[Chem. Pharm. Bull. 17(10)2142—2150(1969)]

UDC 547.743.1.07 : 543.787.07

Synthesis of Nitrogen-containing Heterocyclic Compounds through Nitrilium Salt. I. Reaction of Nitriles with 2-(α-Hydroxymethyl, -ethyl, and -isopropyl)cyclohexanol in the Presence of Acid

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(Received March 24, 1969)

Several kinds of bicyclic nitrogen-containing heterocycles were synthesized by the Ritter reaction of 1,3-glycols (IX, X, and XI) and acetonitrile. Three types of compounds, hexahydrobenzoxazoles (XII and XVIII), hexahydro-3*H*-indoles (XIII, XIX, and XXXII), and hexahydrobenzoxazines (XXX and XXXI), were obtained. XII and XIII were obtained from IX, XVIII and XIX from X, and XXX, XXXI, and XXXII from XI. XIX underwent facile autoxidation to form a 3-hydroxy compound (XXIII).

Electrophilic nitrilium salt (I) is formed by the reaction of alcohol and nitrile in the presence of sulfuric acid, the so-called Ritter reaction condition, or by heating alkyl halide and nitrile in the presence of Lewis acid, like stannic chloride. In this case, a nitrogen-containing heterocycle will be formed if there is an electron-rich site in the molecule. For example, Meyers and others[2] synthesized 1-pyrroline (III) from 2,5-dimethylhexane-2,5-diol (II) under the Ritter reaction conditions, and the present authors synthesized 1-pyrroline (VII and VIII) by heating the glycols (IV and V) and nitrile in the presence of stannic chloride.[3] In the case of the latter, nitrilium salt (VI) is considered to have been formed as an intermediate which underwent cyclization. IV and V do not undergo cyclization by the Ritter reaction condition but does so only under the above condition. It is also interesting that the nitrile has attacked the primary alcohol in IV and V.

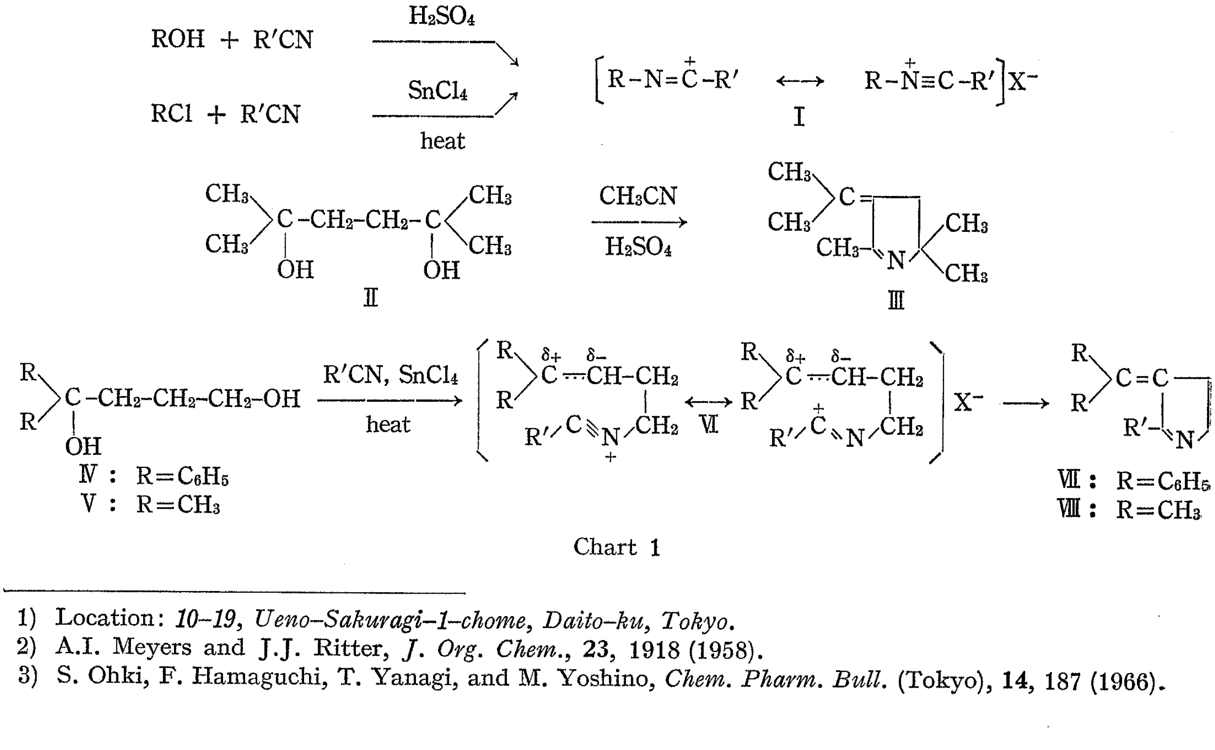

Chart 1

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[1] Location: *10-19, Ueno-Sakuragi-1-chome, Daito-ku, Tokyo.*

[2] A.I. Meyers and J.J. Ritter, *J. Org. Chem.*, 23, 1918 (1958).

[3] S. Ohki, F. Hamaguchi, T. Yanagi, and M. Yoshino, *Chem. Pharm. Bull.* (Tokyo), **14**, 187 (1966).

In such a way, this reaction is a simple and useful method for the synthesis of some kind of N-heterocycles, and it would be possible to obtain various kinds of product by suitably selecting the conditions and reagents.

In the present series of work, an attempt was made to synthesize indole, oxazoline, or oxazine compounds by this method, and cyclization using 2-(α-hydroxymethyl, -ethyl, or -isopropyl) cyclohexanol (IX, X, and XI) was carried out.

Reaction of 2-(Hydroxymethyl)cyclohexanol[4] (IX) and Acetonitrile

Reaction of the *cis* compound[4] (mp 54°) of IX and acetonitrile in the cold, in the presence of conc. sulfuric acid, afforded three kinds of basic substance (XII, XIII, and XIV) in 15%, 25% and not estimated yield, respectively. Infrared (IR) spectrum of XII showed the presence of $-N{=}\overset{|}{C}-$ and $={}\overset{|}{C}-O-$ bonds and absence of OH. Its nuclear magnetic resonance (NMR) spectrum indicated the signals at 1.24 ppm (3H, singlet, $CH_3-\overset{|}{\underset{|}{C}}-$), 1.98 ppm (3H, singlet, $CH_3-\overset{|}{C}{=}N-$), and 3.73 ppm (1H, multiplet, $-\overset{|}{C}H-N=$ or $={}\overset{|}{C}-O-\overset{|}{C}H-$).With consideration of its elemental analytical values, formula XII or XV would be suggested.

Lwowski and others[5,6] assigned 3.8 ppm for the angular proton adjacent to nitrogen and 4.5 ppm for that adjacent to oxygen in oxazoline (XVI), and the signal at 3.8—4.1 ppm (multiplet) to the angular proton adjacent to nitrogen in dehydroxazoline (XVII). Comparison with these values suggests that above base is likely to be 2,7a-dimethyl-3a,4,5,6,7,7a-hexahydrobenzoxazole (XII) with a methine proton adjacent to nitrogen.

XIII was obtained as crystals of mp 142—143°. Its IR spectrum indicated the presence of $-N{=}\overset{|}{C}-$ and secondary amide, and absence of $={}\overset{|}{C}-O-$ bond and OH. Its NMR spectrum showed the presence of $-COCH_3$, $-N{=}\overset{|}{C}-CH_3$, $-NH-$, and two methine protons, $-\overset{|}{C}\underline{H}-N{=}\overset{|}{C}-CH_3$ and $-\overset{|}{C}\underline{H}-NH-$, and absence of proton signal of $-CH_2-\overset{|}{C}{=}N-$. From its elemental analytical values and these spectral evidences, this base was considered to be 3-acetamido-2-methyl-3a,-4,5,6,7,7a-hexahydro-3*H*-indole (XIII). Attempts to derive XIII to indoles by dehydrogenation over palladium-carbon or with sulfur did not materialize.

XIV was obtained in a minute amount as sublimable crystals of mp 267—268° and its structure remains unclarified.

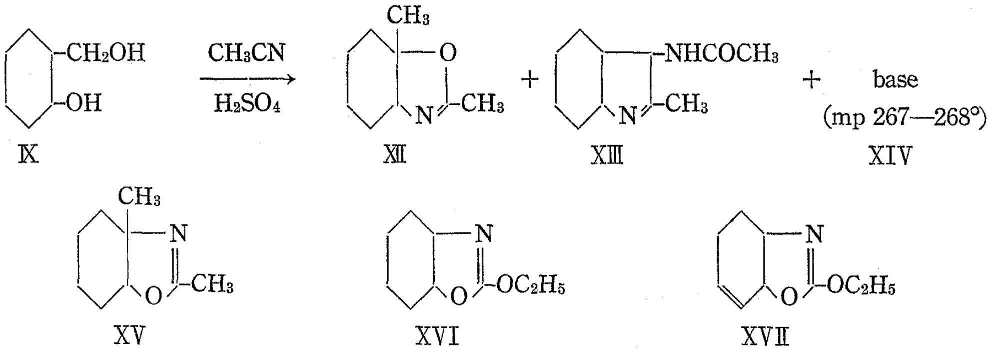

Chart 2

Heating of IX and acetonitrile in the presence of stannic chloride afforded a base whose picrate (mp 228—229° (decomp.)) corresponded to the formula $C_9H_{15}ON \cdot C_6H_3O_7N_3$. This base is probably a mixture of two substances of similar structures because its peak in gas

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[4] H.B. Henbest and B.B. Millward, *J. Chem. Soc.*, **1960**, 3575.

[5] W. Lwowski and T.J. Maricich, *J. Am. Chem. Soc.*, **87**, 3630 (1965).

[6] A. Mishra, S.N. Rice and W. Lwowsky, *J. Org. Chem.*, 33, 481 (1968).

chromatography (SE-30, 70°) was observed as an extremely close two components. Separation of these two components and their structural elucidation have not succeeded.

It is clear that these two compounds are different from XII, XIII and XIV and it is interesting that there is a difference in the reaction according to the kind of condensation agent used.

Reaction of 2-(α-Hydroxyethyl)cyclohexanol[7] (X) and Acetonitrile

Reaction of X and acetonitrile in the presence of conc. sulfuric acid afforded two kinds of a basic substance (XVIII in 16% yield and XIX in 23% yield), and a neutral substance, 2-ethylcyclohexanone[17] (XX).

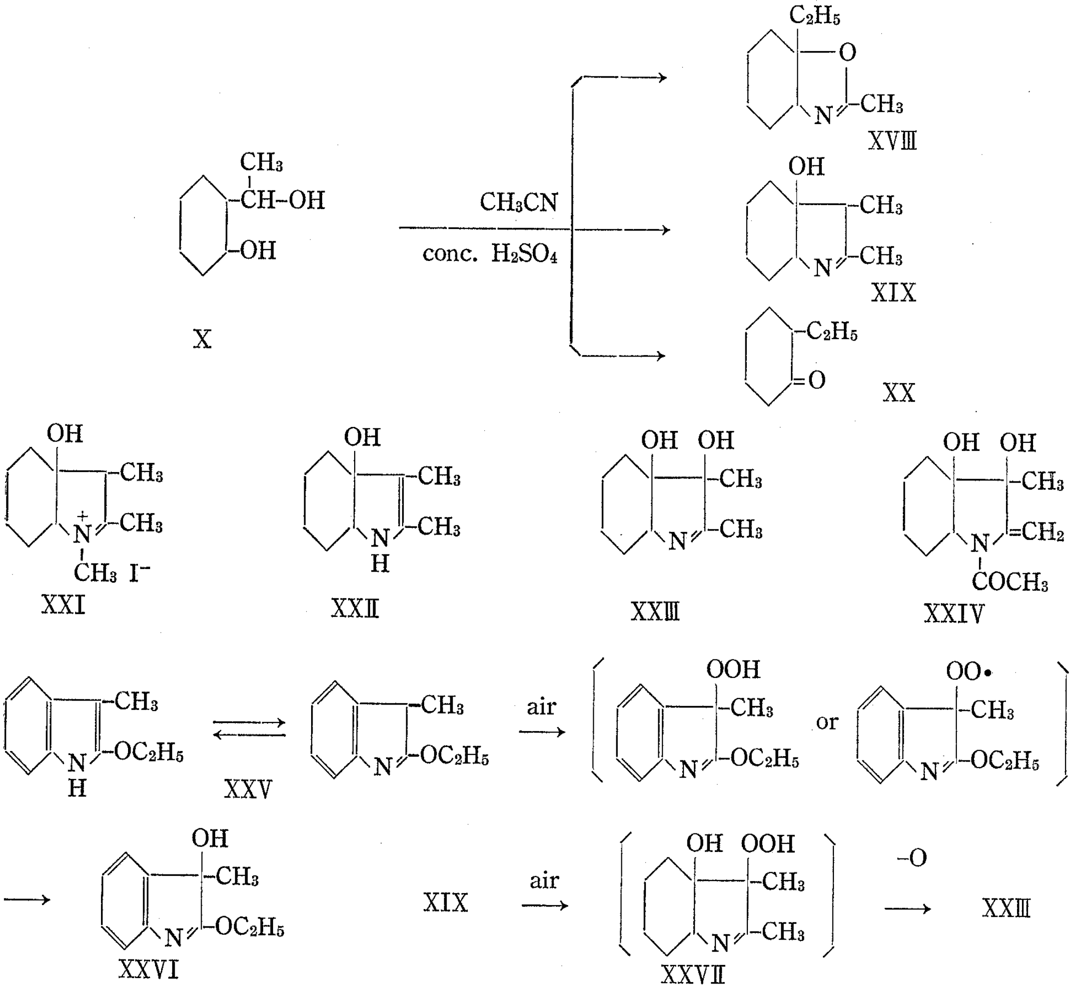

Chart 3

XVIII is a compound that corresponds to XII and was found to be 7a-ethyl-2-methyl-3a,4,5,6,7,7a-hexahydrobenzoxazole.

The elemental analytical values of XIX were the same as that of XVIII, and its IR spectrum lacked the absorption of $=\overset{|}{\mathrm{C}}{-}\mathrm{O}{-}$ but indicated the presence of $-\overset{|}{\mathrm{C}}{=}\mathrm{N}{-}$ and OH. Its NMR spectrum (Fig. 1) showed overlapping of weak signals at 2.07 ppm (singlet) and 1.17 ppm (doublet) on those at 1.99 ppm (singlet, $-\mathrm{N}{=}\overset{|}{\mathrm{C}}{-}\mathrm{CH}_3$) and 1.18 ppm (doublet, $\rangle\mathrm{CH}{-}\mathrm{C}\underline{\mathrm{H}}_3$). In the methiodide (XXI) of XIX, however, its NMR spectrum showed one singlet as the signal for $\mathrm{CH}_3{-}\underset{+}{\overset{|}{\mathrm{N}}}{=}\overset{|}{\mathrm{C}}{-}\mathrm{C}\underline{\mathrm{H}}_3$ and one doublet for $\mathrm{C}\underline{\mathrm{H}}_3{-}\overset{|}{\mathrm{C}}\mathrm{H}{-}$. There was no signal corresponding to

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[7] I.A. Kaye and R.S. Matthews, *J. Org. Chem.*, **28**, 325 (1963).

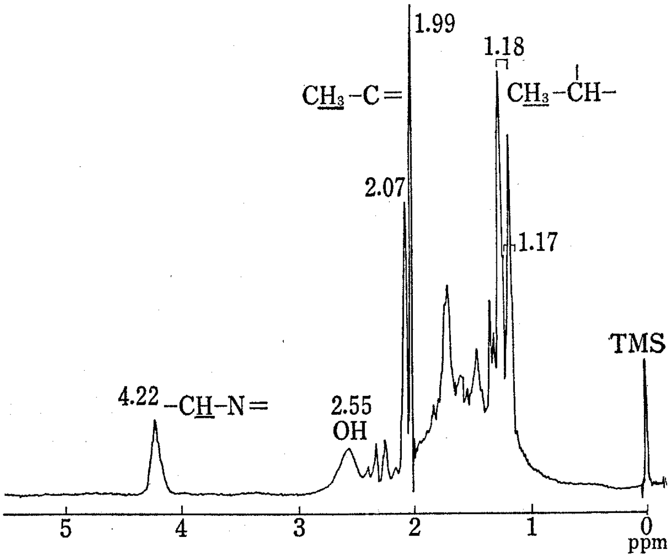

Fig. 1. The NMR Spectrum of XIX in $CDCl_3$

the methine or methylene proton at the base of OH and, since this hydroxyl group is not easily acetylated, it is thought to be a tertiary hydroxyl. From these evidences, XIX is considered to be 2,3-dimethyl-3a-hydroxy-3a,4,5,6,7,7a-hexahydro-3*H*-indole, although there is still a doubt about the overlapping of the signals in its NMR spectrum, whether it is due to steric factors or to the presence of a double-bond isomer (XXII). The assignment of this structure was endorsed by a later structural elucidation of a similar kind of compound (3-ethyl-3a-hydroxy-2-methyl-3a,4,5,6,7,7a-hexahydro-3*H*-indole) to be reported in the following paper.⁸⁾

When ether solution of XIX is allowed to stand, it precipitates out as colorless crystals (XXIII), mp 165—166°. The state of this transition examined by gas chromatography is shown in Fig. 2. XXIII is M^+183, and its NMR spectrum shows a singlet signal for $CH_3\text{–}\overset{|}{\underset{|}{C}}\text{–}$, and the quartet signal for $CH_3\text{–}\overset{|}{C}\underline{H}\text{–}$ seen in XIX has disappeared. One hydroxyl in XIX has increased to two in XXIII and appears as one peak (2.86 ppm), so that XXIII is assumed to be a 1,2-glycol with introduction of hydroxyl into the 3-position of XIX (Fig. 3). Such autoxidation is often observed in partial structure (A), which forms a peroxide (B) in the intermediate and its reduction will lead to the hydroxyl group (C).⁹⁾ Recently, Hino *et al.*¹⁰⁾

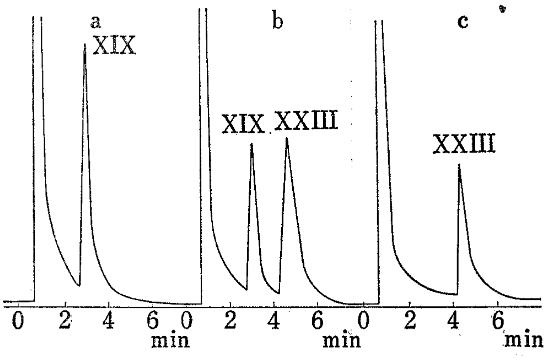

Fig. 2.

a : the gas chromatogram of XIX (immediately after distillation)
b : the gas chromatogram of the mixture of XIX and XXIII (after standing for two days in an open air)
c : the gas chromatogram of XXIII
condition: column: 0.75% SE-30
temperature: 150°
carrier gas: nitrogen
flow rate: 60 ml/min

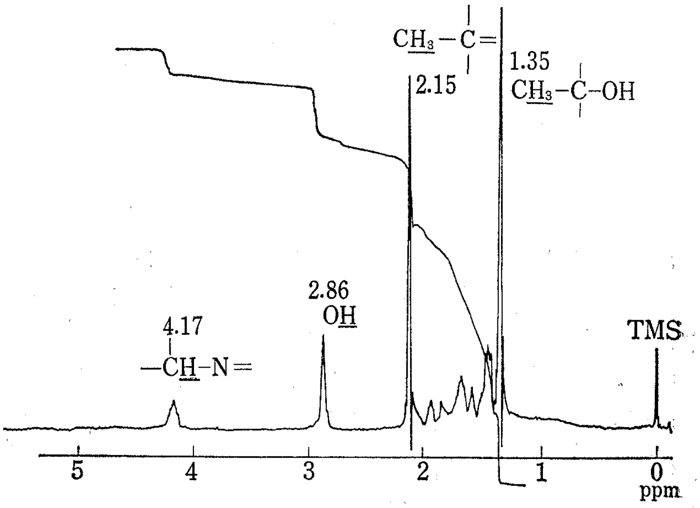

Fig. 3. The NMR Spectrum of XXIII in $CDCl_3$

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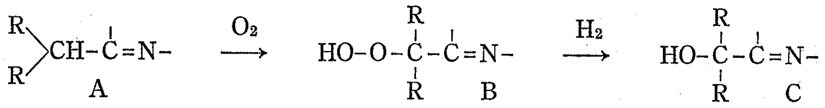
8) M. Yoshino and S. Ohki, *Chem. Pharm. Bull.* (Tokyo), **17**, 2151 (1969).

9) B. Witkop, *J. Am. Chem. Soc.*, **72**, 1428 (1950); L.A. Cohn and B. Witkop, *J. Am. Chem. Soc.*, **77**, 6595 (1955); H.H. Wasserman and M.B. Floyd, *Tetrahedron Letters*, **1963**, 2009; F. Y-H. Chen and E. Leete, *Tetrahedron Letters*, **1963**, 2013; B. Witkop and J.B. Patrich, *J. Am. Chem. Soc.*, **73**, 2188 (1951); T. Hino, M. Nakagawa, T. Wakatsuki, K. Ogawa, and S. Yamada, *Tetrahedron*, **23**, 1441 (1967).

10) T. Hino, M. Nakagawa, and S. Akaboshi, *Chem. Commun.*, **1967**, 656.



reported of an example (XXV→XXVI) of a direct introduction of hydroxy group *via* the peroxide. Formation of XXIII may be considered to be the same as this case. In this case, the peroxide (XXVII) is thought to be quite easily reduced to XXIII and its presence could not be recognized in gas chromatography. The mechanism of this reduction has yet to be examined.[11]

N-Acetyl derivative (XXIV) was obtained by acetylation of XXIII. Its NMR spectrum indicated signals at 1.03 (CH_3–C–), 2.19 (CH_3CO), 2.53 (2H, OH), 4.92, 5.36 (=CH_2), 5.03 ppm (–CH–N–). Therefore, this fact also suggests that XXIII has two *tert*-hydroxy groups.

Dehydrogenation of XIX to derive it to indoles did not materialize but a small amount of N-cyclohexyl-acetamide[12] was obtained on heating XIX with 10% palladium-carbon in decalin. This reaction indicates direct bonding of nitrogen to the cyclohexane ring and suggests the structure of XIX.

Reaction of 2-(α-Hydroxyisopropyl)cyclohexanol (XI) and Acetonitrile

XI was obtained by the reaction of methylmagnesium iodide and methyl *cis*-2-hydroxycyclohexanecarboxylate[4] (XXVIII), together with a by-product formation of partially dehydrated 2-isopropenylcyclohexanol (XXIX). The Ritter reaction of XI and XXIX with acetonitrile afforded three kinds of basic substance (XXX, XXXI, and XXXII) from each. XXX and XXXI were difficult to be fractionated and were separated as picrates. IR spectrum of XXX showed the absorption for –N=C–O–, and its NMR spectrum indicated signals at 1.12 and 1.19 ppm (3H×2, two singlets, >$C(CH_3)_2$), 1.91 ppm (3H, singlet, =N–$C(CH_3)$–O–), and 4.38 ppm (1H, multiplet, >CH–O–C=N–). IR spectrum of XXXI indicated the presence of –N=C–O– bond, and its NMR spectrum showed the signals at 1.03 and 1.15 ppm (3H×2, two singlets, >$C(CH_3)_2$), 1.87 ppm (3H, singlet, –N=$C(CH_3)$–O–), and 3.70 ppm (1H, multiplet, >CH–N=C–O–). It is, therefore, clear that these two compounds are 1,3-oxazine derivatives (XXX or XXXI).

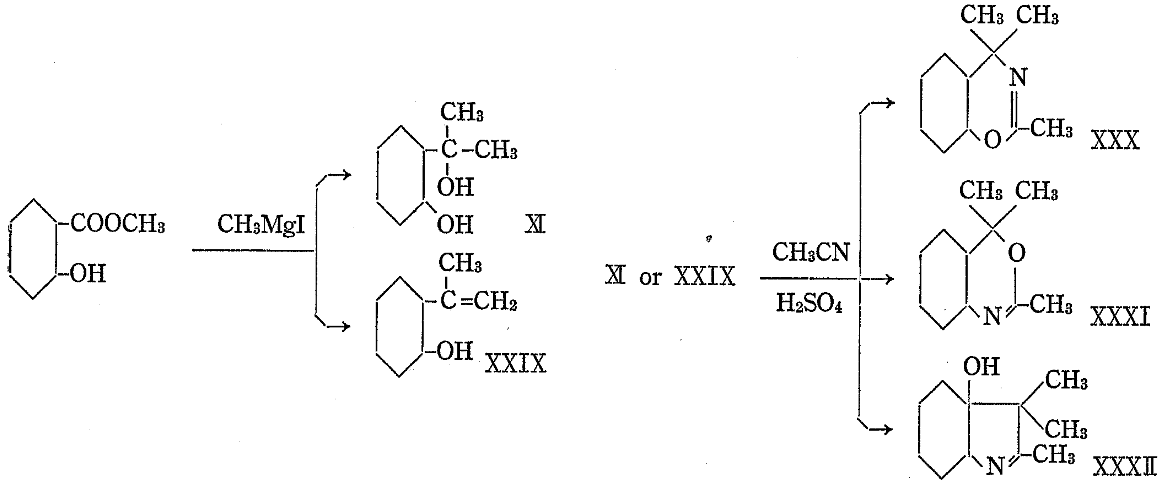


Chart 4

If the values of XVI—XVII and XII—XVIII are applied to the angular proton signals, that at 4.38 ppm would correspond to 2,4,4-trimethyl-4a,5,6,7,8,8a-hexahydro-4*H*-1,3-benzoxa-

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11) Hino has proposed a mechanism for this kind of oxidation reaction (lit. 10).

12) W. Scharvin, *Chem. Ber.*, 30, 2862 (1897).

zine (XXX) and that at 3.70 ppm to 2,4,4-trimethyl-4a,5,6,7,8,8a-hexahydro-4*H*-3,1-benzoxazine (XXXI). Ratio of the formation of XXX and XXXI was 1.2:1 when XI was used as the starting material and 1:1.5 when using XXIX.

XXXII was obtained as crystals of mp 148—150°. Its IR spectrum suggested the presence of $-\overset{|}{C}=N-$ and OH, and its NMR the presence of $-\overset{|}{C}(CH_3)_2$, $CH_3-\overset{|}{C}=N-$, and $-\overset{|}{C}H-N=\overset{|}{C}-$ structures, so that it is 3a-hydroxy-2,3,3-trimethyl-3a,4,5,6,7,7a-hexahydro-3*H*-indole (XXXII), similar in type to XIX. In this reaction 1,3-oxazoline derivative corresponding to XVIII was not obtained as a product.

Reaction of IX, X and XI with acetonitrile in the presence of sulfuric acid is considered to have progress by the following mechanism. 1-Alkylcyclohexene are thermodinamically more stable than the corresponding alkylidenecyclohexane.[13] Therefore IX, X, and XI will

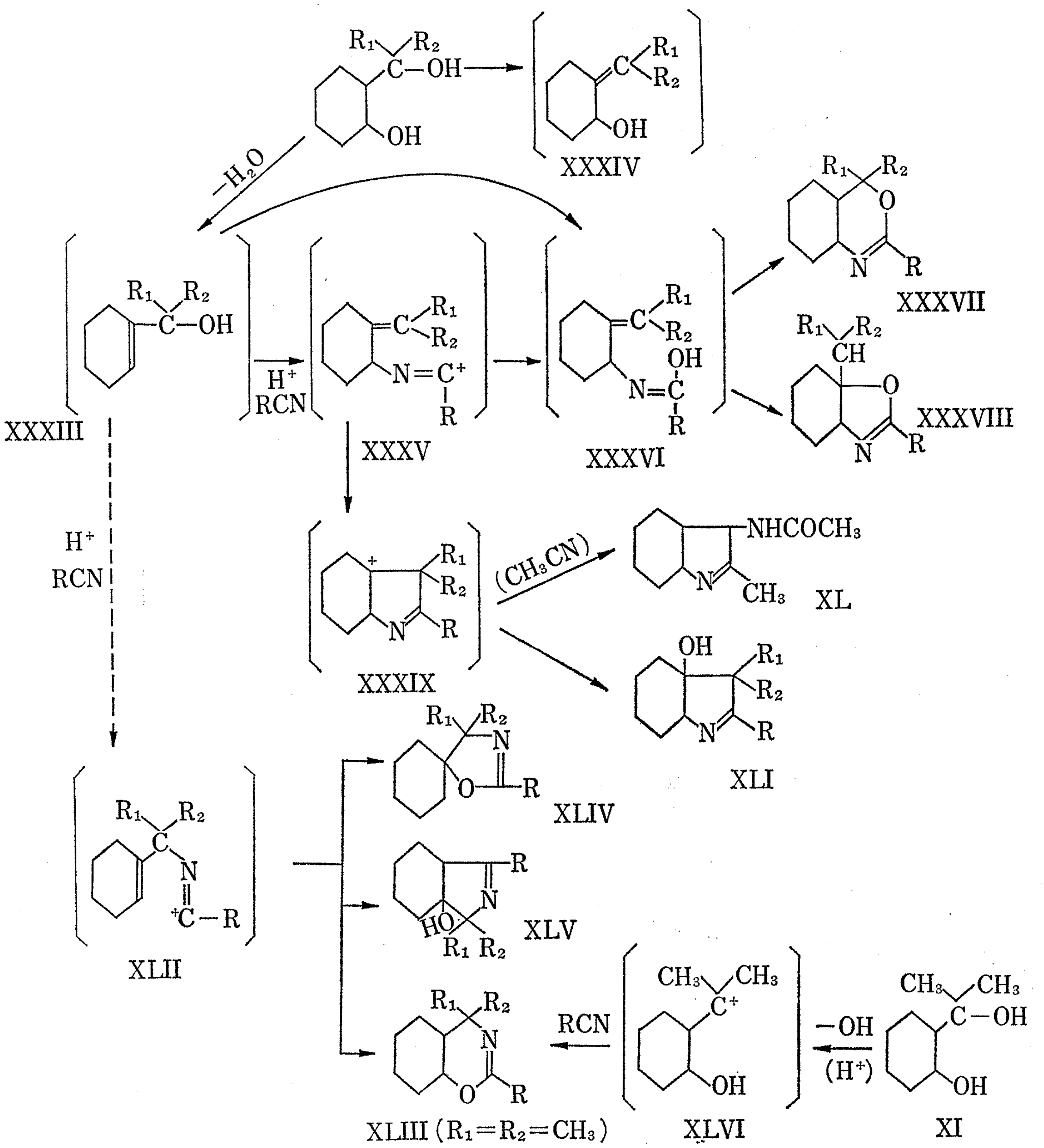

Chart 5

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[13] R.B. Turner and R.H. Garner, *J. Am. Chem. Soc.*, **80**, 1424 (1954); A.C. Cope, D. Ambros, E. Ciganeck, C.F. Howell, and Z. Jacura, *J. Am. Chem. Soc.*, **82**, 1750 (1960); O. Wallach, *Chem. Ber.*, **39**, 2504 (1906); O. Wallach, E. Evans, J.B. Churchill, M. Rentschler, and H. Mallison, *Ann.*, **360**, 26 (1908); D.H. Barton, R.C. Cookson, W. Klyne, and C.W. Shoppee, *Chem. Ind.* (London), **1954**, 21.

be almost present in XXXIII form. In the nucleophilic attack of the nitrile on XXXIII, two mechanism are possible, that is, S_N1 attack on allylic carbonium cation and non–ionic S_N2' attack of substitution with rearrangement.14)

Allylic carbonium cation (S_N1) must be led not only to products, XXXVII, XXXVIII, and XLI derived from XXXV, but also to XLIII, XLIV, and XLV from XLII. However, the more thermodinamically stable member XLII of the pair of nitrilium salts is not intermediate, because XLIII, XLIV and XLV are not presnet. Thus dominant mechanism would be S_N2', substitution with rearrangment.

Therefore, XII and XIII are formed from IX, XVIII and XIX from X, and XXXI and XXXII from XI through nitriluim salt (XXXV). In the case of XI, in addition of S_N2' mechanism, the facile formation of a stable isopropyl cation can also be assumed and led to XXX through polar 1,4-cycloaddition15) of nitrile on XLVI. XX is assumed to progress by the same mechanism reported by Schwartz and others.16)

Reaction of XX and nitrile did not produce XVIII or XIX, and this fact indicate that XX cannot serve as an intermediate.

No further examinations were made on the steric structure of bicyclic heterocycles formed by the present cyclization reaction.

Experimental

Reaction of *cis*-2-(Hydroxymethyl)cyclohexanol4) (IX) and Acetonitrile——To 40 ml of conc. H_2SO_4 chilled to 0—5°, 1.3 g of CH_3CN was added, 4.0 g of IX was added slowly to this mixture with stirring, and staying IX was washed out into the reactant with 0.6 g of CH_3CN. The mixture was stirred for 3 hr at 0—7°, poured into 100 g of ice water, and extracted with $CHCl_3$ to remove the starting materials and resinous substance. The H_2SO_4 layer was basified with 30% NaOH solution while cooling and extracted with ether. The extract solution was dried over Na_2SO_4 and evaporated. 2,7a-dimethyl-3a,4,5,6,7,7a-hexahydrobenzoxazole (XII) was obtained as 0.7 g of colorless liquid, bp 59—60° (6 mmHg). Yield, 15%, and a viscous liquid of bp 145—147° (2 mmHg). The latter crystallized on standing to slightly hygroscopic plates, mp 142—143° (from iso-Pr_2O) affording 1.5 g (25.1%) of 3-acetamido-2-methyl-3a,4,5,6,7,7a-hexahydro-3*H*-indole (XIII). Besides the above two, a small amount of structurally unelucidated crystals (from MeOH) of mp 268° (sublimable) were obtained. Picrate of XII; mp 208—209° from MeOH: *Anal.* Calcd. for $C_9H_{15}ON\cdot C_6H_3O_7N_4$: C, 47.12; H, 4.75; N, 14.66. Found: C, 47.23; H, 4.89; N, 14.82. IR cm^{-1}: 1665 (–N=C), 1241 (=C–O–). NMR (in $CDCl_3$) ppm: 1.24 (3H, singlet, $CH_3{-}\overset{|}{\underset{|}{C}}{-}$), 3.73 (1H, multiplet, $-\overset{|}{C}H{-}N{=}$), 1.98 (3H, singlet, $CH_3{-}\overset{|}{C}{=}N{-}$). XIII: *Anal.* Calcd for $C_{11}H_{18}ON_2$: C, 68.00; H, 9.34; N, 14.42. Found: C, 68.09; H, 9.51; N, 14.72. Picrate of XIII, mp 192—193° from MeOH: *Anal.* Calcd. for $C_{11}H_{18}ON_2\cdot C_6H_3O_7N_3$: C, 48.22; H, 5.00; N, 16.54. Found: C, 48.01; H, 5.06; N, 16.85. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3342 (NH), 1642, 1546 (CONH), 1656 (–N=C–). NMR (in $CDCl_3$) ppm: 1.84 (3H, singlet, $CH_3{-}\overset{|}{C}{=}$), 2.02 (3H, singlet, CH_3CO), 3.47 (1H, triplet, $-NH{-}\overset{|}{C}H{-}C{=}$), 4.09 (1H, multiplet, $-\overset{|}{C}H{-}N{=}$), 5.4 (1H, broad, NH).

Reaction of 2-(*α*-Hydroxyethyl)cyclohexanol7) (X) and Acetonitrile——X was reacted and treated in the same manner as in the case of IX. Basic substances obtained as the products were 7a-ethyl-2-methyl-3a,4,5,6,7,7a-hexahydrobenzoxazole (XVIII) as a colorless liquid of bp 77° (20 mmHg) in 16% yield and 2,3-dimethyl-3a-hydroxy-3a,4,5,6,7,7a-hexahydro-3*H*-indole (XIX) as a viscous colorless liquid of bp 96° (2 mmHg) in 23% yield. A by–product of a neutral substance, 2-ethylcyclohexanone (XX) was obtained in 36.2% yield. 2,4-Dinitrophenylhydrazone, mp 163—164.5°, of XX agreed in all respects with an authentic sample.17) Picrate of XVIII, mp 188—189° from EtOH. *Anal.* Calcd. for $C_{10}H_{17}ON\cdot C_6H_3O_7N_3$: C, 48.48; H, 5.09; N, 14.14. Found: C, 48.10; H, 5.53; N, 14.13. IR cm^{-1}: 1670 (–N=C–), 1239 (=C–O–). NMR (in $CDCl_3$) ppm: 0.9 (3H, triplet, $C\underline{H}_3{-}CH_2{-}$), 1.98 (3H, singlet, $CH_3{-}\overset{|}{C}{=}$), 3.74 (1H, multiplet, $-\overset{|}{C}H{-}N{=}$). Picrate of XIX, mp 209—210° (decomp) from EtOH. *Anal.* Calcd. for $C_{10}H_{17}ON\cdot C_6H_3O_7N_3$: C, 48.48; H, 5.09; N, 14.14. Found: C, 48.33; H, 5.14; N, 14.07. IR cm^{-1}: 1662 (–C=N–), 3298 (OH). NMR (in $CDCl_3$) ppm: 1.18, 1.17 (doublet, doublet, $C\underline{H}_3{-}\overset{|}{C}H{-}$), 1.99, 2.07 (singlet, singlet, $C\underline{H}_3{-}C{=}N{-}$), 4.22 (1H, multiplet, $-\overset{|}{C}H{=}N{-}C\langle$).

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14) A.G. Catchpole, E.D. Hughes, and C.K. Ingold, *J. Chem. Soc.*, **1948**, 8.
15) R.R. Schmidt, *Tetrahedron Letters*, **1968**, 3443.
16) L.H. Schwarz, M. Fell, A.J. Kascheres, K. Kaufmann and A.M. Levine, *Tetrahedron Letters*, **1967**, 3785.
17) G.N. Walker, *J. Am. Chem. Soc.*, **79**, 3508 (1957).

3,3a-dihydroxy-2,3-dimethyl-3a,4,5,6,7,7a-hexahydro-3*H*-indole (XXIII)——An ether solution of XIX was allowed to stand and crystals began to precipitate out gradually. After standing the solution for 5 days, the pale brown crystals were collected by filtration and recrystallized from iso-Pr_2O and acetone to colorless needles, mp 165—166°. *Anal.* Calcd. for $C_{10}H_{17}O_2N$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.77; H, 9.48; N, 7.47. IR ν_{max}^{KBr} cm^{-1}: 1660 (–N=C–), 3488, 3124 (OH). Mass Spectrum *m/e*: 183 (M^+), 41 (CH_3CN^+). NMR (in $CDCl_3$) ppm: 1.35 (3H, singlet, $CH_3\text{–}\overset{|}{\underset{|}{C}}\text{–}$), 2.15 (3H, singlet, $CH_3\text{–}\overset{|}{C}\text{=}$), 2.86 (2H, singlet, OH) which disappeared on the addition of D_2O and shifted on changes in concentration.

Methiodide (XXI) of XIX——An excess of MeI was added to abs. benzene solution of 0.15 g of XIX and the solution was allowed to stand in a refrigerator over night. The crystals that precipitated out were collected by suctional filtration, washed several times with abs. ether, and 0.25 g (90%) of crystals was obtained. NMR (in $CDCl_3$) ppm: 1.50 (3H, doublet, $C\underline{H}_3\text{–}\overset{|}{C}H\text{–}$), 2.60 (3H, singlet, $CH_3\text{–}\overset{|}{C}\text{=}$), 3.04 (1H, quartet, $CH_3\text{–}\overset{|}{C}\underline{H}\text{–}$), 3.65 (3H, singlet, $\text{=}\overset{+}{\underset{|}{N}}\text{–}CH_3$). Because of the difficulty of its recrystallization, the substance was reduced with $NaBH_4$ in MeOH and proved as 3a-hydroxy-1,2,3-trimethyl-2,3,3a,4,5,6,7,7a-octahydroindole (yield, 93%). Its picrate was obtained as yellow crystals (from EtOH), mp 224°. *Anal.* Calcd. for $C_{10}H_{21}ON \cdot C_6H_3O_7N_3$: C, 49.51; H, 5.86; N, 13.59. Found: C, 49.79; H, 6.15; N, 13.95.

1-Acetyl-3,3a-dihydroxy-3-methyl-2-methylene-2,3,3a,4,5,6,7,7a-octahydroindole (XXIV)——Excess of Ac_2O was added to 23 mg of XXIII and the mixture was allowed to stand overnight. The mixture was warmed on a water bath for 30 min, excess Ac_2O was removed by low-pressure distillation, and the crystals obtained were recrystallized from iso-Pr_2O and acetone to 21 mg of colorless plates, mp 168—169.5°. Yield, 75%. *Anal.* Calcd. for $C_{12}H_{19}O_3N$: C, 63.97; H, 8.50; N, 6.22. Found: C, 64.24; H, 8.45; N, 6.55. NMR (in $CDCl_3$) ppm: 1.03 (3H, singlet, $CH_3\text{–}\overset{|}{\underset{|}{C}}\text{–}$), 2.19 (3H, singlet, CH_3–CO), 2.53 (2H, broad, OH), 4.92, 5.36 (1H, 1H, singlet, singlet, =CH_2), 5.03 (1H, multiplet, $\text{–}\overset{|}{C}\underline{H}\text{–}\overset{|}{N}\text{–}$).

Attempted Dehydrogenation of XIX——To the decalin solution of 0.19 g of XIX, 10% Pd–C was added and the mixture was heated at 180—200° for 4 hr. When cooled, ether was added to the mixture which was filtered and the filtrate was extracted with 20% HCl. The acid layer was basified with 10% NaOH, extracted with ether, and the extract solution was dried over Na_2SO_4. Evaporation of ether left some crystals which were recrystallized from petr. ether to 15 mg (9.4%) of crystals of mp 105—106° which agreed with authentic N-cyclohexyl-acetamide.12) Indoles and N-cyclohexyl-acetamide were not obtained from decalin–ether layer. Condition of dehydrogenation reaction were changed variously but the reaction was not effected.

2-(α-Hydroxyisopropyl)cyclohexanol (XI) and 2-(Isopropenyl)cyclohexanol (XXIX)——The Grignard reagent was prepared from 2.72 g(0.028 × 4 mole) and 16 g of MeI (0.028 × 4 mole) in ether by the conventional method. An abs. ether solution of 4.37 g (0.028 mole) of methyl *cis*-2-hydroxycyclohexanecarboxylate (XXVIII) was added dropwise into the Grignard solution, the mixture was stirred for 4 hr, and allowed to stand over night. The reagent was decomposed with saturated NH_4Cl solution with ice cooling and extracted with ether. The extract solution gradually colored yellow. After drying over Na_2SO_4, ether was evaporated and the residue was distilled under a reduced pressure, affording 1.27 g of 2-(isopropenyl)cyclohexanol (XXIX), bp 47—48.5° (1 mmHg), and 1.28 g of 2-(α-hydroxyisopropyl)cyclohexanol (XI), bp 93—94° (1 mmHg). Total yield, 62%. *Anal.* Calcd. for $C_9H_{18}O_2$ (XI): C, 68.31; H, 11.47. Found: C, 68.38; H, 11.39. XXIX: IR cm^{-1}: 3468 (OH), 3092 (=CH_2), 1727, 1647 ($^{R}_{R}{>}C\text{=}CH_2$). NMR (in $CDCl_3$) ppm: 1.78 (3H, singlet, $CH_3\text{–}\overset{|}{C}\text{=}$), 3.99 (1H, multiplet, $\text{–}\overset{|}{C}\underline{H}\text{–}OH$), 4.78, 4.93 (2H, singlet, singlet, CH_2=).

Reaction of 2-(α-Hydroxyisopropyl)cyclohexanol (XI) and Acetonitrile——To 10 ml of chilled conc. H_2SO_4, 320 mg of CH_3CN was added, and 1.03 g (0.008 mole) of XI was added with stirring. The mixture was stirred for 3 hr at 0—5°, allowed to stand overnight, and poured into 23 g of ice water. The mixture was shaken with $CHCl_3$, the aqueous layer was basified with 35% NaOH, and extracted with ether. The extract solution was dried over Na_2SO_4 and evaporated, leaving 363 mg (31%) of a liquid, bp 83—84° (19 mmHg) and 100 mg (9%) of 1-pyrroline derivative (XXXII), bp (bath temp.) 180° (1 mmHg), mp 148—150° (from iso-Pr_2O). The former was found to be a 1.2:1 mixture of two kinds of oxazine, XXX and XXXI. XXX and XXXI were separated as their respective picrate and then liberated as the free base. Picrate of XXX melted partially at 152—154° and the whole melted at 172—174°. The picrate of XXXI melted at 175—176.5°. Mixture of these two picrates showed depression of the melting point. XXX showed shorter retention time than XXXI in gas–liquid chromatography, and larger *Rf* than XXXI in thin–layer chromatography. The lone–pair electrones on the nitrogen in XXX is considered to be more shielded than that in XXXI by the adjacent dimethyl group. *Anal.* Calcd. for $C_{11}H_{19}ON \cdot C_6H_3O_7N_3$ (picrate of XXX, from MeOH): C, 49.75; H, 5.40; N, 13.65. Found: C, 50.04; H, 5.53; N, 13.16. *Anal.* Calcd. for $C_{11}H_{19}ON \cdot C_6H_3O_7N_3$ (picrate of XXXI, from MeOH). Found: C, 49.62; H, 5.49; N, 14.11. *Anal.* Calcd. for $C_{11}H_{19}ON$ (XXXII): C, 72.88; H, 10.57; N, 7.73. Found: C, 73.01; H, 10.69; N, 8.00. XXXII: IR ν_{max}^{KBr} cm^{-1}:

1645 (–C=N–), 3195 (OH). NMR (in $CDCl_3$) ppm: 1.13, 1.18 $\left(3H,\ 3H,\ \text{singlet, singlet, } -\overset{|}{C}\begin{smallmatrix}\diagup CH_3\\ \diagdown CH_3\end{smallmatrix}\right)$, 2.02 (3H, singlet, $-N{=}\overset{|}{C}-CH_3$), 4.16 (1H, multiplet, $-\overset{|}{C}H-N{=}$;).

Reaction of 2-(Isopropenyl)cyclohexanol (XXIX) and Acetonitrile——The reaction was carried out in exactly the same manner as in the case of XI and a similar result was obtained. A mixture (1:1.5) of XXX and XXXI was obtained from 1.5 g (0.0095 mole) of XXIX and 0.45 g of CH_3CN in 23% yield (0.39 g), with 75 mg (4.4%) of XXXII.

Acknowledgement The authors are indebted to Mr. T. Ono of this college for the measurement of NMR spectra and to Mrs. Y. Baba, Miss. S. Suzuki, and Mr. A. Wakamatsu for elemental analyses.