174~175°. *Anal.* Calcd. for $C_{19}H_{16}O_4N_4$(2,4-dinitrophenylhydrazone): C, 62.63; H, 4.43; N, 15.38. Found: C, 62.91; H, 4.36; N, 15.55.

The authors are grateful to Mr. M. Matsui, Director of this Laboratory, and Prof. K. Tsuda of the University of Tokyo for encouragement throughout this work. The measurement of infrared and ultraviolet spectra were carried out by Messrs. H. Higuchi, N. Higosaki and Miss N. Sawamoto. Microanalyses were made by Messrs. T. Onoe, K. Ono, H. Nagashima and Misses H. Ohtsuka and K. Saito to whom the authors' thanks are also due.

Summary

Intramolecular condensational cyclization of the acetylenic compounds to the aromatic nucleus was achieved with polyphosphoric acid, and this reaction was accompanied with dehydrogenation to give naphthalene derivatives. This method can also be used to nitrogen containing acetylenic compounds to prepare carbostryril derivatives.

(Received July 5, 1962)

UDC 547.02 : 543.422.25[539.143.43]

112. Toshihiko Okamoto and Yutaka Kawazoe: Application of Nuclear Magnetic Resonance to Stereochemistry. III.*1 The Spatial Interaction Effect of the Hydroxyl Group to Proton Resonances. (2).*2

(*Faculty of Pharmaceutical Sciences, University of Tokyo**3)

As previously reported,[1] methyl proton resonances have been proved to shift to the lower field by the spatial interaction with the neighbouring hydroxyl group. This spatial relationship was exemplified by 1,3-diaxial position on a cyclohexane or a cyclopentane ring, deduced using a number of steroidal compounds. It was shown, furthermore, that the methyl group spatially interacted by a hydroxyl group could be identified by acetylation of the hydroxyl group, resonating at a remarkably higher field than that of the original hydroxyl derivative. These characteristic features of the methyl signals can be usefully applied to determining the configurations of methyl groups and hydroxyl groups.

Now, this paper concerns the scope and limitations in the application of this relationship. Methin and vinyl protons are also taken into consideration instead of methyl protons. In this paper, the spatial relationships are represented by the distances from the oxygen atom to the carbon or hydrogen atoms concerned (Chart 1) and, in some cases, by the angles between C-OH and C-H bonds. Although these measurements can not clearly elucidate this spatial interaction effect, they will be able to give us

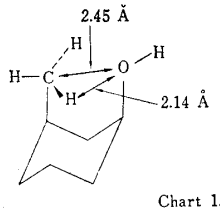


Chart 1.

---

*1 Part II: This Bulletin, **11**, 328 (1963).

*2 Part I: *Ibid.*, **10**, 338 (1962). This paper constitutes Part III of a series entitled "Nuclear Magnetic Resonance Studies" by T. Okamoto and Y. Kawazoe.

*3 Motofuji-cho, Bunkyo-ku, Tokyo (岡本敏彦, 川添 豊).

1) Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto, K. Tsuda: This Bulletin, **10**, 388 (1962).

an evidence of the interaction between both groups. These values were obtained by using the Bücki's molecular model. It may be roughly considered that the error of ±0.05 Å may be included in each distance-measurement.

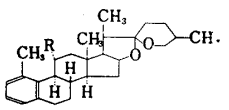
Experimental

NMR measurements were carried out by a Varian Associates DP 60 NMR spectrometer, operating at 60 Mc.p.s. in dilute $CHCl_3$ solutions. The zero reference in each spectrum was taken as the resonance position of one drop of cyclohexane dissolved in each solution measured. The chemical shift are given in p.p.m. unit, the sign of the shift being chosen as positive when the resonance falls in a higher field than the reference.

Results and Discussions

Meteogenine Derivatives*4

The structure of meteogenine, a steroidal sapogenine, was recently determined as (Ib) by Igarashi[2] (Chart 2). The ring conversion may be possible for this ring system with respect to both rings of B and C. Ring B seems to be easily converted to a boat



I, a) R : H Deoxymeteogenine
b) R : OH Meteogenine
c) R : OAc Meteogenine acetate

Chart 2.

form without so much ring strain or steric hindrance of the substituents, while the conversion of ring C must accompany a large ring strain. It can, therefore, be considered that the conversion to a boat form should be taken into consideration only with ring B. Thus, under the assumption that the possible conformational flapping of meteogenine may be only with ring B, the distances between 11α-oxygen atom and 1-methyl group were measured and are shown in Table I. The results make us conclude that the boat is more reliable one from consideration of repulsion between 1-methyl group form and 11α-substituent (even a hydrogen as the substituent). Now, the chemical shifts of 1-methyl protons are listed on the first row in Table II. A lower shift of −0.28 p.p.m. was observed by introduction of a hydroxyl group to 11α-position, going from deoxymeteogenine to meteogenine. On the other hand, acetylation of meteogenine brought a large higher shift of +0.27 p.p.m. to the signal of 1-methyl protons. These observations of the methyl proton resonance are quite consistent with those found in a series of 1,3-diaxial methyl and hydroxyl groups on a chair cyclohexane ring. 1-Methyl and 11α-hydroxyl groups in these molecules are more closely situated than in the case of

Table I. Distances between 1-Methyl and 11α-Substituents of Deoxymeteogenine Derivatives

Conformation of ring B	Boat form (Å)		Chair form (Å)	
11-Substituent (R)	R-$\underline{C}H_3$	$\underline{C}H_3$-R[a]	R-$\underline{C}H_3$	$\underline{C}H_3$-R[a]
H	1.85	1.60	1.45	1.25
OH	1.80	1.60	1.30	1.10

a) Although the distances between 11α-substituent atoms and methyl protons are variable depending on C-CH_3 bond rotation, nearer protons at the gaush conformation to 11α-substituents were taken for the above measurements.

*4 These compounds were kindly provided by Dr. Kikuo Igarashi of Research Laboratory, Shionogi and Co., Ltd.

2) K. Igarashi : This Bulletin, 9, 723 (1961).

Table II. Spatial Interaction Effect of Hydroxyl and Acetoxyl Groups

	Signal in question	Chemical shift[a] R=H	R=OH	R=OAc	Substituent effect Δ_{OH-H}	Δ_{OAc-OH}
11α-Substituted deoxymeteogenine (I)	C_1-CH_3	−0.90	−1.18	−0.91	−0.28	+0.27
1-Substituted 5,8-dimethyl-1,2,3,4-tetrahydro-1-naphthol (II)	C_4-CH_3	−0.74	−0.94	−0.77	−0.20	+0.18
7β-Substituted 15β-hydroxypregn-4-ene-3,20-dione (III)	15α-H	−2.87	−3.04	−2.65	−0.17	+0.38

a) Chemical shifts are given in p.p.m. unit from the reference signal of internal cyclohexane. The sign of minus is for the signals in lower field than the position of the reference.

1,3-diaxial substituents on a chair cyclohexane but it is noteworthy that C-CH_3 and C-OH bonds are arranged not in parallel, as shown in Chart 3. Therefore, the parallel arrangement of C-CH_3 and C-OH bonds like 1,3-diaxial substituents was proved to be not essential for this spatial interaction effect of the hydroxyl group to the methyl proton resonances.

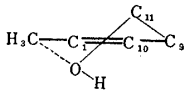


Chart 3.

5,8-Dimethyl-1,2,3,4-tetrahydro-1-naphthol

5,8-Dimethyl-1,2,3,4-tetrahydro-1-naphthol (II, R=OH) may be in an equilibrium as shown in Chart 4. Although the conformer (a), where the hydroxyl group is equatorial, seems to be energetically favourable, the steric hindrance between the methyl and the

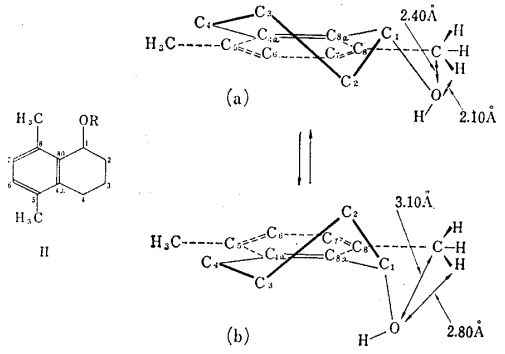


Chart 4.

hydroxyl groups may make the conformer (b) more preferable as a whole. In any way, whichever the conformation of this molecule may be, some spatial interaction effect of the hydroxyl group can be expected to the methyl proton resonance because of their vicinal location.

The nuclear magnetic resonance data of the methyl protons listed on the second row in Table II shows a downward shift of −0.20 p.p.m. by introduction of a hydroxyl group and an upward shift of +0.18 p.p.m. by its acetylation. Such a spatial relationship as in this molecule, where C-CH_3 and C-OH bonds are not parallel, was now proved again to produce the characteristic features of the spatial interaction effect of the hydroxyl group to the methyl proton resonances.

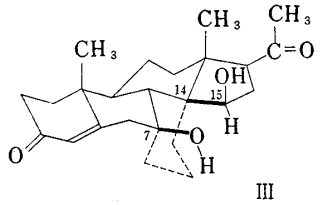
7β,15β-Dihydroxypregn-4-ene-3,20-dione

In spite of a good agreement of the chemical shifts of 15α protons in various 15β-hydroxysteroids (−2.86 p.p.m.)[3] a widely different value of −3.04 p.p.m. was observed as the chemical shift of 15α proton in 7β,15β-dihydroxypregn-4-ene-3,20-dione (III), as

3) Y. Kawazoe, Y. Sato, T. Okamoto, K. Tsuda: This Bulletin, **11**, 328 (1963).

shown on the third row in Table II. The C_{14}-C_{15} bond and the C_7-$O_{7\beta}$ bond in this molecule are arranged in parallel just as the 1,3-diaxial substituents on a cyclohexane ring as illustrated in Chart 5. Thus, 15α proton can be regarded as one of the methyl protons interacted 1,3-diaxially by a hydroxyl group (7β-OH).

Therefore, the deviation of −0.17 p.p.m. from the resonance position reported for 15α protons of 15β-hydroxy-steroids can be reasonably understood as a result of the spatial interaction of 7β hydroxyl group.



III

Chart 5.

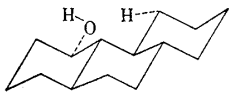


Chart 6.

This assignment was, furthermore, confirmed by an upward shift of 0.38 p.p.m.*5 shown by its 7β-monoacetylated derivative. This result will be able to apply to determine the relative configuration of hydroxyl groups in 7,15-dihydroxy-steroids and, in general, in hydroxyl derivatives having the partial structure shown in Chart 6.

2-Methylcyclohexanol Derivatives

The hydrogen atoms of a methyl group which is substituted at α-position of a hydroxyl group on a cyclohexane or a cyclopentane ring are borne on γ-carbon atom with reference to the hydroxyl group, while those are on δ-carbon in the case of 1,3-diaxial methyl and hydroxyl. In the former case, therefore, attention should be paid to the electron-withdrawing effect of the hydroxyl group beside its spatial interaction effect.

As a matter of fact, it has been shown to be true by many examples*6 that the methyl protons resonate in somewhat lower fields (usually, by 0.1 to 0.2 p.p.m.) by introducing a hydroxyl group to the α-position on the same ring. Then, it is interesting to see if the acetylation of the hydroxyl group might cause the methyl resonance to shift upward as been seen when they are situated in 1,3-diaxial relationship. *Cis*- and *trans*-2-methylcyclohexanols (IVa, b), testosterone (V), and N-methylisoorixidinine[6,7] (VI) (Chart 8) were taken as the model compounds for this purpose. The nuclear magnetic resonance data are shown in Table III with those of their acetylated derivatives. The distances between 18-methyl and 17β-hydroxyl group in testosterone molecule are shown in Chart 7 as an example of the spatial relationship of both groups. There appears to be no regularity of the acetylation shifts as far as these data are concerned. As a conclusion, both of the electron-withdrawing effect and the spatial interaction effect may take places in these cases, although more data may be required for clear solution for this problem.

*5 The downward shift of the methyl resonance caused by the spatial interaction effect of a hydroxyl group are usually compensated in a part or, sometimes, at all by the acetylation of the hydroxyl group. But this is the only one exception that the proton resonance of the acetylated derivative went up to a higher field than that of the original deoxy compound.

*6 For example, *trans*-2-methylcyclohexanol (Δ=0.11 p.p.m.)[4] and 5α-hydroxy-steroids against 19 methyl resonance (Δ=0.17 p.p.m.).[5]

4) J. I. Musher : J. Am. Chem. Soc., **83**, 1148 (1961).
5) J. C. Jacquesy, J. M. Lehn, J. Levisalles : Bull. soc. chim., France, **1961**, 2444.
6) K. Narahashi : This Bulletin, **10**, 792 (1962).
7) M. Terasaka, K. Yamamoto (Narahashi), Y. Kawazoe : *Ibid.*, **11**, 108 (1963).

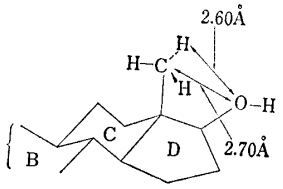
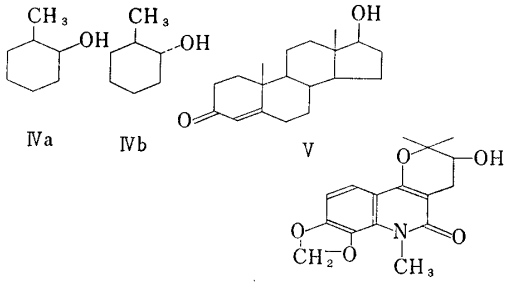


Chart 7.



IVa IVb V VI

Chart 8.

TABLE III. Acetylation Shifts of Methyl Protons neighboured by the Hydroxyl Group at their α-Position on the Six-membered Ring

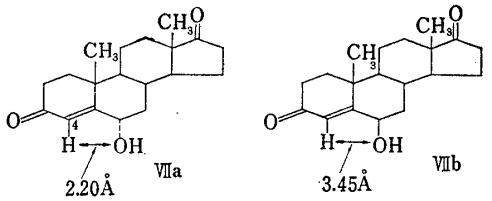
	Signal in question	Chemical shift[a] R=OH	Chemical shift[a] R=OAc	Acetylation effect Δ_{Ac-OH}
2-Substituted *cis* (or *trans*)-methylcyclohexane (IVa (or IVb))	C_1-CH_3	+0.50	+0.55	+0.05
2-Substituted *trans* (or *cis*)-methylcyclohexane (IVd (or IVa))	C_1-CH_3	+0.43	+0.55	+0.12
N-Methylisoorixidinine (VI)	*gem*-CH_3	(+5.76)[b]	(+5.88)[b]	(+0.12)
		(+5.88)[b]	(+5.88)[b]	(0.00)
17β-Substituted androst-4-en-3-one (V)	18-CH_3	+0.62	+0.57	−0.05

a) Chemical shifts (except for those in parentheses) are given in p.p.m. unit from the resonance signal of internal cyclohexane. Plus sign means the signal in higher field than the reference.
b) These are given in p.p.m. unit from the resonance signal of the solvent chloroform.[7]

4-Vinyl Proton of 6-Hydroxy-3-keto-Δ^4-steroids

Nuclear magnetic resonance measurements were made on 6α- and 6β-hydroxy-androst-4-ene-3,17-diones (VIIa and VIIb, R=OH), in which a vinyl proton at the 4-position is closely placed to the hydroxyl group at the 6-position. The spatial relationship of these groups is illustrated in Chart 9.

The nuclear magnetic resonance data are given in Table IV. It has been proved by many examples[8,9] that 4-vinyl protons of 3-ketosteroids usually resonate at about −4.30 to −4.32 p.p.m. The hydroxylation at the 6-position, with either configuration



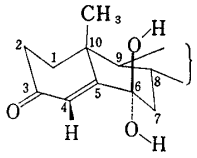


Chart 9.

8) J.N. Shoolery, M.T. Rogers: J. Am. Chem. Soc., 80, 5121 (1958).
9) Our unpublished data.

Table IV. The Chemical Shifts of Vinyl Protons of 6-Substituted Androst-4-ene-3,17-diones

	Signal in question	Chemical shift[a]			Substituent effect	
		H	OH	OAc	Δ_{OH-H}	Δ_{OAc-OH}
6α-Substituted androst-4-ene-3,17-dione (Va)	C_4-H	−4.30	−4.75	−4.52	−0.45	+0.23
6β-Substituted androst-4-ene-3,17-dione (Vb)	C_4-H	−4.30	−4.42	−4.54	−0.12	−0.12

a) Chemical shifts are given in p.p.m. unit from the reference signal of internal cyclohexane. The sign of minus is for the signals in lower field than the position of the reference.

of α or β, is expected to affect the resonance frequency of 4-vinyl proton by the inductive effects of the substituents. With regard to 6β derivatives where the C_6-OR bond is almost perpendicular to C_4-H bond, the experimental data shows that a lower shift of 0.12 p.p.m. was occurred by substitution of a hydroxyl group and that a further lower shift of 0.12 p.p.m. was observed by its acetylation. These results can be reasonably explained by the inductive effect of the hydroxyl or acetoxyl group. On the other hand, it is noteworthy to note that 4-vinyl proton resonance of 6α-hydroxyl derivative, where C_6-OR bond is nearly parallel to C_4-H bond, showed a much larger downward shift of 0.45 p.p.m. and that a remakable upward shift of 0.23 p.p.m. was observed by its acetylation. It seems to be clear that 6α-hydroxyl group must spatially interact with the 4-vinyl proton to give the characteristic features which have been proved as due to the spatial interaction effect of a hydroxyl group, although the inductive effect is taking place to some extent at the same time. As a result, the α configuration of the hydroxyl group at the 6-position in Δ^4-steroids can be predicted by the nuclear magnetic resonance features of 4-vinyl protons.*7

6-Vinyl Protons of 3α-Hydroxyl-5-cholenates

As previously reported,[8] the resonance positions of 6-vinyl protons in the 3β-hydroxy-Δ^5-steroids do not shift by the acetylation of 3β-hydroxyl group. On the other hand, with regard to 3α-hydroxyl epimers, acetylation of 3α-hydroxyl was found to cause the 6-vinyl proton to shift upwards by 0.20 p.p.m., resonating at −3.95 for methyl 3-hydroxy-5-cholenate and at −3.75 p.p.m. for its acetate from the internal cyclohexane.[10] The fact that a considerable amount of upward shift was observed by the acetylation suggests the spatial vicinity of 3α-hydroxyl group to 6-vinyl proton. Although the distances between the atoms concerned seem to be rather large, as shown in Chart 10, the vinyl proton Ha and the hydroxyl group in the partial structure (VIII) might be regarded as near 1,3-diaxial relationship. Infrared evidence[11] for the for-

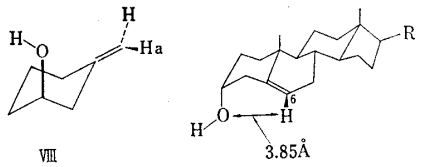


Chart 10.

*7 It can be also done by considering the half-width of the signals of H-C_6-OR.[2] 6β-Hydroxyl group, on the other hand, can be assigned by its interaction effect to 19-methyl proton resonances.[1]

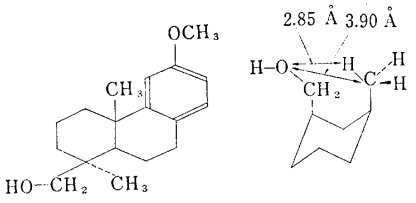
10) T. Okamoto, R. Osawa, Y. Kawazoe, T. Murata: To be submitted to this Bulletin.

11) M. Oki, H. Iwamura: Bull. Chem. Soc. Japan, **32**, 307 (1959).

mation of π-electron complex between 3α-hydroxyl proton and Δ^5-double bond in steroidal compounds supports the spatial vicinity of both groups.

Methylpodocarpol Derivatives

Methylpodocarpol (IX) includes a methyl group and an hydroxymethylene group in such a situation as shown in Chart 11. This situation is often encountered in natural products. The nuclear magnetic resonance frequencies of the angular methyl groups showed no difference between methylpodocarpol and its acetate, their chemical shift being 0.37 p.p.m. from the internal cyclohexane.*[8] It can be, therefore, concluded that no interaction effect is expected to the methyl signals in this system.



IX

Chart 11.

Conclusion

In order to clarify the scope and limitations of the spatial interaction effect of the hydroxyl group to the proton resonances, various kinds of compounds, having a hydroxyl group and the protons easily assignable on the nuclear magnetic resonance spectrum, were studied as the model compounds. The correlations were made on the spatial relationships of these groups with the nuclear magnetic resonance features which have been proved to be characteristic to the methyl protons interacted 1,3-diaxially with the hydroxyl group, that is, one is the remarkable downward shift (more than 0.17 p.p.m.) by introduction of a hydroxyl group to its neighbourhood and the other is the upward shift by its acetylation. Thus, the following results were obtained. (i) The hydroxyl group shows the interaction effect to the resonances of such protons as denoted in the partial structures shown in Chart 1, 3, 4, 5, 6, 9 (VIIa), 10 (VIII), to give the above characteristic features to their nuclear magnetic resonance spectra. (ii) In the formula IVa, IVb, V, and VI in Chart 8, although the substitution of a hydroxyl group causes a downward shift to the proton resonance, there is no regularity on the direction of the acetylation shift, upwards in some cases but downwards in other cases. Then, more experimental data seem to be needed for its application to the structural assignments. (iii) In the structure shown in Chart 11, there is no significant interaction between methyl and hydroxyl groups.

Although it seems to be true that this interaction effect depends on the spatial vicinity of the two groups, the dependence on the relative direction of these groups is still not clear. This interaction effect should, furthermore, be investigated in connection with those of other functional groups, e.g., halogens,[5] nitril,[5] amines, etc., which are magnetically anisotropic or produce strong electric fields on the neighbouring protons. Further studies along this line are now being pursued in this laboratory.

*[8] The signal of the angular methyl group was distinguished from that of C_1-CH_3, following the NMR analysis of the diterpenes which was done by Wenkert and Beak.[12]

12) E. Wenkert, P. Beak : Tetra. Letters, **1961**, 358.

The authors express their deep gratitudes to Dr. Yoshiro Sato, Institute of Applied Microbiology, University of Tokyo, for his helpful discussion. They are also indebted to Drs. Ken-ichi Takeda and Kikuo Igarashi, Research Laboratory, Shionogi and Co., Ltd., for their kind providing meteogenine derivatives and Dr. Akira Tahara, Institute for Physical and Chemical Research, for his kind offering methylpodocarpol derivatives for this study. Thanks are also due to Drs. Osamu Yamamoto and Teruo Suzuki, the Government Chemical Industrial Researh Institute of Tokyo, for making an NMR spectrometer available for the present work. 1,4-Dimethyltetralol-5(ac) was kindly provided by Dr. Tadamasa Onaka, Faculty of Pharmaceutical Sciences, University of Tokyo.

Summary

The scope and limitations of the spatial interaction effect of the hydroxyl group to the proton magnetic resonance are discussed in details.

(Received July 20, 1962)

UDC 547.92

113. Kiyoshi Sakai*1 und Kyosuke Tsuda*2: Untersuchungen über Steroide. XXX.[1] Versuche zur Synthese von Brassicasterin.

(*Takamine Forschungslaboratorium, Sankyo A.G.,*1 *und Institut für angewandte Mikrobiologie, Universität Tokio*2)

Im Jahre 1935 hat Leven, Marker[2] berichtet, daß sich der optisch aktive Kohlenwasserstoff, (−)-Methyläthylisopropylmethan konfigurativ von der (−)-2,3-Dimethylbuttersäure ableiten läßt. Aus dieser optisch aktiven Säure ergibt sich durch Veresterung und anschließende Reduktion ein optisch aktiver Alkohol, (−)-2,3-Dimethylbutanol. Wird dieser Alkohol bromiert, cyaniert und dann verseift, so entsteht (−)-3,4-Dimethylvaleriansäure, deren Ester durch Reduktion in (−)-3,4-Dimethylpentanol übergeht. Dieser läßt sich über das Bromid in (−)-Methyläthylisopropylmethan umwandeln.

(+)-Isopropylbernsteinsäure, deren absolute Konfiguration durch eine Ableitung aus (+)-α-Phellandren bereits aufgeklärt worden ist, ließ sich im Jahre 1954 von Freudenberg, *et al.*[3] über (−)-2-Isopropyl-1,4-butandiol in (−)-Methyläthylisopropylmethan überführen, womit sich die absolute Konfiguration dieses links drehenden Kohlenwasserstoffes eindeutig als zur S-Reihe gehörig erwies.

Aus den zwei obengenannten Arbeiten folgte, daß die links drehende 2,3-Dimethylbuttersäure konfigurativ zur R-Reihe gehören muß.

Vor einigen Jahren haben Tsuda, *et al.*[4] das aus 5-Dihydroergosterylacetat durch Ozonisation erhaltene (−)-2,3-Dimethylbutanal in (−)-2,3-Dimethylbutanol durch Lithiumaluminumhydrid-Reduktion überführt. Somit ließ sich die absolute Konfiguration der Methylgruppe an C_{24} des Ergosterins als β (24 S) bestimmen, da das obengenannte

*1 Nishishinagawa, Shinagawa-ku, Tokio (酒井 浄).
*2 Hongo, Bunkyoku, Tokio (津田恭介).

1) XXIX. Mitteil: Dieses Bulletin, **11**, 529 (1963).
2) P.A. Leven, R.E. Marker: J. Biol. Chem., **111**, 299 (1935).
3) K. Freudenberg, W. Lwowski: Ann., **587**, 213 (1954).
4) K. Tsuda, R. Hayatzu, Y. Kishida: Chem. & Ind. (London), **1959**, 1411; J. Am. Chem. Soc., **82**, 3396 (1960).