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41. Wataru Nagata, Ikuo Kikkawa, and Manabu Fujimoto: Angular Substituted Polycyclic Compounds. VII.*1 Cyanation of $\Delta^{1,9}$-2-Octalone(4,4a,5,6,7,8-hexahydro-2(3*H*)-naphthalenone).

(*Research Laboratory, Shionogi & Co., Ltd.**2)

Recently it was shown that cyanation at angular positions of polycyclic enones[1] could be smoothly achieved, and the introduced cyano group could then be transformed into other functional groups.[1c,2)]*1 The reaction of this conjugate addition was utilized successfully in the course of synthesis of steroids.[1a,3)] We were interested in studying this reaction in the bicyclic system and in comparing behaviors of thus obtained angular substituted products with those of tetracyclic series from a stereochemical point of view. This paper presents results of cyanation of $\Delta^{1,9}$-2-octalone(4,4a,5,6,7,8-hexahydro-2(3*H*)-naphthalenone)(I) and some observation on the reactivity of thus introduced angular cyano and amino groups.

The starting material I was prepared from cyclohexanone and methyl vinyl ketone according to the method of Bergmann, *et al.*[4] The crude product was purified by repeated, careful fractional distillation to an extent of ca. 95% purity*3,*4 and was employed for further reactions. The cyanation of I was performed at first under the conditions which we reported earlier;[1c] $\Delta^{1,9}$-2-octalone was treated with two mole equivalents of potassium cyanide and 1.5 mole equivalents of ammonium chloride in aqueous dimethyl formamide solution at room temperature. After 29 hours the complete disappearance of the conjugated ketone was observed by the infrared spectrum.

trans-2-Oxo-9-decalincarbonitrile (IIa), m.p. 56~58° and *cis*-2-oxo-9-decalincarbonitrile (IIIa) were obtained by alumina chromatography of the crude product in a yield of 43% (partly as its semicarbazone IIb, m.p. 210~214°) and in a yield of 16% (as its semicarbazone IIIb, m.p. 216~220°), respectively. Additional amount of IIb, IIIb, and their mixture were isolated by further chromatography of the combined mother liquors of each semicarbazone in 1.4%, 6.4%, and 4.8% yield, respectively. Consequently the yield of the *trans*- and the *cis*-product are 44.4% and 22.4%, respectively, indicating that the formation of the former to the latter is in a ratio of ca. 2:1.*5 The pure sample of

*1 Part VI: W. Nagata, S. Hirai, H. Itazaki, K. Takeda: Ann., **641**, 196 (1961).

*2 Fukushima-ku, Osaka, Japan (永田 亘, 橘川郁男, 藤本 学).

*3 The degree of purity was estimated roughly from its IR spectra and gas chromatographic data. We also observed the existence of nonconjugated ketonic substance as impurity, as shown in the paper of Dr. W.L. Meyer (reference *4). See also D.J. Baisted and J.S. Whitehurst: J. Chem. Soc., **1961**, 4089. In most cases, this starting material was freshly distilled before use, because the formation of a considerable amount of a substance with a higher boiling point (dimeric product?) was observed after longer storage.

*4 W.L. Meyer, N.G. Schnautz: J. Org. Chem., **27**, 2011 (1962). We are grateful to Dr. Meyer for a copy of this paper prior to publication, and for kindly supplying us with samples of 2-oxo-9-carboxamides (VI) and (VII).

*5 The more exact estimation of the ratio of IIa and IIIa by gas chromatographic analysis failed. The IR-spectrum of the crude reaction product shows the complete conversion of I into IIa and IIIa, but difficulties in separating both isomers lowered the total yield considerably.

1) *a*) W. Nagata, T. Terasawa, S. Hirai, K. Takeda: Tetrahedron Letters, No. **17**, 27 (1960). *b*) A. Bowers: J. Org. Chem., **26**, 2043 (1961). *c*) W. Nagata, S. Hirai, H. Itazaki, K. Takeda: *Ibid.*, **26**, 2413 (1961). *d*) W. Nagata, T. Terasawa, T. Aoki, K. Takeda: This Bulletin, **9**, 783 (1961). *e*) W. Nagata: Tetrahedron, **13**, 268, 278, 287 (1961).

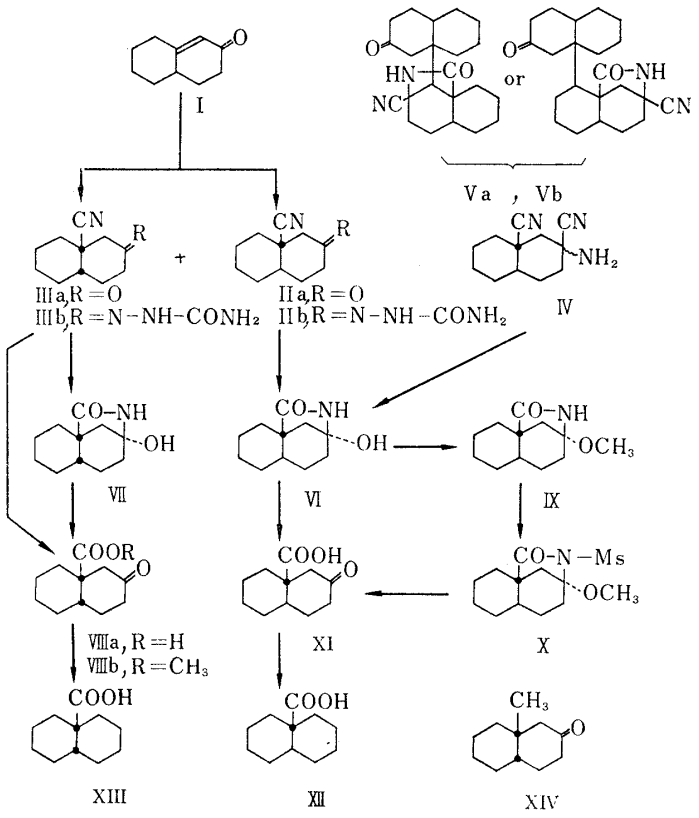
2) W. Nagata, S. Hirai, H. Itazaki, K. Takeda: Ann., **641**, 184 (1961).

3) W. Nagata, I. Kikkawa, K. Takeda: This Bulletin., **9**, 79 (1961).

4) *a*) E. Bergmann, R.I. Kan, H. Weiter-Feilghenfeld: Bull. soc. chim. France, **1957**, 290. See also *b*) H. Christol, M. Mousseron, R. Salle: *Ibid.*, **1958**, 556.

cis-2-oxo-9-decalincarbonitrile (IIIa), b.p. 129° (0.7 mm. Hg), was obtained from its semicarbazone IIIb by treatment with pyruvic acid. The analytical values and ultraviolet spectra of both *cis*- and *trans*-oxonitriles (nitrile and carbonyl bands: 2236 cm^{-1}, 1727 cm^{-1}, and λ_{max} 285 mμ for IIa, and 2237 cm^{-1}, 1727 cm^{-1}, λ_{max} 285 mμ for (IIIa)) confirm their structures.

Next, the same reaction was examined under various experimental conditions. Elevation of the reaction temperature could not give better results, and in some case there were obtained dimeric products Va, m.p. 282~285°, and Vb, m.p. 263~266°, in 18% yield, besides IIa (33%) and IIIa (1.2%). Va and Vb were isomeric, having the same molecular formula of $C_{22}H_{30}O_2N_2$ which was supported by molecular weight determination and elemental analysis. Moreover, the spectral data (UV and IR) showed the presence of nitrile, isolated carbonyl and lactam groups. Therefore, we assumed the structure of the by-products as showh by formula V, although the decision awaits further study.*[6] In refluxing I with two mole equivalents of potassium cyanide and 1.7 moles equivalents of ammonium chloride in aqueous methanol for 9 hours, there was isolated a crystalline product, m.p. 165~174°, in 22% yield, together with IIa (17.1%) and IIIa (7.7%). This product of m.p. 165~174° shows the presence of cyano and amino groups and the absence of other functional groups in its infrared spectrum. The analytical values coincide with the molecular formula of $C_{12}H_{17}N_3$ despite of the wide range of its melting point, suggesting that the product consists mainly of the C_2 epimer. In addition to these data, the smooth conversion of this product into the lactam VI (see below) in 83.5% yield by treatment with diluted alkali seems to allow the structural assignment IV.



Chart

*[6] The possibility that these by-products came from a dimeric self-condensed product, which had existed originally in the starting material I, can not be excluded because in this experiment I was not redistilled before use. cf. reference *[3].

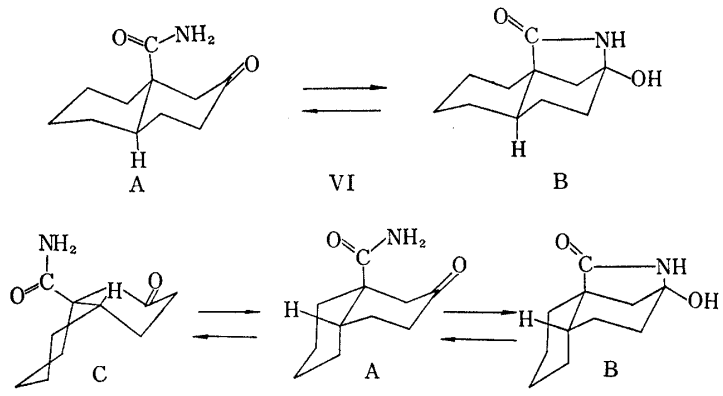
The assignment of the steric configurations of both oxonitriles, namely the *trans* IIa for the solid isomer and the *cis* IIIa for the oily one, was achieved by the following reactions. When both compounds were subjected to oxydative hydrolysis with hydrogen peroxide in an alkaline medium, the oily isomer could be hydrolyzed soomthly to carboxamide VII, m.p. 135~137°, whereas the solid one resisted this hydrolysis and its conversion into another carboxamide VI, m.p. 172~174°, proceeded only in a 15% yield along with 17% recovery of the starting material. However, on normal alkaline hydrolysis with 10% alcoholic sodiumhydroxide, the oily isomer did not give the carboxamide VII, but the oxocarboxylic acid VIIIa in 76% yield. On the contrary, the solid one was converted by this treatment into the carboxamide VI in 59% yield. This marked difference in reactivity between the angularly situated cyano groups of both isomers is clearly due to that of conformational orientations of the functional groups, as shown in the case of 3-oxocholestan-5-carbonitrile.[1c] In this *cis*-isomer the cyano group which is in the equatorial position for one of the two rings is more rapidly hydrolyzed than that of the *trans*-isomer, which is orientated axially for both rings. On this basis, the oily isomer can be safely assigned to *cis*-configuration IIIa and the solid one, m.p. 56~58°, to *trans*-configuration IIa. With regard to the above two isomeric carboxamides VI and VII, the structures of which may be supported by the optical (see below) as well as analytical data, the former should therefore be considered as *trans*-isomer and the latter as *cis*-isomer. This assignment was further confirmed by comparison with the authentic specimens*4 whose structures were deduced by Meyer and Schnautz on a similar basis, and by conversion of VI and VII into the known 9-decalincarboxylic acids (XII) and (XIII), respectively. *cis*-Carboxamide VII underwent hydrolysis with 20% methanolic sodium hydroxide at boiling temperature for 7 hours to give *cis*-2-oxo-9-decalincarboxylic acid (VIIIa) in 59% yield along with the 26.4% recovery of VII. The oily VIIIa was characterized by converting into its methylester, b.p. 130° (bath temperature, at 0.03 mm. Hg). Under this experimental condition, however, the *trans*-carboxamide VI could not be hydrolyzed as might be expected, and was recovered unchanged. It could be converted into thed esired *trans*-2-oxo-9-decalincarboxylic acid (XI), m.p. 118~120° in 76% yield only under the more drastic condition, namely by heating with 2% aqueous potassium hydroxide at 200° for 8 hours. The marked difference observed in alkaline hydrolysis of each angular amido group between VII and VI is clearly due to their conformational situations in the decalin system, as in the case of the 2-oxo-9-decalincarbonitriles IIIa and IIa (see above and cf. Chart 1). That no epimerisation at C_9 had occurred during the drastic alkaline treatment of *trans*-carboxamide VI, was verified by its smooth conversion into XI by our another method[1e,2] which had been already proved by us to be more advantageous because of the milder experimental condition. Thus VI was converted with methanolic hydrochloric acid into the lactamol methyl ether IX, m.p. 133~134°, which was mesylated in an atomosphere of nitrogen with mesyl chloride and sodium hydride in toluene to give X, m.p. 118~119.5°. X was then degradated by refluxing it in diluted aqueous dioxane solution to afford in an excellent yield (92%) an oxocarboxylic acid which was identical with the above mentioned specimen of XI, m.p. 118~120°. Finally, VIIIa and XI were converted by the Huang-Minlon reduction into the known *cis*- and *trans*-9-decalincarboxylic acid (XIII), m.p. 122~124° and XII, m.p. 133~134°. The melting points of these compounds are in good agreement with those reported in the literatures.[5],*4

The fact that the angular situated amido groups in the decalin system undergo ready alkaline hydrolysis in comparison with those in 3-oxo-5α- and 5β-cholestan-

5) *a*) R. E. Pincock, E. Grigat, P. D. Bartlett : J. Am. Chem. Soc., **81**, 6332 (1959). *b*) M. Idelson, E. H. Becker : *Ibid.*, **80**, 908 (1958). *c*) W. G. Dauben, R. C. Tweit, R. L. MacLean : *Ibid.*, **77**, 48 (1955). cf. *d*) P. F. Somer, V. P. Arya, W. Simon : Tetrahedron Letters, No. 20, 18 (1960).

5-carboxamides, where the direct hydrolysis of the amide groups to carboxylic acids could not be attained without decomposition,[2] may mainly be attributable to its less rigidity*7 in the molecule in the former ring system than in the latter, because the possible participation[5c]*4 of the oxo group to amide group should affect both ring systems to the same extent (see below).

The *trans*-oxoamide VI was proved undoubtedly to exist in equilibrium with the lactam structure B in solution, by the following spectral data. The bands at 3600, 3504, 3390, 3308 (broad), and 1689 cm^{-1} in the infrared spectrum of VI in chloroform solution can be assigned to -OH, bonded -OH, -NH-, bonded -NH- and -CO-NH-, respectively. This assignment was ascertained by measuring its infrared spectrum in highly diluted carbon tetrachloride solution by the use of lithium fluoride optics, where only two sharp singlets ascribable to -OH (at 3595 cm^{-1}) and -NH- (at 3422 cm^{-1}) and no doublet for primary amide in the region of 3400~3500 cm^{-1} [6] were observed. The absence of the second band 1620~1590 cm^{-1} in the infrared spectrum in chloroform and no absorption for isolated carbonyl group in the region of 270~300 mμ in the ultraviolet spectrum clearly shows the lactam structure of VI even in polar solvents. The infrared spectra of *cis*-amide VII in chloroform and in carbon tetrachloride are almost identical in the group frequency region: In chloroform, the bands occur at 3596 (-OH), 3504 (bonded -OH), 3390 (-NH-), 3316 (broad, bonded -NH-), and 1689 cm^{-1} (-CO-NH-), and in carbon tetrachloride the bands at 3593 (-OH), and 3422 cm^{-1} (-NH-). This demonstrates the existence of VII in the lactam structure B in equilibrium in these solvents. The ultraviolet spectrum of VII in 95% alcohol, however, shows a very weak, broad absorption band centered at ca. 285 mμ for isolated carbonyl, indicating an existence of the true amido structure (A and C) to an extent of ca. 10% in this solvent. Therefore, a conclusion is drawn that *cis*-2-oxo-9-decalincarboxamide (VII) exists in the form of lactam completely in non-polar solvents and predominantly in polar ones, as was the case with 3-oxo-5α- and -5β-cholestan-5-carboxamide.[1c] This suggestes that the favorable attraction between the two functional groups, the carbonyl and the amido groups, dominates the equilibrium.



VII

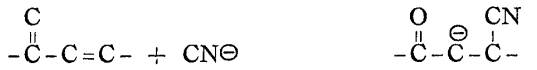
Chart 1.

We discuss now the stereochemistry of cyanation of $\Delta^{1,9}$-2-octalone (I). The earlier procedure for 1,4-addition reaction of hydrogen cyanide to α,β-unsaturated ketones with potassium cyanide in polar solvents is considered as a thermodynamically controlled

*7 The work "rigidity" is used here to mean less ability of distortion and less mobility of conformations in a transition state.

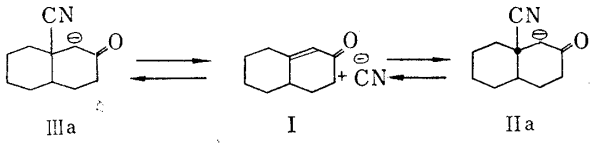
6) L. J. Bellamy: The Infra-red Spectra of Complex Molecules, Second Ed., Methuen & Co., 1958, p. 205.

one, since an equilibrium is caused by the reverse Michael type addition, namely by β-elimination, as shown in equation (1). This relationship is true in the case of the cyanation at angular positions of polycyclic ring systems,



(1)

where the *cis*- and *trans*-stereoisomer should be formed and the equilibrium between three species exists (equation (2)).[1c]



IIIa I IIa (2)

In a strong basic medium in which the earlier cyanation was performed, the reverse reaction is predominant and frequently only poor results were obtained, especially in the case of cyanation at the highly hindered angular position.*8 Moreover, in most cases, employment of potassium cyanide gives rise to undesirable side reactions, such as hydrolysis, dimerisation, and isomerization, due to its strong basic character, and this lowers the usefulness of this reaction for synthetic purposes. In our earlier paper, therefore, we reported an improved procedure using ammonium chloride to buffer the reaction medium. This procedure actually eliminates the above side reactions and has been proved by us to be very efficient for synthetic purposes.[1a,1c,1e,3)]*1 However, the thermodynamically controlled character of this procedure still seems to remain to some extent. We consider that the somewhat less stereospecificity of this procedure must partly be due to its thermodynamically controlled character.

Recently, we have succeeded in finding a new method which was proved to be completely kinetically controlled with regard to 1,4-addition and moreover a most potential one.*8 The new method consists in treatment of α,β-unsaturated ketones with hydrogen cyanide and alkyl aluminum compound in nonpolar solvents, such as ether, tetrahydrofuran, and benzene.*9 This new method was now applied to the cyanation of $\Delta^{1,9}$-2-octalone (I). When I was treated with hydrogen cyanide (2 moles equivalents) and triethyl aluminum (3 moles equivalents) in tetrahydrofuran, the reaction proceeded rapidly as expected, and was completed in one hour at room temperature. The crude product gave the *trans*-oxonitrile IIa by direct crystallization in 60.5% yield. Chromatography of the mother liquor on alumina afforded an additional amount of IIa (11% yield, totally 71.5%) and *cis*-oxonitrile IIIa in 3.15% yield (as its semicarbazone).*5 The ratio of the isolated *trans*-isomer IIa to *cis*-isomer IIIa is therefore ca. 24 to 1, indicating the high stereospecificity of this method. This kinetically controlled, procedure made it easier to inspect the stereochemistry of cyanation at angular positions. The *cis*-direction of nucleophic addition of the cyanide ion to activated molecule XV should be favored, if the cyanide anion is sufficiently bulky due to the solvation, since in this case, the steric hindrance should be significant in the *trans*-direction (Chart 2). On the contrary, the latter direction should be dominating, if the cyanide ion is not so highly solvated, since the *trans*-direction is much more favorable from a stereoelectrical point of view. Thus while maximum overlapping of cyanide ion with the vacant orbital at the trigonal angular carbon atom in *trans*-direction causes the stable transition molecule with *half-chair* conformation XVI, approach of the cyanid ion from *cis*-direction leads to a high energetic transition state XVII with distorted *pre-boat* conformation, which is transformed

*8 See our later paper.
*9 The detailed description of this method and its mechanism will soon be published elsewhere.

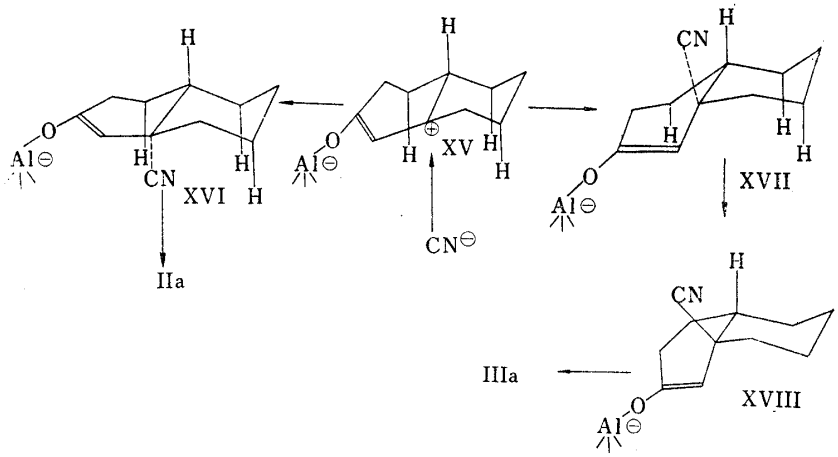


Chart 2.

to boat conformation XVIII.[7] The highly predominant formation of *trans*-isomer shows that the stereoelectrical factor dominates in this newly developed procedure. It is noteworthy that the addition of methylmagnesium iodide to $\Delta^{1,9}$-2-octalone (I) in the presence of cuprous bromide as studied by Birch and Robinson,[8] gave exclusively the *cis*-9-methyl-2-decalone (XIV) in 60% yield. Although our new cyanation reaction seems to be similar to the Grignard reaction in nature, the marked difference in steric direction is to be noted. The reason for this can probably be sought in the bulkiness of the Grignard reagents in nonpolar solvents.*[10] In a typical example of the cyanation of I under the buffered condition, namely, by the use of potassium cyanide and ammonium chloride in aqueous dimethylformamide, the formation of *trans*- IIa and *cis*-isomer IIIa was in a ratio of ca. 2:1, as shown earlier. In this case, the steric hindrance in the above mentioned sense can not be negligible, because in such a polar solvent, especially in the presence of water, the solvation of cyanide anion should be high and the nucleophilic species is more bulkier than in the nonpolar solvent. Therefore, it seems that the less stereospecificity of this procedure is due partly to steric and partly to thermodynamic factors.

Experimental*[11]

Reaction of $\Delta^{1,9}$-2-Octalone (4,4a,5,6,7,8-Hexahydro-2-(3*H*)-naphthalenone) (I) with KCN——A. A solution of $\Delta^{1,9}$-2-octalone[4a,4b],*[12] (3.0 g., 0.02 mole) in dimethylformamide (50 ml.) was added to a solution of KCN (2.605 g., 0.04 mole) and NH_4Cl (1.605 g., 0.035 mole) in H_2O (5 ml.) and the mixture was stirred at 20~21° under an atomosphere of N_2 for 29 hr. The disappearance of the unsaturated ketone group was checked by IR spectrum in the course of the reaction. After being cooled, the mixture was neutralized with AcOH and the solvent was evaporated *in vacuo*. H_2O was then added and the product was extracted with $CHCl_3$. The combined extracts were washed with H_2O, dried, and evaporated *in*

*[10] The mechanism of Grignard addition to α,β-unsaturated ketones in the presence of cuprous halogenide has been recently developed by Munch-Petersen *et al.*, but not from a stereochemical point of view. cf. J. Munch-Petersen, C, Bretting, P.M. Jφrgensen, S. Refn, V.K. Andersen: Acta Chem. Scand., **15**, 277 (1961).

*[11] Melting points were measured on a Kofler-block "Monoscope" (Hans Bock Co., Frankfurt am Main, Germany) and are corrected. For elemental analysis, the samples having the melting points of below 120°, 120~180° and over 180°, were dried for 3 hr. over P_2O_5 *in vacuo* (1~2 mm.Hg) at room temperature ~60°, 70~90°, and 100~120°, respectively. Chromatography was performed according to the method described by Reichstein and Shoppee (T. Reichstein, C.W. Shoppee: Disc. Trans. Farad. Soc., No. 7, 305 (1949).) and the neutral Al_2O_3 (Woelm, activity II) was employed.

*[12] Newly distilled. UV: $\lambda_{max}^{95\%\ EtOH}$ 239 mμ (ε 15000).

7) cf. J. Valls, E. Toromanoff: Bull. soc. chim. France., **1961**, 758.

8) A.J. Birch, R. Robinson: J. Chem. Soc., **1943**, 501.

vacuo. The residue (3.97 g.) was chromatographed on Al_2O_3 and elution with petr. ether-benzene (9 : 1) (Fraction A) gave 1.0064 g. of a crude oil. Further elution with petr. ether-benzene (9 : 1, 4 : 1, and 1 : 1), benzene, and benzene-$CHCl_3$ (9 : 1) (Fratcion B) and recrystallization from Et_2O and pentane afforded 1.411 g. (40 %) of *trans*-oxonitrile IIa, m.p. 56~58°; $b.p_{0.8}$ 132°; UV $\lambda_{max}^{95\%\ EtOH}$: 285 mμ (ε 20). IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 2236, 1727. *Anal.* Calcd. for $C_{11}H_{15}ON$: C, 74.53; H, 8.53; N, 7.90. Found : C, 74.56; H, 8.67; N, 8.09. Semicarbazone IIb : m.p. 210~214°, needles from $CHCl_3$ and MeOH. IR ν_{max}^{Nujol} cm^{-1} : 3460, 3326, 3240, 2240, 1689, 1642, 1563. *Anal.* Calcd. for $C_{12}H_{18}ON_4$: C, 61.51; H. 7.74; N, 23.91. Found : C, 61.66; H, 7.97; N, 24.04.

The mother liquor from fraction B was converted into its semicarbazone and 141.7 mg. (3%) of IIb was obtained.

Fraction A was converted into its semicarbazone and the semicarbazone was crystallized from $CHCl_3$ and MeOH to afford 753.6 mg. (16.0 %) of *cis*-oxonitrile semicarbazone IIIb, m.p. 200~207°. The analytical specimen from the same solvent melted at 216~220°. IR ν_{max}^{Nujol} cm^{-1} : 3530, 3265, 3236, 2240, 1689, 1567. *Anal.* Calcd. for $C_{12}H_{18}ON_4$: C, 61.51; H, 7.74; N, 23.91. Found : C,61.31; H, 7.79; N, 23.82.

To a solution of IIIb (2.0 g.) in $CHCl_3$ (40 ml.) and EtOH (20 ml.) was added pyruvic acid (4 ml.), and then the mixture was refluxed for 2 hr. The reaction mixture was evaporated *in vacuo* and extracted with Et_2O. The extract was washed with H_2O, dried, and evaporated. A colorless oil IIIa was obtained by distillation at reduced pressure; $b.p_{0.7}$ 129°, n_D^{25} 1.4973; IR $\nu_{max}^{CH\ Cl_3}$ cm^{-1} : 2237 (C≡N), 1727 (C=O), UV $\lambda_{max}^{95\%\ EtOH}$: 285 mμ (ε 30). *Anal.* Calcd. for $C_{11}H_{15}ON$: C, 74.53; H, 8.53; N, 7.90. Found: C, 73.93; H, 8.81; N, 7.77.

The conbined mother liquors of IIb and IIIb were chromatographed on Al_2O_3. IIb, IIIb, and the mixture of IIb and IIIb were obtained in 4.5 %, 6.4 %, and 4.9 % yield, respectively.

The ratio of *cis*- to *trans*-isomer was 1 : 2.

B. A solution of $\Delta^{1,9}$-2-octalone (I)*[13] (5.0 g., 0.0334 mole), KCN (3.3 g., 0.05 mole), and NH_4Cl (2.15 g., 0.04 mole) in H_2O (8 ml.) and dimethylformamide (80 ml.) was heated at 100° with stirring for 6.5 hr. under an atomosphere of N_2. After being cooled, the mixture was neutralized with AcOH and worked up as above, giving 6.47 g. of a crude oily product. The product was crystallized from Et_2O to give 789 mg. (13.4 %) of a dimer Vb, m.p. 253~260°. The analytical specimen from $CHCl_3$ and Me_2CO melted at 263~266°. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3400 (>NH), 2250 (C≡N), 1712 (C=O), 1687 (CO-NH). *Anal.* Calcd. for $C_{22}H_{30}O_2N_2$: C, 74.54; H, 8.53; N, 7.90, mol. wt. 354.48. Found : C, 74.27,; H, 8.64; N, 8.06, mol. wt. (Rast), 382.

The mother liquor was distilled at reduced pressure and yielded 2.70 g. of oil, $b.p_{0.8}$ 129.5~130°. The amount of a red brown oily residue was 1.541 g.

The distillate was crystallized from Et_2O and pentane to give 1.025 g. (17.4 %) of IIa and chromatography of the mother liquor afforded 623.6 mg. (10.55 %) of IIa and 966 mg. of a mixture of IIa and IIIa. The above residue was chromatographed and elution with benzene-$CHCl_3$ (4 : 1) gave 85.3 mg. (1.45 %) of the dimer Vb, m.p. 260~263°. Further elution with benzene-$CHCl_3$ (1 : 1 and 1 : 2) and crystallization from $CHCl_3$ and Et_2O afforded 27.5 mg. of a dimer Va, m.p. 275~278°. The analytical specimen from the same solvent melted at 282~285°, IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3403 (>NH), 2256 (C≡N), 1711 (C=O), 1689 (CO-NH-). *Anal.* Calcd. for $C_{22}H_{30}O_2N_2$: C, 74.54; H, 8.53; N, 7.90, mol. wt. 354.48. Found : C, 74.29; H, 8.58; N, 8.04, mol. wt. (Rast) 369. Besides, there were obtained 163.7 mg. (2.77 %) of a mixture of Va and Vb, m.p. 257~261°.

The mixture (966 mg.) of IIa and IIIa was converted into the semicarbazones, and chromatographed, giving 427 mg. (5.5 %) of IIb, 95 mg. (1.2 %) of IIIb, and 70 mg. (1.0 %) of a mixture IIb and IIIb.

Totally the *cis*-product was obtained in 1.2 % yield and the *trans*-product in 33.3 % yield, and the ratio of *cis* and *trans* is ca. 1 : 33. Besides, dimers Va and Vb were obtained in 18 % yield.

C. A solution of $\Delta^{1,9}$-2-octalo ne I*[12] (21.6 g., 0.144 mole) in MeOH (430 ml.) was added to a solution of KCN (18.7 g., 0.288 mole) and NH_4Cl (13.0 g., 0.245 mole) in H_2O (43 ml.) and the mixture was refluxed for 9 hr. After being coold, the reaction mixture was acidified with AcOH, evaporated *in vacuo*, and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated *in vacuo*. The residue was crystallized from Et_2O and pentane to give 6.31 g. (21.7 %) of 2-amino-29-decalin dicarbonitrile (IV), m.p. 165~174°, as prisms. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3364, 3305, 2235 (C≡N), 1610~1592 (broad, NH_2); IR ν_{max}^{Nujol} cm^{-1} : 3360, 3300, 1598 (NH_2), 2235 (C≡N). *Anal.* Calcd. for $C_{12}H_{17}N_3$: C, 70.90; H, 8.43; N, 20.67. Found : C, 70.63; H, 8.51; N, 20.58.

To a solution of 200 mg. of IV in 20 ml. of MeOH was added 5 ml. of 2*N* NaOH and the mixture was refluxed for 2 hr. Evolution of NH_3 was observed. The reaction mixture was evaporated *in vacuo* H_2O (10 ml.) was added, and the mixture was extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated *in vacuo*. Crystallization of the residue from $CHCl_3$ and Et_2O gave 159.5 mg.

*[13] The material which had been stored in an ample for two months after distillation was used. Some amount of a dimer (?) may be contained in this material.

(83.5% from IV) of *trans*-2α-hydroxy-2β-amino-9β-decalincarboxylic acid lactam (VI), m.p. 172~174°, as plates. IR $\nu_{max}^{CHCl_3}$ cm^{-1} (0.25 mm. cell, prism NaCl) : 3600 (OH), 3504 (bonded OH), 3390 (>NH), 3308 (broad, bonded NH), 1689 (CO-NH-); IR $\nu_{max}^{CCl_4}$ cm^{-1} (2 cm. cell, prism LiF, $3\,M\times10^{-3}$ per liter) : 3422 (NH), 3595 (OH). *Anal.* Calcd. for $C_{11}H_{17}O_2N$: C, 67.11; H, 8.78; N, 7.17. Found : C, 67.49; H, 8.83 N, 7.03.

The mother liquor of IV was distilled under reduced pressure, giving 0.761 g. of an oil, $b.p_{0.7}$ 110~132° and 10.202 g. of an oil, $b.p_{0.7}$ 133~137°. Conversion of the latter distillate (10.2 g.) into its semicarbazone and crystallization from $CHCl_3$ and MeOH afforded 4.49 g. (13.35%) of IIb, m.p. 210~214° and 1.2 g. (3.58%) of IIIb, m.p. 212~214°. Repeated chromatography of the mother liquor yielded 1.257 g. (3.74%) of IIb, 1.38 g. (4.12%) of IIIb, and 3.357 g. (10%) of a mixture IIb and IIIb.

Reaction of $\Delta^{1,9}$-2-Octalone (I) with HCN and Et_3Al——To a solution of 6.85 g. (0.06 mole) of Et_3Al in 40 ml. of anhyd. tetrahydrofuran, a solution of 1.08g. (0.04 mole) of HCN in 10 ml. of anhyd. tetrahydrofuran was added under ice-cooling in an atomosphere of N_2. This mixture was added to a solution of 3.0 g. (0.02 mole) of $\Delta^{1,9}$-2-octalone (I) in 40 ml. of anhyd. tetrahydrofuran. After being allowed to stand for 1 hr. at room temperature, the reaction mixture was gradually poured into ice-cooled 2*N* NaOH (ca. 100 ml) and then extracted with $CHCl_3$. The organic layer was washed with H_2O, dried and evaporated *in vacuo*. The residue (3.46 g.) was crystallized from Et_2O and pentane to give 2.137 g. (60.5%) of IIa, m.p. 56~58°. The mother liquor (1.24 g.) was chromatographed on 30 g. of Al_2O_3. Elution with petr. ether-benzene (9 : 1 and 4 : 1) (Fraction A) afforded 124.7 mg. of a crude oxonitrile as an oil and elution with petr. ether-benzen (4 : 1) and benzene (Fraction B) and crystallization gave 388.5 mg. (11%) of IIa, m.p. 55~57°. Fraction A and the mother liquor of fraction B were combined and converted into the semicarbazones. Repeated fractional crystallization gave 147 mg. (3.15%) of IIIb, m.p. 204~207°, and 125 mg. (3%) of a mixture of IIb and IIIb. The ratio of the *cis*- and the *trans*-product is ca. 1 : 24.

Saponification of *cis*-2-Oxo-9-decalincarbonitrile (IIIa). **i) With H_2O_2 and Na_2CO_3**——To a solution of 300 mg. of IIIa in 3 ml. of Me_2CO were added 4 ml. of 10% H_2O_2 and 0.3 ml. of 10% Na_2CO_3, and the mixture was allowed to stand at room temperature for 4 days. After the reaction mixture was acidified with AcOH and evaporated *in vacuo*, H_2O was added to the residue and the mixture was extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated *in vacuo*. The residue (309 mg.) was chromatographed, and elution with petr. ether-benzene (1 : 2) and benzene gave 62.4 mg. of the starting material IIIa, and elution with $CHCl_3$-MeOH (99 : 1, 98 : 2, 95 : 5), 146.6 mg. (45%) of *cis*-2α-hydroxy-2β-amino-9β-decalincarboxylic acid lactam (VII), m.p. 135~137°, as needles (from Et_2O). IR $\nu_{max}^{CHCl_3}$ cm^{-1} (0.25 mm. cell, prism NaCl) : 3596 (OH), 3504 (bonded OH), 3390, 3316 (broad, bonded NH), 1689 (CO-NH-); IR $\nu_{max}^{CCl_4}$ cm^{-1} (2 cm. cell, prism LiF, 0.003*M* per liter) : 3422 (>NH), 3593 (OH). UV $\lambda_{max}^{95\%\ EtOH}$: 285 mμ (ε 2). *Anal.* Calcd. for $C_{11}H_{17}O_2N$: C, 67.66; H, 8.78; N, 7.17. Found : C, 67.72; H, 8.81; N, 7.29.

ii) With H_2O_2 and NaOH——To a solution of 200 mg. of IIIa in 3 ml. of Me_2CO were added 3 ml. of 15% H_2O_2 and 0.3 ml. of 10% NaOH, and the mixture was allowed to stand at room temperature for 4 days. Working up as in i) gave 268 mg. of the crude product which afforded 95.1 mg. (43.2%) of *cis*-lactam VII, m.p. 129~132° by chromatography.

iii) With Alcoholic NaOH——IIIa (520 mg.) was dissolved in 20 ml. of 10% alcohlic NaOH and the solution refluxed for 7 hr. in an atomosphere of N_2. The reaction mixture was evaporated *in vacuo*, and the residue was acidified with 20 ml. of 2*N* HCl and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried, and evaporated *in vacuo*. The residue (565 mg.) was dissolved in 20 ml. of 2*N* Na_2CO_3, extracted with Et_2O, and the Et_2O layers were washed with H_2O, dried, and evaporated to give 76.3 mg. of an oil. It exhibited that a lactone band was at 1760 cm^{-1} and a lactam band at 1590 cm^{-1} in the IR spectrum, but was not examined further. On the other hand, the alkaline solution was acidified with 2*N* HCl and then extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated *in vacuo* to give 435 mg. (76%) of a nearly colorless oil, crude VIIIa. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3500 (OH), 2640 (broad, COOH), 1712 (COOH), 1702 (C=O).

The crude product was added to a solution of CH_2N_2 (prepared from 5 g. of N-nitrosomethylurea) in 30 ml. of Et_2O, and the mixture was allowed to stand at room temperature for 2 hr. After being evaporated *in vacuo*, the reaction mixture was made alkaline with 2% Na_2CO_3 and extracted with Et_2O. The extract was washed with H_2O, dried, and evaporated to furnish 460 mg. of a product which was distilled at 0.03 mm.Hg and a bath temperature of 130° to give oily VIIIb, n_D^{22} : 1.4989; IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1722 (C=O), 1195 (OCH_3). *Anal.* Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found : C,68.74; H, 9.04.

Saponification of *trans*-2-Oxo-9-decalincarbonitrile (IIa) **i) With H_2O_2 and Na_2CO_3**——A mixture of IIa (300 mg.), 10% H_2O_2 (4 ml.), 10% Na_2CO_3 (0.3 ml.), and Me_2CO (3 ml.) was allowed to stand at room temperature for 4 days. Working up as above gave 288.6 mg. of a crude crystalline product which melted at 56~58° after recrystallization from Et_2O and pentane and was proved to be the starting material IIa.

ii) With H_2O_2 and NaOH——A mixture of IIa (248 mg.), 15% H_2O_2 (6 ml.), 2*N* NaOH (0.3 ml.) and

Me_2CO (6 ml.) was allowed to stand at room temperature for 4 days. The reaction solution was kept alkaline by addition of 2*N* NaOH, and worked up as above.

The residue (206 mg.) was chromatographed, and elution with benzene and benzene-$CHCl_3$ (9 : 1) gave 40.9 mg. (16.5 %) of the starting material IIa. Elution with $CHCl_3$-MeOH (99 : 1, 97.5 and 2.5) and recrystallization from $CHCl_3$ and Et_2O afforded 40.2 mg. (15 %) of *trans*-lactam VI, m.p. 172~174°.

iii) With Alcoholic NaOH——IIa (1.44 g.) was dissolved in 56 ml. of 10 % alcoholic NaOH and the mixture was refluxed for 7 hr. The reaction mixture was worked up in the usual way, and there were obtained lactam VI, m.p. 166~169° in 48.6 % yield (772 mg.) from the $CHCl_3$ extract, and 286 mg. of an acid product, from the alkaline aqueous layer. The latter product was not examined further.

Hydrolytic Cleavage of *cis*-2α-Hydroxy-2β-amino-9β-decalincarboxylic Acid Lactam (VII)——VII (670 mg.) was dissolved in 30 ml. of 20% methanolic NaOH and the mixture was refluxed for 7 hr. under N_2 atomosphere. The reaction mixture was worked up as usual, and there were obtained 176.6 mg. (26.4 %) of the starting material VII and 391.5 mg. (58.5 %) of an oily product which was identical with VIIIa in the IR spectrum.

Hydrolytic Cleavage of *trans*-2α-Hydroxy-2β-amino-9β-decalincarboxylic Acid Lactam (VI)——A solution of 933 mg. of VI in 50 ml. of 2% KOH was heated at 200° for 8 hr. in an autoclave. After being cooled, the yellow brown reaction mixture was saturated with CO_2 gas and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated *in vacuo* to give 96 mg. of a yellow oil, which was not examined further.

The H_2O layer was acidified with HCl and extracted with Et_2O. The Et_2O extract afforded 741 mg. (76 %) of XI, m.p. 118~120°, as colorless needles from $CHCl_3$ and ligroin. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3618, 3505 (OH), 3350 (broad), 2550 (broad) (COOH), 1755 (COOH), 1715 (C=O). *Anal.* Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found : C, 67.16; H, 8.28.

***trans*-2α-Methoxy-2β-amino-9β-decalincarboxylic Acid Lactam (IX)**——A solution of 780 mg. of *trans*-lactam VI in 40 ml. of methanolic HCl 37.5% (w/w) was allowed to stand overnight at room temperature. After removal of the solvent *in vacuo*, the reaction mixture was worked up in the usual way. The crystalline residue (790.2 mg.) was chromatographed, and elution with benzene-$CHCl_3$ (9 : 1, 4 : 1, 2 : 1) and crystallization from Me_2CO and Et_2O gave 455.8 mg. (54.5 %) of *trans*-2-methyl ether IX, m.p. 133~134°, as plates. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3395 (>NH), 1699 (-CONH-), 1089 (OCH_3). *Anal.* Calcd. for $C_{12}H_{19}O_2N$: C, 68.86; H, 9.15; N, 6.69. Found : C, 68.72; H, 9.24; H, 6.66.

Further elution with $CHCl_3$-MeOH (98 : 2 and 95 : 5) gave 116.7 mg. (15 %) of the starting material VI, m.p. 165~170°.

***trans*-N-Mesyl-2α-methoxy-2β-amino-9β-decalincarboxylic Acid Lactam (X)**——IX (244.7 mg.) was dissolved in 50 ml. anhyd. toluene and a small portion of toluene was distilled off to remove any trace of H_2O in the solution. Then 128 mg. of 54.5% NaH was added and the mixture was refluxed for 1 hr. A solution of 350 mg. of methylsulfonyl chloride (MsCl) in 350 ml. of anhyd. toluene was added dropwise with stirring to this mixture over a period of 15 min. and the mixture was then refluxed for 2.5 hr.

After the reaction mixture was cooled to 5°, H_2O (ca. 10 ml.) was added carefully and the organic layer was separated. The H_2O layer was extracted with $CHCl_3$, and the organic layer and the $CHCl_3$ extract were combined, washed with H_2O, dried over Na_2SO_4, and evaporated *in vacuo*. The residue (392.7 mg.) was chromatographed, and elution with petr. ether-benzene (1 : 1 and 1 : 2) and benzene gave 223.5 mg. (67.7 %) of X, m.p. 118~119.5°, as plates from Me_2CO and Et_2O. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1738 (CO-N-SO_2-), 1362, 1146 (SO_2-N-), 1092 (OCH_3). *Anal.* Calcd. for $C_{13}H_{21}O_4NS$: C, 54.33; H, 7.37; N, 4.87; S, 11.16. Found : C, 54.46; H, 7.48; N, 4.57; S, 11.01.

Hydrolytic Degradation of *trans*-N-Mesyl-2α-methoxy-2β-amino-9β-decalincarboxylic Acid Lactam (X)——To a solution of 110 mg. of X in 10 ml. of dioxane was added a solution of 400 mg. of NaOH in 2.5 ml. of H_2O and the mixture was refluxed for 2 hr. under N_2 atomosphere. After being cooled, the reaction mixture was diluted with 10 ml. of H_2O and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated to give 18 mg. of an unknown product. The H_2O layer was acidified with conc. HCl, extracted with $CHCl_3$, and worked up as usual. 69.2 mg. (91.5%) of *trans*-2-oxo-decaline-9-carboxylic acid (XI), m.p. 115~118° was obtained.

Huang-Minlon Reduction of *cis*-2-Oxo-9-decalincarboxylic Acid (VIIIa)——A mixture of 300 mg. of VIIIa, 1.5 ml. of 80% $N_2H_4 \cdot H_2O$, 1.03 g. of KOH and 12 ml. of triethylene glycol was heated to 140~145° slowly, maintained at the same temperature for 1 hr., and further heated at 210~220° for 4 hr. The reaction mixture was poured into 30 ml. of H_2O and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated *in vacuo* to give 37.6 mg. of an oil which was not examined further.

The H_2O layer was acidified with conc. HCl and extracted with $CHCl_3$. The extracts were washed with H_2O, dried, and evaporated *in vacuo*. Recrystallization of the crystalline residue (227.5 mg. 81.5%) yielded 180.5 mg. (65.5 %) of *cis*-9-decalincarboxylic acid (XIII), m.p. 122~124° (ref.[5a] m.p. 122°). IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3620, 3460 (OH), 3040 (broad), 2600 (broad), 1690 (C=O). *Anal.* Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found : C, 72.51; H, 9.93.

Huang-Minlon Reduction of *trans*-2-Oxo-9-decalincarboxylic Acid (XI)——A mixture of XI (300.8 mg.), 80% $N_2H_4 \cdot H_2O$ (1.5 ml.), KOH (1.03 g.) and 12 ml. of triethylene glycol was worked up as above. There were obtained 35.5 mg. of an oil and 246 mg. (88.5 %) of *trans*-9-decalincarboxylic acid (XII), m.p. 130~134°, as needles (ref. m.p. 133~134°,[5a] m.p. 133~134°[5c]). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3625, 3465, 3020 (broad), 2675~2615 (broad), 2695. *Anal.* Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.55; H, 10.08.

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Summary

Cyanation at the angular position of $\Delta^{1,9}$-2-octalone (I) was conducted with potassium cyanide in the presence of ammonium chloride in polar solvent, or with hydrogen cyanide and triethyl aluminum in tetrahydrofuran. In the latter case, high stereospecificity of the reaction was observed and the formation of *trans*-2-oxo-9-decalincarbonitrile (IIa) to its *cis*-isomer IIIa was in a ratio of 24:1. The structures and the configurations of the products were determined by conversion into the known *trans*- XII and *cis*-9-decalincarboxylic acid (XIII). Moreover the stereochemistry of this cyanation reaction was discussed.

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42. Kazuo Tori, Masaru Ogata, and Hideo Kano: Pyridazines. IV.[*1] Nuclear Magnetic Resonance Studies of Pyridazine N-Oxide and Its Derivatives.

(*Research Laboratory, Shionogi & Co., Ltd.*[*2])

In recent years, the syntheses of pyridazine N-oxide derivatives has been reported by many authors. In this field, determination of the position of the N-O group in these N-oxides is of great importance. In the previous paper of this series,[*1] the authors reported the location of the N-O group in monomethylpyridazine N-oxides determined by means of dipole moment studies. Among the newer techniques which can be applied to structural studies on pyridazine N-oxide derivatives, nuclear magnetic resonance (NMR) spectroscopy may give more detailed information on this problem.

The present paper describes the application of NMR spectroscopy for determination of the position of the N-O group in pyridazine N-oxide derivatives and the analysis of N-oxidation reaction mixture. The electronic structures of pyridazine N-oxide and its derivatives will be discussed briefly in connection with the chemical shifts.

Experimental

All the spectra were taken with a Varian A-60 analytical NMR spectrometer system on 10% (w/v) deuterochloroform solutions containing about 1% of tetramethylsilane as an internal reference. However, as 4-nitropyridazine 1-oxide (II) and pyrazine di-N-oxide are slightly soluble in the solvent,

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*2 Fukushima-ku, Osaka (通 和夫, 尾形 秀, 加納日出夫).