HNR_2$) which scarecely occurred in the usual aliphatic and alicyclic amines[13] would be explained if some initial bond-cleavage takes place in the benzylically activated 1—2 position of M^+, to give ion **a** which then loses an amine unit accompanying migration of hydrogen to give ion **b** or **b**′.

12) S.J. Angyal, "Organic Reactions," Vol. 8, Chapter 4, John Wiley and Sons, Inc., New York, 1954.
13) H. Budzikiewicz, C. Djerassi and D.H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, Inc., San Francisco, 1964, pp. 63—90.

Ion **b** would lose an ethylene unit to give ion **c**, from which a hydrogen may be eliminated to produce ion **d** ($C_{11}H_9$ by hrms). Ion **d** would be also formed by loss of an ethyl radical from ion **b** (m* 117 for **b**→**d**, Calcd. 117). Furthermore, loss of an acetylene unit from **d** would produce ion **e** (C_9H_7 by hrms). For the formation of ion **g** ($C_{10}H_8$ by hrms) two processes may be possible, *i. e.* rupture of a propylene unit from **b** would give **g** directly, and loss of an allyl radical from **b'** would yield ion **f** ($C_{10}H_9$, by hrms) which the nloses a hydrogen to give **g**.

The only notable difference in the spectra of the primary amine (VIII) and the tertiary amine (IX) was appearance of a peak at *m/e* 172 ($C_{12}H_{14}N$ by hrms, ion **h**) on passing to the tertiary amine.

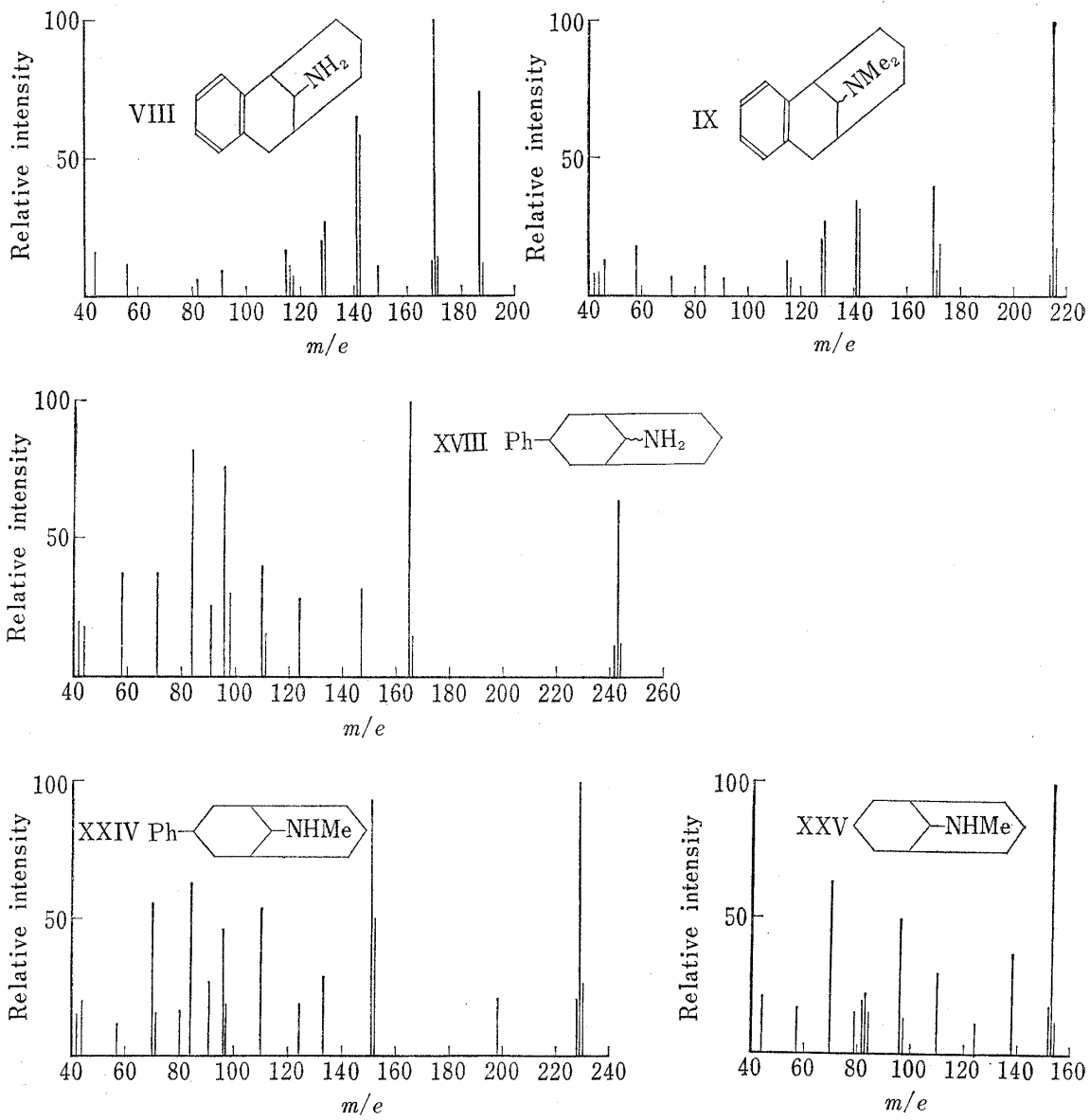


Fig. 5. Mass Spectra of VIII, IX, XVIII, XXIV and XXV

In the spectrum of XVIII, M–$HNMe_2$ peak (*m/e* 198) was almost neglisible, while the most abundant ion occurred at *m/e* 165 (ion **j**) which would be formed from M^+ through an intermediate ion **i** by losses of C_6H_5 and H·. Migration of a hydrogen from 9 to 3 in ion would produce ion **k**, from which methyl radical and methyl isocyanide unit would be successively eliminated to give ion **l** (C_8H_{14} by hrms). Ion **j** would decompose further through fission of allylically activated C–C bond at 4—5 and the subsequent expulsion of allyl radical

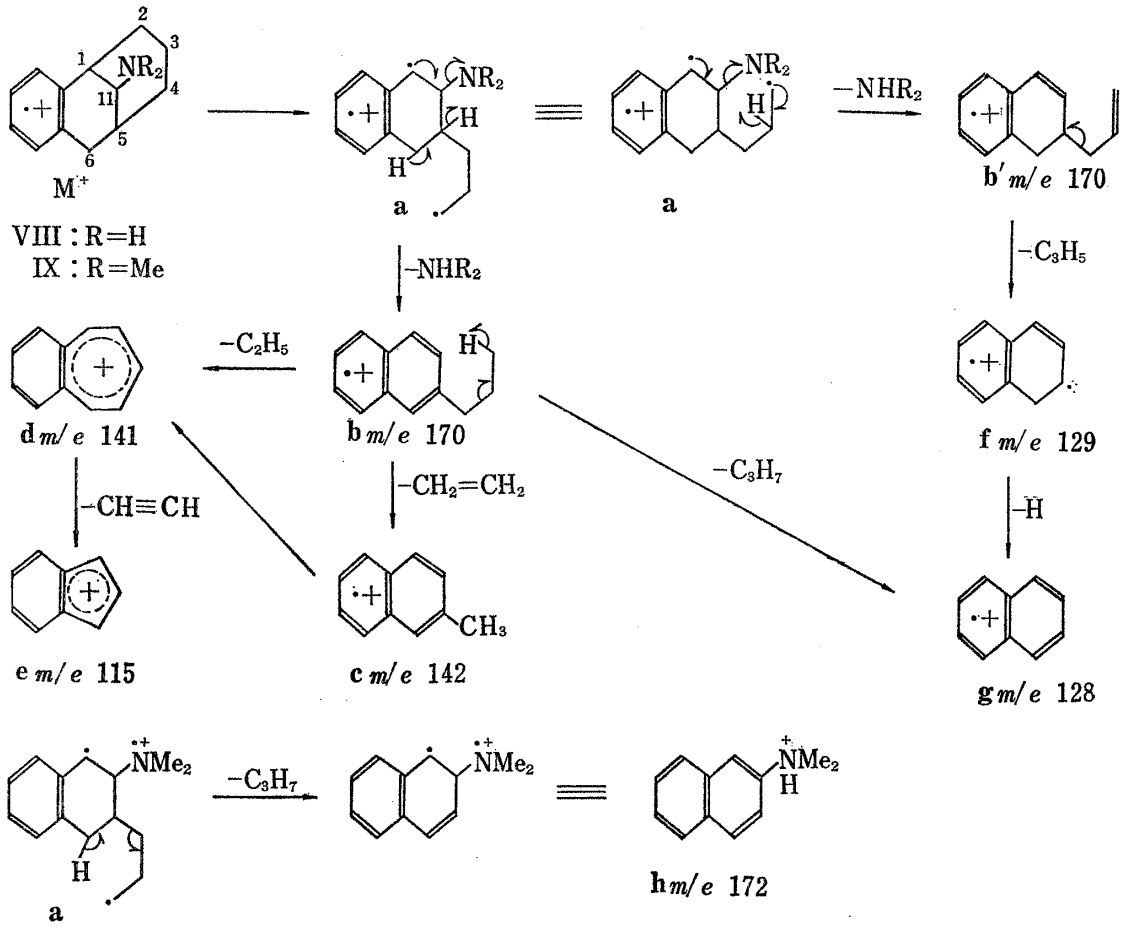


Chart 7

to ion **m** ($C_8H_{14}N$ by hrms). Alternatively, cleavage of C–C bond at 1—9 in **j** would give ion **n**, and further break-up of **n** through cleavage of C–C β to nitrogen atom with concerted rupture of γ-bond would produce ion **p** ($C_5H_{10}N$ by hrms). Ion **p'** (C_4H_9N by hrms) would arise from ion **o** through a hydrogen transfer and the subsequent α-cleavage. Fragmentation process for the formation of ion **s** ($C_{10}H_{13}N$ by hrms) and ion **t** (C_7H_{12} by hrms) may be proposed as follows. Initial cleavage of benzylically activated bond at 2—3 in M^+ would produce ion **q** which would rearrange to give ion **r**. A concerted homolytic fission of the four-membered ring would form ion **s** or ion **t**.

The mass spectrum of monomethylamino derivative (XXIV) showed exactly similar fragmentation process to that of dimethyl-amino derivative (XVIII).

In case of 9-methylaminobicyclo[3.3.1]nonane (XXV), the spectrum showed a moderately intense peak of M–Me at *m/e* 138. The fragment at *m/e* 110 (C_8H_{14}) (ion **u**) would arise from M^+-1 ion through the loss of HCN and Me radical. An α-cleavage at 1—9 bond in M^+ would give ion **v** from which ions **x**, **x'**, **y** and **z** would be produced throuh processes similar to those of XVIII.

Experimental[14]

2,3-Benzo-Δ^6-bicyclo[3.3.1]nonen-9-one (V)——A mixture of 5.5 g of β-tetralon (I) and 4.4 ml of pyrrolidine in benzene (100 ml) was refluxed under water separator for 3.5 hr. After evaporation of the solvent and the excess of pyrrolidine *in vacuo*, the crude crystalline enamine was dissolved in 45 ml of dioxane.

14) All melting points were determined on a Yanagimoto Micro Melting Point Apparatus and uncorrected. NMR spectra were taken on a JNM-C-60H recording spectrometer in CCl_4 with TMS as an internal standard.

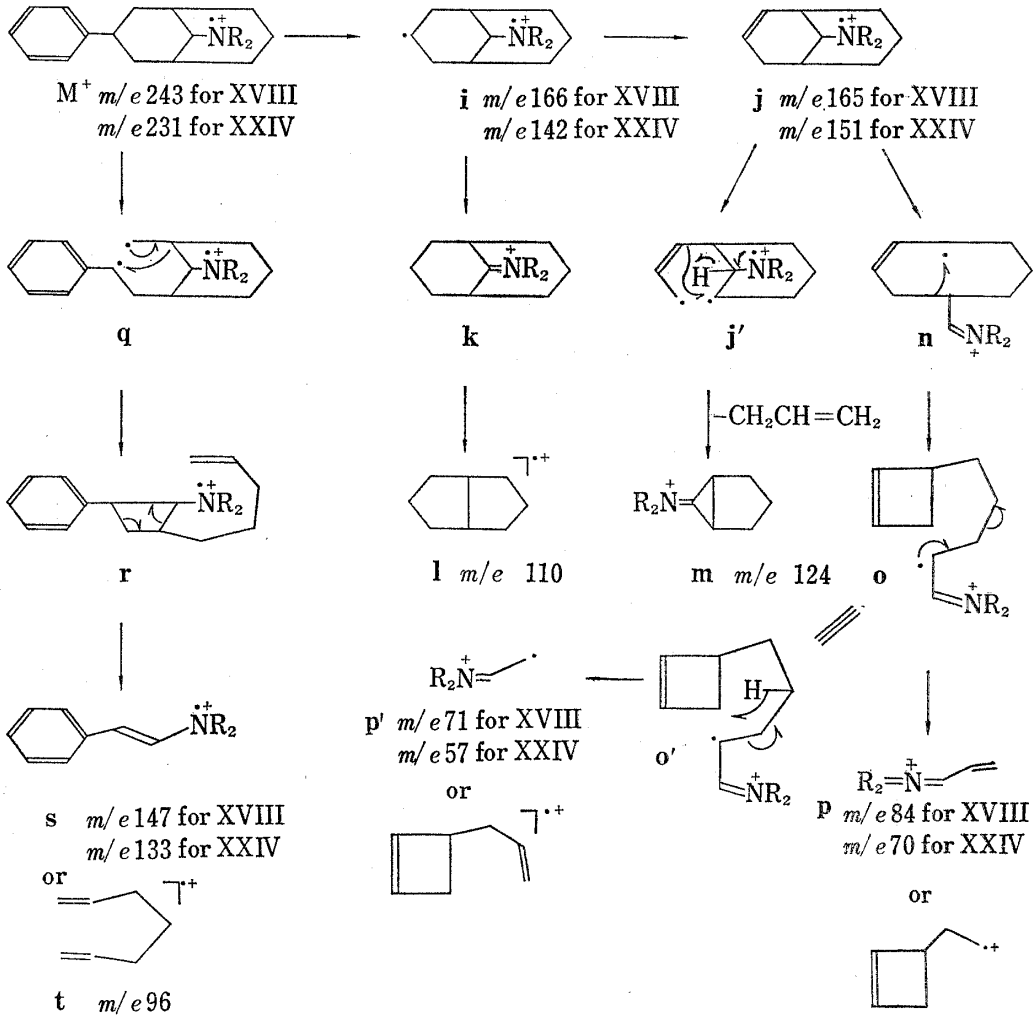


Chart 8

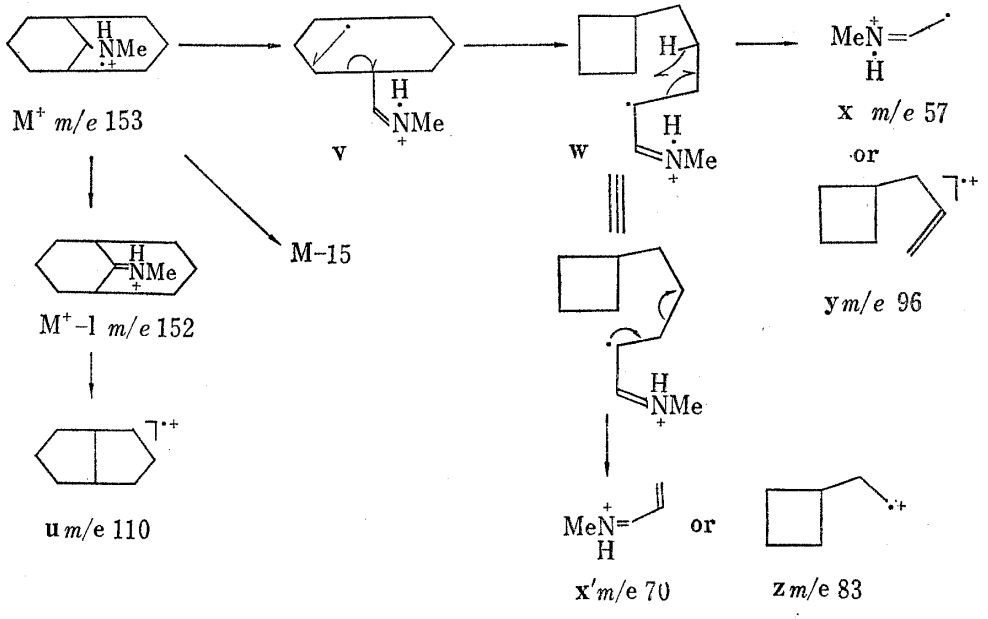


Chart 9

To this solution 2.0 g of acrolein in 5 ml of dioxane was added with cooling and stirring, and stood for 1.5 hr at room temperature. After evaporation of the solvent, the residual syrup was distilled *in vacuo*, and a fraction boiling at 165—185° (0.5 mmHg (7.8 g)) was collected.

A mixture of the distillate (7.8 g) (III), 25 g of ethylene glycol and 9 g of *p*-toluenesulfonic acid was heated on a water bath for 2.5 hr. After cooling, the mixture was poured into ice cold KOH solution (9 g in 250 ml) and extracted with ether. The residue of the dried ethereal solution was distilled *in vacuo* to give 7.0 g of light brown viscous oil (bp 160—185°/0.2 mmHg), which exhibited no $\nu_{C=O}$ absorption. The distillate (7.0 g) was dissolved in 20 ml of MeOH, and refluxed with 10 ml of H_2O_2 (30%) on a water bath for 7 hr.

To the cooled solution a small amount of palladium black was added to decompose the excess peroxide and stirred at room temperature for 30 hr. After removal of the catalyst and the solvents, the residue was pyrolyzed at 150—200° and 5—6 mmHg. The product which had distilled into an ice-salt cooled trap was dissolved in ether and washed with 10% HCl, with 5% $NaHCO_3$ and water. After the solvent had been removed, the residue was distilled *in vacuo* to yield a distillate of bp 100—175° (1.5 mmHg (2.0 g)). A solution of the distillate (2.0 g) and 10 ml of 3% HCl in 30 ml of MeOH was refluxed for 3 hr. The solution was cooled, diluted with 100 ml of water, and extracted with ether. The extract was washed with water, dried over Na_2SO_4 and evaporated the solvent.

Distillation of the pale yellow residue gave 1.5 g of a colorless viscous oil of bp 100—135° (1.0 mmHg). The distillate (1.5 g) was chromatographed on a silica gel (60 g) column, and an eluate with benzene gave 0.8 g of V as a pale yellow oil boiling at 125—135° (1.5 mmHg). The distillate exhibited one peak in gas chromatography (SE-30 5%, 1.5 m, column temp. 145°) and one spot in thin-layer chromatography on silica gel. IR ν_{max}^{liq} cm^{-1}: 3000, 1705, 1625, 1490, 769, 748, 720 708 and 695.

2,3-Benzobicyclo[3.3.1]nonan-9-one (VI)——A solution of 0.8 g of V in EtOH (15 ml) was shaken with H_2 over Pd-C (40%). After uptake of 100 ml of H_2, the solution was filtered and the solvent evaporated yielding 0.8 g of colorless viscous oil, which was distilled *in vacuo*, bp 100—135° (1.5 mmHg).

The distillate exhibited two peaks in gas chromatography (ratio: *ca.* 4:1) which were separated preparatively by gas chromatography. The fraction of the shorter retention time (major component) solidified and was recrystallized from *n*-hexane to give colorless fine needles, mp 49.5—52°. IR ν_{max}^{KBr} cm^{-1}: 1720 ($\nu_{C=O}$). *Anal.* Calcd. for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.96; H, 7.73.

The fraction of the longer retention time (minor component) showed no $\nu_{C=O}$ absorption in IR spectrum and exhibited signals attributable to ethoxyl group in NMR spectrum.

Hydrolysis of the fraction by refluxing with dil. HCl in MeOH afforded the ketone (VI).

9-Amino-2,3-benzobicyclo[3.3.1,]nonane (VIII)——A solution of 286 mg of VI, 200 mg of $NH_2OH \cdot HCl$ and 300 mg of AcONa in 50% EtOH (5 ml) was refluxed for 2 hr. After evaporation of EtOH, the residue was dissolved in $CHCl_3$ and washed with water and with $NaHCO_3$ solution then dried over Na_2SO_4.

The colorless syrupy residue (271 mg) of the chloroform solution was hydrogenated on a platinum catalyst (50 mg) in AcOH (6 ml). After uptake of 75 ml of H_2, the solution was filtered and the solvent evaporated. The residue was dissolved in $CHCl_3$, washed with dil. NaOH and with water. Evaporation of the dried extract and distillation of the residue gave the amine (VIII) as a colorless oil, bp 110—130° (1 mmHg).

Hydrochloride: colorless needles, mp~250° (sublime) (MeOH–AcOEt). *Anal.* Calcd. for $C_{13}H_{17}N \cdot HCl$: C, 69.78; H, 8.11; N, 6.26. Found: C, 70.90; H, 8.21; N, 6.13.

Two epimers (VIIIa and VIIIb) were separated by preparative gas chromatography, both of which exhibited parent peak at *m/e* 187 and the same fragmentation pattern in mass spectrum.

VIIIa (shorter retention time): IR ν_{max}^{liq} cm^{-1}: 3390, 3280 (broad, ν_{NH}), 1580 (broad, δ_{NH}), 765 and 725.
VIIIb (longer retention time): IR ν_{max}^{liq} cm^{-1}: 3390, 3300 (broad, ν_{NH}), 1580 (broad, δ_{NH}), 763, 737, 721 and 703.

9-(N,N-Dimethylamino)-2,3-benzobicyclo[3.3.1]nonane (IX)——a) A mixture of VIII (14.3 mg) and formalin (37%, 0.02 ml) in MeOH (10 ml) was shaken with H_2 over Pd-C (40%) for 5 hr. After removal of the catalyst and the solvent, the resultant syrup was dissolved in $CHCl_3$ and washed with $NaHCO_3$ solution and with water. The residue (14.0 mg) of the dried $CHCl_3$ solution was distilled *in vacuo* to give IX as a colorless oil, bp 100—120° (5 mmHg (bath temp.)). IX was submitted to preparative gas chromatography to separate the two epimers (IXa and IXb).

IXa (shorter retention time): IR ν_{max}^{liq} cm^{-1}: 2805, 2760 ($N-Me_2$), 765, 757, 725 and 717. Picrate: yellow sandy crystals, mp 200—205° (decomp.) (MeOH). *Anal.* Calcd. for $C_{15}H_{21}N \cdot C_6H_3O_7N_3$: C, 56.75; H, 5.44; N, 12.61. Found: C, 56.65; H, 5.36; N, 12.72.

IXb (longer retention time): IR ν_{max}^{liq} cm^{-1}: 2805, 2760 ($N-Me_2$), 763, 740 and 720. Picrate: yellow prisms, mp 205—209° (decomp.) (MeOH). *Anal.* Calcd. for $C_{15}H_{21}N \cdot C_6H_3O_7N_3$: 56.75; H, 5.44; N, 12.61. Found: C, 56.75; H, 5.46; N, 12.68.

b) A mixture of VIII (0.19 g), formalin (37%, 0.3 ml) and HCO_2H (0.5 ml) was heated on a water bath for 1 hr. After evaporation of the excess formalin and formic acid, the residue was dissolved in dil. HCl and extracted with ether. The ethereal extract was washed with $NaHCO_3$ solution and with water, and dried over Na_2SO_4. The IR spectrum of the residue (92 mg) of the ethereal solution was superimposable with that of VI.

The acidic aqueous layer was made alkaline with NaOH and extracted with $CHCl_3$. The residue (69 mg) of the dried extract was distilled *in vacuo*, bp 85—105° (3 mmHg (bath temp)), to give a colorless oil (60 mg). The IR spectrum of the distillate was superimposable with that of IX.

7-Phenyl-Δ^2-bicyclo[3.3.1]nonen-9-one (XIV)——A mixture of 20 g of 4-phenylcyclohexanone,[7] 12 g of morpholine and 0.1 g of *p*-toluenesulfonic acid in 100 ml of toluene was refluxed with a water separator for 4 hr. After evaporation of the solvent under reduced pressure, the light yellow residue was distilled *in vacuo* to give the enamine (XI) as a slightly yellow viscous oil, bp 160—180°/0.5 mmHg, which solidified on standing at room temperature. Yield, 20 .6 g. IR ν_{max}^{liq} cm^{-1}: 1647 ($\nu_{C=C}$), 1130, 762, 702. To a solution of XI (13.5 g) in benzene (60 ml) a solution of acrolein (7.0 g) in benzene (40 ml) was added with cooling and stirring in 30 min. The reaction mixture was stood over night at room temperature and then evaporated the solvent and the excess acrolein. The light brown residue was distilled *in vacuo* to give crude XII (12.7 g) of bp 180—215° (0.5 mmHg). IR ν_{max}^{liq} cm^{-1}: 1735 ($\nu_{C=O}$), 1127, 760 and 708.

A mixture of XII (12.7 g), *p*-toluenesulfonic acid (10 g) and ethylene glycol (44 g) was heated on a water bath for 2 hr. After cooling, the mixture was poured into ice-cooled NaOH solution and extracted with ether. The residue of the dried extract was distilled *in vacuo* and a fraction of bp 175—205° (0.5 mmHg) was collected. Yield, 9.0 g.

The distillate (9.0 g) was dissolved in MeOH (50 ml) and mixed with 30% H_2O_2 (18 ml). After refluxing for 7.5 hr, a small amount of palladium black was added to the mixture to decompose the excess peroxide, and stood for 3 days. The solution was filtered and the solvent evaporated *in vacuo* below 60°.

The syrupy residue was pyrolyzed at 155—205° (1 mmHg). The product which had distilled into an icesalt cooled trap was dissolved in ether and washed with 10% HCl, with 5% $NaHCO_3$ and with water. The residue (6.0 g) of the dried ethereal solution was refluxed with 10% HCl (20 ml) in MeOH (100 ml) for 1.5 hr. After evaporation of the solvents, the residue was dissolved in ether washed with 5% $NaHCO_3$ and with water. The ethereal solution was dried and the solvent evaporated to leave 5.3 g of crude XIV as a viscous syrup from which 1.2 g of crystalline product was obtained by treating with ether. The residue of the mother liquor was chromatographed on a silica gel (150 g) column and an elute fraction with benzene gave 1.35 g of pure XIV, mp 134—135° (colorless needles, from ether). IR ν_{max}^{KBr} cm^{-1}: 1747 ($\nu_{C=O}$), 1645 ($\nu_{C=C}$), 760, 755, 712, 700. *Anal.* Calcd. for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 84.86; H, 7.47.

3-Phenylbicyclo[3.3.1]nonan-9- (XV) and Its Oxime (XVI)——XIV (1.0 g) in EtOH (70 ml) was shaken with H_2 over Pd–C (40%) at room temperature. After uptake of 110 ml of H_2, the solution was filtered and the solvent evaporated to leave a colorless syrup (0.8 g) which was found to be contaminated with the diethyl ketal (XV′) and the hydroxyl derivative (XV″) by NMR and IR spectra. The crude reduction product was refluxed with 30 ml of 10% HCl in EtOH (100 ml) for 2 hr to hydrolyze the ketal, and the solvent evaporated. The residual solid was dissolved in ether and washed with 5% $NaHCO_3$ and with water. The residue (1.0 g) of the dried extract was converted to the oxime (XVI) by the usual procedure and recrystallized from MeOH to a constant mp 209—211°. *Anal.* Calcd. for $C_{15}H_{19}ON$; C, 78.56; H, 8.35; N, 6.11. Found: C, 78.77; H, 8.33; N, 6.05.

The oxime (XVI) was hydrolyzed by refluxing with 10% H_2SO_4 to give pure ketone (XV), mp 97—101° (colorless needles, from ether). IR ν_{max}^{KBr} cm^{-1}: 1737 ($\nu_{C=O}$), 757, 700. *Anal.* Calcd. for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 84.04; H, 8.41.

3-Phenyl-9-aminobicyclo[3.3.1]nonane (XVII)——The oxime (XVI) (0.52 g) in AcOH (70 ml) was shaken with Adams catalyst (0.1 g) in a H_2 atmosphere. Hydrogenation was completed in 3.5 hr with absorption of 188 ml of H_2. The catalyst was removed by filtration and the solvent was evaporated to leave a colorless oil. The oil was dissolved in 10% HCl and washed with ether to remove any neutral material. The acidic aqueous layer was basified with K_2CO_3 and extracted with $CHCl_3$. After drying over K_2CO_3, the solvent was evaporated and the residual oil was distilled *in vacuo* to give XVII as a colorless oil, bp 135—150° (0.5 mm (bath temp.)). Yield, 0.45 g. IR ν_{max}^{liq} cm^{-1}: 3370, 3300 (ν_{NH}), 1600 (broad, δ_{NH}), 750, 700. Hydrochloride: colorless sandy crystals (MeOH–AcOEt), sublime at~250° without melting. *Anal.* Calcd. for $C_{15}H_{21}N \cdot HCl \cdot H_2O$: C, 66.77; H, 8.97; N, 5.19. Found: C, 66.75; H, 9.06; N, 5.23.

3-Phenyl-9-(N,N-dimethylamino)bicyclo[3.3.1]nonane (XVIII)——A mixture of XVII (205 mg) and formalin (37%, 0.15 ml) in MeOH (60 ml) was shaken with Pd–C (40%) in a H_2 atmosphere. After uptake of 35.5 ml of H_2, the catalyst and the solvent were removed. The residual oil was dissolved in ether, washed with water, dried over K_2CO_3, and evaporated the solvent. The residue was distilled *in vacuo* to give 207 mg of XVIII as a colorless oil, bp 130—140° (0.5 mmHg (bath temp.)), which solidified on standing. Hydrochloride: colorless needles (MeOH–AcOEt), sublime at~250° without melting. *Anal.* Calcd. for $C_{17}H_{25}N \cdot HCl \cdot 1/2H_2O$: C, 70.68; H, 9.52; N, 4.85. Found: C, 71.56; H, 9.45; N, 4.91.

The epimers (XVIIIa) and (XVIIIb) of the N,N-dimethylamino derivative were separated by preparative gas chromatography. XVIIIa (shorter retention time): bp 130—140° (0.5 mmHg), mp 80—86°. IR ν_{max}^{KBr} cm^{-1}: 2800, 2765 (N–Me_2), 813, 750, 695. XVIIIb (longer retention time): bp 130—140°/0.5 mmHg, mp 106—110°. IR ν_{max}^{KBr} cm^{-1}: 2800, 2760 (N–Me_2), 755, 700.

Δ^2-Bicyclo[3.3.1]nonen-9-one Oxime (XVII)——A mixture of 0.8 g of Δ^2-bicyclo[3.3.1]nonen-9-one (XX) prepared according to the procedure of Foote and Woodward,[4a] 0.8 g of $NH_2OH \cdot HCl$ and 1.2 g of AcONa

in 70% EtOH (30 ml) was refluxed on a water bath for 2 hr. After evaporation of the solvent, the residue was dissolved in $CHCl_3$, washed with 5% $NaHCO_3$ and with water. The residue of the dried solution was recrystallized from dil. MeOH to give XXII as colorless needles, mp 140—142°. Yield, 0.8 g. IR_{max}^{KBr} cm^{-1}: 3240 (broad), 3080, 2990, 1685. *Anal.* Calcd. for $C_9H_{13}ON$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.20; H, 8.74; N, 9.20.

9-Aminobicyclo[3.3.1]nonane (XXIII)——Crude XXII (0.8 g) was hydrogenated on a platinum catalyst in AcOH (100 ml). The uptake of H_2 was completed in 1 hr. After removal of the catalyst and the solvent, the residual syrup was dissolved in 10% HCl and washed with ether. The acidic aqueous layer was basified with 10% NaOH, extracted with $CHCl_3$ dried over K_2CO_3 and evaporated the solvent. The residue (0.5 g) was converted to the hydrochloride and recrystallized from MeOH–AcOEt to give colorless silky needles, which sublime at ~215° without melting. *Anal.* Calcd. for $C_9H_{17}N \cdot HCl$: C, 61.74; H, 10.27; N, 7.93. Found: C, 61.56; H, 10.45; N, 7.97. IR_{max}^{KBr} cm^{-1}: 3000 (broad), 2700, 2600, 2500 (broad), 2020 (broad), 1605.

Reactions of VIII, XVII and XXIII with Formalin in Acidic Methanol——a) VIII: A mixture of VIII (94.1 mg), formalin (37%, 0.5 ml) and AcOH (1 drop) in MeOH (5 ml) was refluxed for 1 hr. To the mixture 10% HCl (5 ml) was added and then refluxed for 4 hr. After evaporation of the solvents, the residue was dissolved in water and extracted with ether. The ether extract was washed with $NaHCO_3$ solution and with water, and dried over $MgSO_4$. The IR spectrum of the solid residue (36.3 mg) of the extract was identical with that of VI.

The acidic aqueous layer was made alkaline with 10% NaOH and extracted with $CHCl_3$. The residual basic product (XIX) (32.0 mg) was distilled *in vacuo* to give a colorless oil of bp 100° (0.2 mmHg (bath temp.)). IR_{max}^{liq} cm^{-1}: 3320 (broad, ν_{NH}), 2770 (N–Me), 1580 (broad, δ_{NH}), 765, 760, 738, 722.

b) XVII: A mixture of XVII (127 mg), formalin (37%, 1.0 ml) and AcOH (0.1 ml) in MeOH (5 ml) was refluxed for 7 hr, then 10% HCl (5 ml) was added to the mixture and refluxed for additional 0.5 hr. The reaction mixture was treated as described for the reaction of VIII.

The crystalline neutral product (77.5 mg) was identified with XV by the comparison of the IR spectra and mixed melting point measurement.

The oily basic product (XXIV) (43.2 mg) was distilled *in vacuo* to give a colorless oil of bp 130—140° (0.5 mmHg (bath temp.)). IR_{max}^{liq} cm^{-1}: 3340 (ν_{NH}), 2760 (N–Me), 750, 700. *Anal.* Calcd. for $C_{16}H_{23}N$: C, 83.78; H, 10.11; N, 6.11. Found: C, 83.85; H, 10.27; N, 6.19.

c) XXIII: A mixture of XXIII (0.5 g), formalin (37%, 1.0 ml) and AcOH (0.1 ml) in MeOH (10 ml) was refluxed for 5 hr. After refluxing with 2 ml of 10% HCl for additional 0.5 hr, the reaction mixture was treated as described for the reaction of VIII.

The IR spectrum of the crystalline neutral product (224 mg) was identical with that of bicyclo[3.3.1]-nonan-9-one (XXIV) prepared from XXI by the method of Foote and Woodward.[4a]

The colorless oily basic product (171 mg), bp 120—130°(20 mmHg (bath temp.)) was characterized as 9-(N–methylamino)-bicyclo[3.3.1]nonane (XXV). IR_{max}^{liq} cm^{-1}: 3340 (broad, ν_{NH}), 2780 (N–Me). *Anal.* Calcd. for $C_{10}H_{19}N$: C, 78.36; H, 12.50; N, 9.14. Found: C, 78.43; H, 12.76; N, 8.96.

Mass Spectral Measurements——The spectra were measured by the direct sample introduction technique on a JEOL Double-focussing Mass Spectrometer Model JMS–OlS and a Hitachi Mass Spectrometer Model RMU 6C. The heating temperature varied between 40° to 80°. The ionizing current was maintained at 75 eV.

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