5α-Pregnane-3β,6α,16β,20β-tetrol (XIII)——A solution of 5 g. of Xb and 0.25 g. of pyridine hydrobromide in 10 cc. of Ac_2O was heated under gentle reflux for 3.5 hr. and diluted with 60 cc. of AcOH. To this solution was added at 11～13° a mixture of 2 g. of CrO_3 in 2.5 cc. of water and 7.5 cc. of AcOH within 15 min. After stirring at room temperature for 40 min., the reaction mixture was treated with aq. $NaHSO_3$ (1.25 g.) and evaporated under vacuum. The residue was mixed with water and extracted with benzene, which was washed with aq. Na_2CO_3 and water, dried over Na_2SO_4, and evaporated. The syrupy residue was dried completely over P_2O_5.

The crude 3β,6α,16β--trihydroxy-5α-pregnan-20-one 3,6-diacetate 16-(4-methyl-5-acetoxyvalerate) (XII) thus obtained was dissolved, without further purification, in 100 cc. of Et_2O and the solution was added dropwise to a mixture of 3.75 g. of $LiAlH_4$ in 200 cc. of Et_2O at room temperature. The reaction mixture was stirred for 8 hr. at the same temperature and refluxed for 3 hr. Usual treatments yielded a powdery product which was acetylated with 70 cc. of pyridine and 40 cc. of Ac_2O at 80° for 3 hr. The mixture was poured into water and the powdery acetate obtained was chromatographed over 100 g. of Florisil. Elution with CH_2Cl_2 gave 1.9 g. of thick paste which was rechromatographed with 30 g. of the same absorbent. After washing with benzene, the column was developed with benzene-AcOEt (95 : 5) which eluted 1 g. of non-crystalline fractions.

This substance was hydrolyzed under reflux with 0.5 g. of KOH in 1.5 cc. of water and 40 cc. of MeOH for 2 hr. Treatment of the reaction mixture in the usual way and recrystallization from Me_2CO and then from MeOH-Me_2CO afforded 850 mg. of colorless prisms, m.p. 242～244°; $[\alpha]_D^{20}$ +34° (c=0.36, $CHCl_3$+10% MeOH). *Anal.* Calcd. for $C_{21}H_{35}O_4 \cdot {}^6/_5H_2O$: C, 68.62; H, 10.33. Found : C, 68.62; H, 10.22.

The authors express their deep gratitude to Dr. S. Kuwada, Director of these Laboratories, for his encouragement and to Drs. T. Matsukawa and Y. Abe for their helpful advices.

Thanks are also due to Mr. M. Kan for elemental analyses and to Mr. H. Nakamachi for optical measurement.

Summary

5α-Pregnane-3β,5,6β,20α-tetrol (IIIa), 5α-pregnane-3β,5,6β,20β-tetrol (IV), 5α-pregnane-3β,6β,16β,20α-tetrol (VIIIa), 5α-pregnane-3β,6α,16β,20α-tetrol (XIa), and 5α-pregnane-3β,6α,16β,20β-tetrol (XIII) were synthesized according to the schemes shown in Chart 1 and Chart 2.

(Received February 19, 1962)

UDC 547.94:582.751.9

21. **Masanobu Terasaka**,[*1] **Kazuko Yamamoto** (neé Narahashi),[*1] and **Yutaka Kawazoe**[*2] : Alkaloids of Root-bark of *Orixa japonica* Thunb. XII.[*3] Nuclear Magnetic Resonance Study of N-Methylorixidinine, N-Methylisoorixidinine, and N-Methylorixidine.

(*Women's Department, Tokyo College of Pharmacy*[*1] *and Faculty of Pharmaceutical Sciences, University of Tokyo*[*2])

The structures of N-methylorixidinine, N-methylisoorixidinine, and N-methylorixidine, derived from orixine,(1) have been proposed on chemical and spectroanalytical evidences as I, III, and V, respectively, as shown in Chart 1.(2) It will be shown in this paper that the analysis of the nuclear magnetic resonance spectra of these com-

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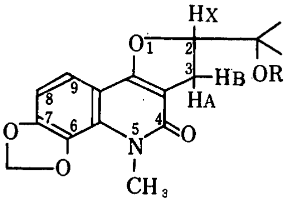
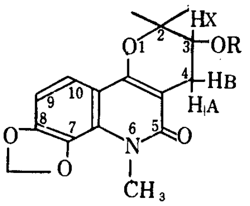
[*3] Part XI. K. Narahashi : This Bulletin, **10**, 792 (1962).
1) M. Terasaka : *Ibid.*, 8, 523 (1960).
2) K. Narahashi : *Ibid.*, **10**, 792 (1962).

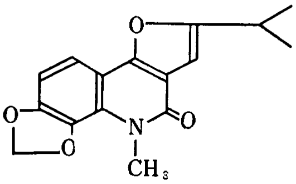
pounds has provided unequivocal evidence for these proposed structures. In addition, a strong evidence has been provided for the conformational relationship of the substituents.



I R=H
II R=—COCH$_3$



III R=H
IV R=—COCH$_3$



V

Chart 1.

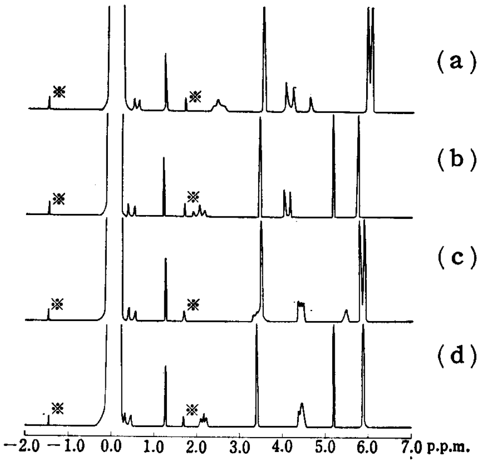


Fig. 1. NMR Spectra measured in Chloroform

(a): N-methylorixidinine (I)
(b): N-methylorixidinine acetate (II)
(c): N-methylisoorixidinine (III)
(d): N-methylisoorixidinine acetate (IV)

Zero reference is the resonance position of solvent chloroform.

* The signals due to ^{13}CHCl$_3$.

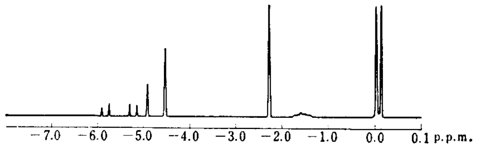


Fig. 2. NMR Spectrum of N-Methylorixidine (V), measured in Carbon Disulfide

Zero reference is the resonance position of internal cyclohexane

The NMR measurements were made on N-methylorixidinine (I) and its acetate II, N-methylisoorixidinine (III) and its acetate IV and, in addition, N-methylorixidine (V). These spectra are shown in Figs. 1 and 2. Chloroform was used for the first four compounds as the solvent and carbon disulfide was used for the last one. The individual peaks were measured by the audiofrequency side band method relative to the signal of solvent chloroform for the chloroform solutions and to the signal of internal cyclohexane for the carbon disulfide solution. The positions of the resonances in Fig. 1 are plotted on a chemical shift in p.p.m. unit from the above internal references. τ-Values can be roughly estimated for the chloroform spectra by adding 2.57 to each of the shift, since the resonance of the solvent chloroform was calibrated against tetramethylsilane in a separate experiment. Approximate τ-values for the carbon disulfide spectrum can be obtained by adding 8.56 to those reported in Fig. 2.

(1) Spectra measured in Chloroform

C-CH$_3$ Resonances

In each spectrum there are two sharp and strong peaks which occur at the characteristic field for C-CH$_3$ protons, an area intensity of each peaks corresponding to three protons. The appearance of these signals at somewhat lower than usual can be explained by the fact that the methyl groups are bonded to a carbon atom which bears an oxygen atom. With the conversion of I to its acetate II, a downward shift of about 0.1 p.p.m.

was observed in the NMR absorptions of these protons. This paramagnetic shift caused by acetylation is known for the system of "CH_3-C-OR"[3] and it provides confirmation of the structure assignment. On the other hand, in the case of III and its acetate IV, no shift was observed in the methyl signals. This fact lends credence to the formulas III and IV, since in these structures the acetylable oxygen atoms should be sufficiently far removed from the methyl groups to greatly affect their chemical shifts. In the spectra of all compounds, except IV, two lines of methyl proton absorptions appear at slightly different fields from each other. It is obvious that the two methyl groups of the compounds III and IV are differently shielded. One explanation for this is that the residence times in the three possible comformations differ slightly and, as a result, magnetic neighbouring effects to these two methyl groups are not be equivalent.[4,5] An alternative possibility, the existence of CH function adjacent to the methyl groups resulting in splitting methyl signals into a doublet by spin-spin coupling, can be eliminated by the fact that the spacing between two methyl resonances of the compound III changed from 7.0 c.p.s. to 5.3 c.p.s. by addition of a trace of acetic acid. If this splitting into two lines might be due to spin-spin coupling, the spacing should not differ by such a slight change of the nature of the solvent.

N-CH_3 and CO-CH_3 Resonances

In each spectrum the signal falling between 3.40 and 3.50 p.p.m. can be assigned to the resonance of the methyl group attached to quinolonenitrogen, on the basis of its chemical shift, relative intensity and lack of fine structure. The analogies of N-methylquinolones[4] and N-methylpyridones[6] are known. II and IV have another single sharp signal at 5.18 and 5.26 p.p.m., respectively, of areas corresponding to three protons. These signals can be assigned to the methyl resonances of acetoxyl groups.

O-CH_2-O Resonances

The proton resonance of methylenedioxy group located on aromatic ring has already been studied.[7] In the spectrum of lunine (VI) reported by Goowin *et al.*,[4] it is observed a relative shift of 1.28 p.p.m. between the proton resonances of methylenedioxy group and solvent chloroform. In the spectra of I, II, III, and IV, there are single sharp lines at 1.23, 1.28, 1.27, and 1.27 p.p.m., respectively, corresponding to two protons. There is no doubt that these lines can be assigned to the methylene resonances of methylenedioxy groups in these compounds.

Conformation of Substituents on Dihydrofuran Ring

The signals from the resonances of the three protons located on dihydrofuran ring

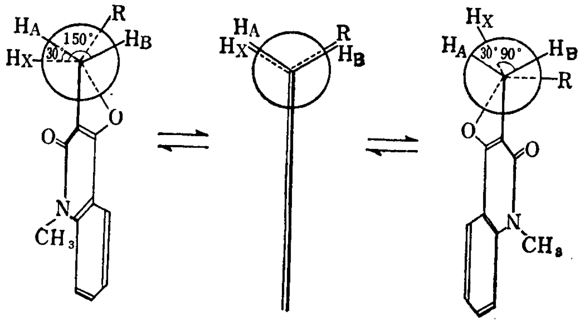


Fig. 3.

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3) L. M. Jackman: "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 47, Pergamon Press, New York (1960).
4) S. Goodwin, J. N. Shoolery, L. F. Johnson: J. Am. Chem. Soc., **81**, 3065 (1959).
5) R. J. Abraham, H. J. Bernstein: Cand. J. Chem., **39**, 39 (1961).
6) L. M. Jackman: J. Chem. Soc., **1961**, 859.
7) Y. Sasaki: Yakugaku Zasshi, **80**, 241 (1960).

of the compound II appeared as a doublet at 4.11 and a triplet at 2.05 p.p.m., relative intensity being 2 to 1. Since these three protons can be expected to give ABX type spectrum, the facts that a doublet of two proton intensity and a triplet of one proton intensity were observed on the spectrum and that all the spacing of these doublet and triplet are same as each other indicate that there is no difference of the chemical shift between the two protons on C-3 atom, H_A and H_B, and that both of the coupling constants, J_{AX} and J_{BX}, are equal to 9.3 c.p.s.[*4]

Now, with regard to conformational mobility of the dihydrofuran ring of the compound II, the C-2 atom can be considered to flap within the angle of about 60° as illustrated in Fig. 3, leading to consideration of each the three extreme structures, A, B, and C. The structure B, in which all of the carbon atoms of dihydrofuran ring are coplaner, must be disregarded by the following two reasons. Firstly, in this conformer the substituents H_A and H_X, H_B and 1-acetoxy-1-methylethyl group are eclipsed, making this conformation energetically unfavourable. Secondly, this eclipsed structure does not fit the NMR spectrum, since H_A and H_B which appeared as equivalent protons in the spectrum, would be expected to have quite different magnetic environment in the conformer B. Then, with regard to the conformers A and C, where the equivalency of the proton A and B may be reasonably explained by assuming the accidental compensation of the effects of bulky 1-acetoxy-1-methylethyl group and quinolone ring current with each other, the magnitude of coupling constant will be taken into consideration, as follows.

As illustrated by Fig. 3, the dihedral angle between H_A and H_X can be considered to change from 30° to $-30°$ via 0° on converting the conformation of the dihydrofuran ring. The theoretical correlation of the coupling constant with the dihedral angle by both of the valence bond method (by Karplus[10)]) and the molecular orbital method (by Conroy[11)]) predict as 6.0 c.p.s. for 30° and 8.3 c.p.s. for 0° as the expected coupling constant. Experimental data seem to support the validity of this theoretical correlation between 0° and around 120° (except for over 120° to 180°), many experimental values falling in a certain range (supposed to be within 2 c.p.s.) around the predicted values theoretically.[12~19)] The magnitude of 9.3 c.p.s. for J_{AX} may, therefore, be agreeable for any conformational relationship, no matter how much the dihedral angle between H_A and H_X may be. On the other hand, the fact of J_{BX} equal also to such a large value as 9.3 c.p.s. seems to insist on the dihedral angle betwee H_B and H_X to be at largest of

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[*4] Whenever there is no chemical shift difference between H_A and H_B, the spectrum of X part of ABX system appears as a triplet whose spacing is equal to $1/2\cdot(J_{AX}+J_{BX})$. It does not mean $J_{AX}=J_{BX}$. Therefore, only the appearance of a triplet as X part of ABX does not derive a conclusion of $J_{AX}=J_{BX}$. It is required for the above conclusion that a doublet is observed as its AB part.[8,9)]

8) J.A. Pople, W.G. Schneider, H.J. Bernstein : "High-resolution Nuclear Magnetic Resonance," p. 132, McGraw-Hill, New York (1959).

9) J.D. Roberts : "An Introduction to Spin-spin Splitting in High Resolution Nuclear Magnetic Resonance Spectra," p. 71, W.A. Benjamin, Inc., New York (1961).

10) M. Karplus : J. Chem. Phys., **30**, 11 (1959); J. Phys. Chem., **64**, 1793 (1961).

11) H. Conroy : "Advances in Organic Chemistry. Methods and Results. Vol. II" p. 265, Interscience Publishers, Inc., New York (1960).

12) F.A.L. Anet : Canad. J. Chem., **39**, 789 (1961).

13) A.D. Cohen, N. Sheppard, J.J. Turner : Proc. Chem. Soc., **1958**, 118.

14) J.I. Musher : J. Phys. Chem., **34**, 594 (1961).

15) E.J. Corey, M. Ohno, S.W. Chow, R.A. Scherrer : J. Am. Chem. Soc., **81**, 6305 (1959).

16) K.L. Williamson, W.S. Johnson : *Ibid.*, **83**, 4623 (1961).

17) A.A. Bothner-By, C. Naar-Colin : *Ibid.*, **83**, 231 (1961).

18) Private communication from Professor Shigenobu Okuda, Institute of Microbiology, University of Tokyo, concerning the NMR data of many morphinan derivatives.

19) Our unpublished data with borneol and its acetate.

those of possible conformations, although the ring conversion enables the angle to change from 150° to 90°. If the angle were 120°, for instance, J_{BX} would be 2 to 3 c.p.s. as shown theoretically[10,11] and experimentally.[12,19] It is clearly too small for agreement with experimental value, 9.3 c.p.s. Thus, assuming that the actual molecular conformation in II may be in the proximity of the structure A and may move within a angle of Δ (denoted in Fig. 4) one can easily understand that J_{AX} equals J_{BX} in a good approximation and that its magnitude is very large for this kind of coupling constants. It may be illustrated by equation (1) and Fig. 4 (with thick lines).

$$\int_{30}^{30-\Delta} P(\theta)\cdot J(\theta)\cdot d\theta = \int_{150}^{150-\Delta} P(\theta)\cdot J(\theta)\cdot d\theta \qquad (1)$$

$P(\theta)$: Probability of existence at the dihedral angle of θ.

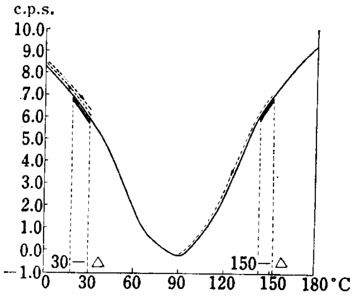

Fig. 4.

On the other hand, conformer C seems to be unreliable structure, where the dihedral angle between H_B and H_X is 90°, resulting nul c.p.s. as the expected coupling constant.*[5] Moreover, the possibility of its free ring conversion in an equilibrium of Fig. 4 can be also eliminated, since the equation (2) can not be satisfied as illustrated in Fig. 4 with dotted lines.

$$\int_{30}^{-30} P(\theta)\cdot J(\theta)\cdot d\theta = \int_{150}^{90} P(\theta)\cdot J(\theta)\cdot d\theta \qquad (2)$$

Because the left term is expected to be always larger than that on the right.

As a conclusion, the above result provided a strong support for the structure fixed so that a bulky 1-acetoxy-1-methylethyl group is almost quassi-equatorial.

With regard to N-methylorixidinine (I), the corresponding broadened peaks of H_A, H_B and H_X appeared as a doublet at 4.13 and a triplet at 2.44 p.p.m. The above discussion of its acetate (II) may be applied to I but the equivalence of H_A and H_B and the equality of J_{AX} and J_{BX} may become vague to give rise to the broadened lines. This sensitivity toward changes in neighbouring groups may indicate that it is accidental for II to give a clear A_2X type spectrum.

With N-methylisoorixidinine (III) and its acetate IV, the corresponding peaks due to these three protons appeared as multiplets, centered at 4.46 and 3.41, and 4.46 and 2.15 p.p.m., respectively. These could not be analyzed as ABX type because of poor resolution.

Characterization of CH Proton attached to Oxygen

In the spectrum of III the signal centered at about 3.4 p.p.m., partly overlapping with the peak of N-methyl protons, could be assigned to the single proton H_X on C_2 atom carrying an alcohol group. This signal become sharper on the addition of a trace of acetic acid although overlapping is still remained. This can be explained by rapid

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*[5] Any of experimental data does not show an apparent coupling constant at the dihedral angle of 90° as predicted theoretically.[12,15,18,20]

20) W.D. Kumler, J.N. Shoolery, F.V. Brutcher: J. Am. Chem. Soc., 80, 2533 (1958).

exchange of the alcoholic proton to cause spin decoupling. In the spectrum of IV, the absorption of the C_3 proton is shifted downward by 1.25 p.p.m. from that in the spectrum of the original alcohol III. From these facts it can be concluded that III possesses a secondary alcoholic function. A downward shift of 0.39 p.p.m. was observed for the C_2 proton of I relative to its acetate II. This shift of 0.39 p.p.m. seems to be consistent with the shift observed when acetylation occurs in the system of "-CH-C-OH" as in I. The chemical shifts of 2.44 and 2.05 p.p.m. observed for the C_2 protons in I and II appear to be low for the protons of "-CH-O-" group. This can be, however, explained by the fact that this proton is shifted to lower field as would be expected from its proximity to the aromatic ring. This effect must be more important in I than in III.

Resonances of Aromatic Protons

Since these compounds were derived by a mild acid-degradation from orixine, it is evident that a methylenedioxy group in their structure must be on C_7 and C_8 atoms of the quinolone ring. · The NMR signals of the protons on C_5 and C_6 atoms can, therefore, be expected to consist of two doublets. Less than one p.p.m. must be expected to be the magnitude of the relative shift between those protons as shown in the spectra of naphthalenes and quinolines. On the other hand, according to Goodwin *et al.*,[4] the anisotropic effect of the carbonyl group of γ-quinolones causes a relative shift which is greater than one p.p.m. between the protons on C_5 and C_6 of the carbostyril derivatives.[*6] In each spectrum of I, II, III and IV, there is a doublet at 0.56, 0.46, 0.49 and 0.44 p.p.m., respectively, each of which has an area intensity of one proton. These appear to be one part of the AB type system. Since there are no signal in lower field other than the signal of solvent chloroform, the resonance of the other part of the AB type must be overlapped by the resonance of chloroform proton. Strong support can be provided for this speculation by the fact that in the spectrum of N-methylorixidine (V) measured in carbon disulfide, the expected second doublet was observed at lower field by 0.62 p.p.m. from the first. On the assumption that one doublet may be hidden in the absorption of chloroform, one can conclude that the relative shift between two protons on C_5 and C_6 in these compounds must fall within a range of 0.65 p.p.m. at maximum and that, as a result, the quinolone system in the compounds studied here must be carbostyril. The spin coupling constants, 8.2 c.p.s. for four of these compounds and 8.5 c.p.s. for one of them, are in good agreement for those between *ortho* protons on an aromatic ring.

OH Resonances

The broadened signals at 4.58 and 5.44 p.p.m. in the spectra of I and III, respectively, could be assigned to the resonances of the alcoholic protons. This was verified by a downward shift observed upon the addition of a trace of acetic acid.

(2) Spectrum of the Compound V measured in Carbon Disulfide

All features of the spectrum can be reasonably assigned to the appropriate protons. A doublet centered at 0.56 p.p.m. must arise from two $C-CH_3$ groups ($J=6.6$ c.p.s.), a singlet at 2.23 p.p.m. from $N-CH_3$ group, a singlet at 4.53 p.p.m. from methylenedioxy group, a singlet at 4.93 p.p.m. corresponding to one proton from vinyl proton and two doublets centered at 5.14 and 5.75 p.p.m. from C_5 and C_6 protons, respectively. In addition, a multiplet at around 1.60 p.p.m. can be assigned as the resonance arising from CH proton next to two methyl groups.

[*6] A substituent, increasing the electron density mainly on the proton on C_5 like 8-methoxy compound, decreases the magnitude of this shift down to a little less than one p.p.m. as shown by the same author.[4]

Experimental

The NMR spectra were obtained in about 5% $CHCl_3$ solutions or 5% CS_2 solution using a Varian Associates DP 60 NMR spectrometer, operating at 60 Mc.p.s. Compounds studied were prepared by one of us (K. Y.), the detail of which has been already published.[2]

The authors are indebted to Professor T. Okamoto of University of Tokyo for his advices and encouragement. Thanks are also indebted to Dr. Peter Beak of University of Illinois, U. S. A. for reviewing of this manuscript before publication. They are also grateful to Mr. H. Hotta of University of Tokyo for his helpful discussion and Dr. K. Nukada and Mr. T. Suzuki of the Government Chemical Industrial Research Institute of Tokyo for making an NMR spectrometer available for the present work.

Summary

The structures of N-methylorixidinine, N-methylisoorixidinine and N-methylorixidine have been verified by NMR analysis. In addition, the conformation of the substituents on dihydrofuran ring was discussed, based on the relationship between the dihedral angle and the spin coupling constant.

(Received August 16, 1962)

UDC 547.852.2.07

22. **Tatsuya Horie and Takeo Ueda** : Studies on Pyridazine Derivatives. IV.[1] N-Oxidation of 3-Aminopyridazine and Its Ring Substitutes.

(*Pharmaceutical Institute, Keio-Gijuku University*[*1])

As pyridazine comprises two vicinal nitrogen atoms, there should exist two position isomers in any pyridazine N-monoxide derivatives having an unsymmetrical structure, in respect of the position of N-oxide group. Regarding N-oxidation of pyridazine derivatives, it is of interest to decide positions of N-oxide groups in resulting derivatives of pyridazine N-oxide.

Although many of heterocyclic N-oxide have been extensively investigated by a number of researchers, little is known as for pyridazine N-oxide. Itai[2], Igeta[3,4], Kumagaya[5] and Nakagome[6,7] reported about N-oxidation of some pyridazine derivatives having substituent group at 3- or 3- and 6- positions on the ring such as alkoxy, chloro, methyl and phenyl. However, N-oxidation of 3-aminopyridazine derivatives has never been revealed in any literature up to date.

A number of compounds of 3-amino-6-substituted pyridazine were synthesized by the authors, as described in the previous report[8]. Attempts were made on the N-oxidation

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[*1] Shinano-machi, Shinjuku-ku, Tokyo (堀江達也, 上田武雄).
1) Part III. T. Horie, T. Ueda : This Bulletin, **10**, 595(1962).
2) T. Itai, H. Igeta : Yakugaku Zasshi, **75**, 966 (1955).
3) H. Igeta : This Bulletin, **7**, 938 (1959).
4) *Idem* : *Ibid.* 8, 599 (1960).
5) M. Kumagaya : Nippon Kagaku Zasshi, **81**, 1148 (1960).
6) T. Nakagome : Yakugaku Zasshi, **82**, 244 (1962).
7) *Idem* : *Ibid.* 82, 249 (1962).
8) Part I. T. Horie, T. Ueda : This Bulletin, **10**, 580(1962).