Meta-, and *p*-chloro- and fluoro-phenobarbital, prominal and phenobarbital showed the most potent shortening effect among above all compounds. *Para*-hydroxyphenobarbital and α-3-hydroxyhexobarbital, the hydroxylated metabolite of phenobarbital and hexobarbital, respectively, were less effective stimulator. *Para*-substituted nitro-, amino-, dimethylamino- and diethylamino-phenobarbital exhibited no stimulation, while corresponding *m*-derivatives and *m*- and *p*-methoxy-phenobarbital showed certain activities.

Pretreatment of rats with *m*-chlorophenobarbital also markedly activated the metabolism of hexobarbital *in vitro*.

(Received September 12, 1964)

[Chem. Pharm. Bull. 13(3) 285~291 (1965)]

UDC 547.457.03 : 543.422.25

35. Tetsuo Hiraoka, Tadahiro Iwashige, and Issei Iwai : Nuclear Magnetic Resonance Spectral Studies on some Anhydro Furanose Derivatives.

(*Research Laboratories, Sankyo Co., Ltd.*[*1])

Recently, many conformational studies on pyranose[1] and furanose[2] derivatives have been made on the basis of proton magnetic resonance spectra. One of the most interesting works in this field has been given by Jardetsky[3] who confirmed that the conformation of D-ribose in purine nucleosides is different from that in pyrimidine nucleosides. These early investigations made use of the Karplus equation[4] or that with modified parameters.[5] However, in the case of the cyclic compounds containing an orbital other

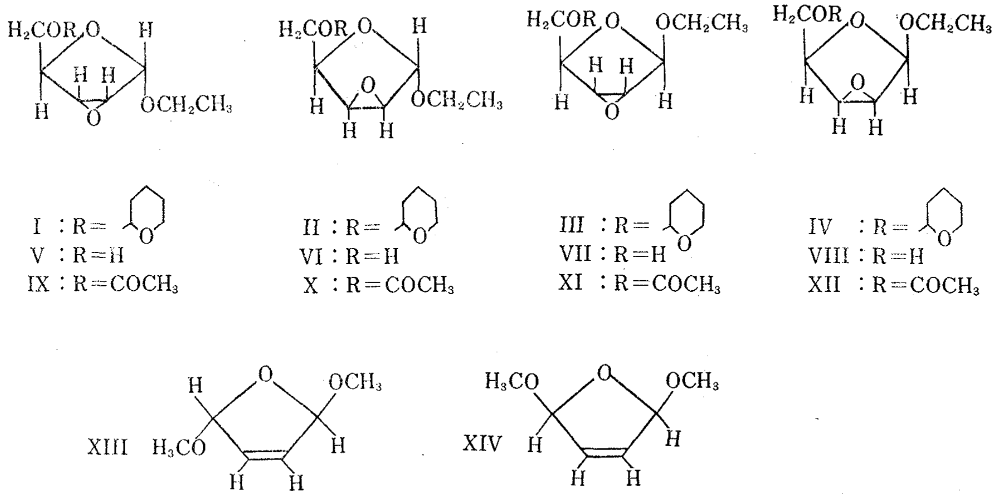


Chart 1.

[*1] Nishi-shinagawa, Shinagawaku, Tokyo (平岡哲夫, 岩重忠博, 岩井一成).

1) R. V. Lemieux, *et al.* : J. Am. Chem. Soc., **79**, 1005 (1957) ; *Idem* : *Ibid.*, **80**, 2237 (1958); *Idem*: *Ibid.*, **80**, 6098 (1958); W. Hofheinz, H. Grisebach : Tetrahedron Letters, **1962**, 377 ; L. D. Hall, L. Hough : Chem. & Ind., **1962**, 1465.

2) R. J. Abraham, *et al* : Chem. & Ind. **1962**, 213.

3) C. D. Jardetzky : J. Am. Chem. Soc., **82**, 229 (1960).

4) M. Karplus : J. Chem. Phys., **30**, 11 (1959).

5) R. J. Abraham, *et al.* : J. Chem. Soc., **1962**, 3699.

than "sp^3" hybridization, the Karplus equation is no longer applicable to the system. Then in these compounds it is important to examine the nuclear magnetic resonance spectra of the stereo-isomers whose configuration is established. Presently, four kinds of stereo-isomers of anhydrosugars and related compounds were examined in the proton magnetic resonance spectra and the conformational structures discussed from the spectral data. The compounds investigated here, are 2,3-anhydropentofuranoside whose synthetic methods were reported elsewhere,[6] and *trans*-2,5-dimethoxy-2,5-dihydrofuran (XIII) and *cis* isomer (XIV). These structures are shown as follows : *2

Experimental

The spectra were obtained by Varian Associates DP 60 and A 60 spectrometers at 60 Mc.p.s. Calibration was made by interpolation between side-bands produced by audio modulation, and tetramethylsilane was used as internal reference. The compounds were dissolved in $CHCl_3$ at a concentration of 10% (w/v) with a small amount of tetramethylsilane.

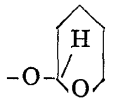
Results and Discussion

1. Spectral Assignment and General Features

The complete assignment of the spectra of compounds (I～XII) was not possible because peaks due to C_2 and C_3 hydrogens overlapped with those of methylene of ethoxy group, and the results obtained from the analysis of the spectra are summarized in Table I. The spectra are also shown in Fig. 1. From these spectra the following observations and conclusions were obtained :

Peaks due to C_1-H were observed as the lowest field signals consisting of a sharp singlet except in one case, I. In the usual furanose derivatives, the anomeric hydrogen at C_1 are split into a doublet owing to coupling with C_2-hydrogen,[7] whereas both *cis* and *trans* compounds (II～XII) exhibited negligible coupling between C_1- and C_2-hydrogens. Similar results were obtained by Hall.[8] Therefore it is apparent that the coupling

Table I.

No.	C_1-H	C_4-H	C_5-H_2	$OCH_2\underline{CH_3}$		OH	$OCOCH_3$
I	4.76	5.61		8.73	5.42		
II	4.95	5.90		8.78	5.36		
III	5.00	5.76		8.79	5.42		
IV	4.89			8.73	5.33		
V	4.73	5.68		8.74		6.99	
VI	4.93	5.94		8.77		7.41	
VII	4.94	5.74		8.77		6.98	
VIII	4.93			8.76		6.89	
IX	4.80	5.56	5.82	8.74			7.94
X	4.94			8.77			7.89
XI	4.93			8.79			7.89
XII	4.93			8.76			7.93

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*2 The numbering of the carbon atoms of compounds (XIII and XIV) is different from that of compounds (I～XII), because XIII and XIV are not sugar derivatives but dihydrofuran derivatives.

[6] T. Iwashige, M. Asai, I. Iwai : This Bulletin, **11**, 1569 (1963).

[7] C. D. Jardetzky : J. Am. Chem. Soc., **84**, 62 (1962); R. V. Lemieux, J. W. Lown : Can. J. Chem., **41**, 889 (1963).

[8] L. D. Hall : Chem. & Ind., **1963**, 950.

constants of these anhydrofuranose derivatives (II~XII) do not coincide with the Karplus equation[4] even considering the conformational structures, to be discussed later in this paper. Since the compounds (I), (V), and (IX) have the same configuration and only I gave $J_{1\sim2}=2.5$ c.p.s., the dihedral angle between C_1-H and C_2-H of the compound (I) may be different from those of V and IX. In compound (I) the bulkyl pyranyl group might affect the dihedral angle between C_1-H and C_2-H.

Considering the fact that no coupling was observed between C_1-H and C_2-H except with one compound, supposedly there is also no coupling between C_3-H and C_4-H, because, as will be noted later, the four carbon atoms of C_1, C_2, C_3, and C_4 lie in one plane. Thus the relation between C_1 and C_2 can be applied to that of C_3 and C_4. Practically as shown in Fig. 1, the peaks due to C_4-H and C_5-H of IX showed a typical AB_2 spectra.

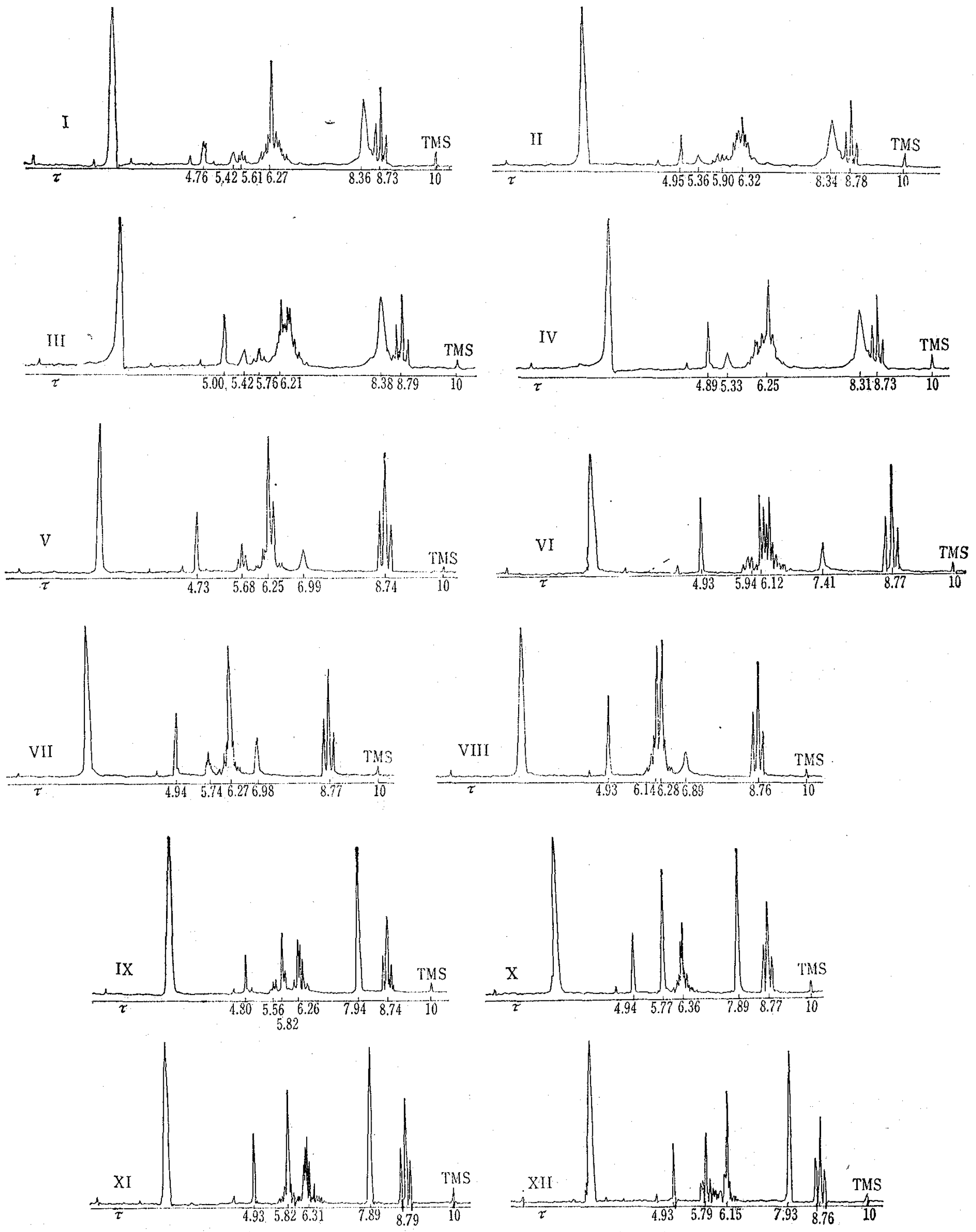


Fig. 1.

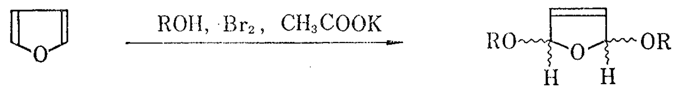
Then it may be concluded that the coupling between C_3-H and C_4-H are not observed in these spectra.

In compounds (I), (V), and (IX), which have the same configuration C_1-H peaks are shifted to lower field as compared with the other compounds. This shift is probably not mainly caused by anisotropic effects of the epoxide group, because in IV, VIII, and XII, C_1-H peaks do not shift to any remarkable extent and in these compounds the geometric relations between C_1-H and the epoxide ring are similar to those of I, V, and IX. The possibility of a ring current in cyclopropane has been considered recently by Wiberg and Nist⁹⁾ and in fact an epoxide ring current effect has been observed in a diterpene.¹⁰⁾ In the present compounds, hydrogens attached to C_1 and C_4 carbons are out of plane which includes the epoxide ring, and moreover those hydrogens are not located just above or below the epoxide ring. Therefore, the effect of the epoxide ring would be small.

In compounds (I~IV), signals of C_1-H of the tetrahydrofuran ring appeared at a lower field than those of C'_1-H of tetrahydro pyran ring.

No noticeable shift was observed in the peaks of methyl groups in C_1-OCH_2CH_3 when the configuration is changed. Methylene peaks of this group should appear as a quartet as a result of coupling with methyl group, however, practically no clear quartet peaks were found in the region around 6.3 τ although overlapping with other peaks occurred in this region. This fact is due to the non-equivalence of the methylene protons. This phenomenon has been previously observed in another case.¹¹⁾ The assignment of the hydrogens attached to epoxide ring was not possible because of their overlapping with other peaks.

Next we examined nuclear magnetic resonance spectra of *trans*- and *cis*-2,5-dimethoxy-2,5-dihydrofuran, XIII and XIV which are very similar to 2,3-anhydropentofuranosides. A mixture of XIII and XIV was first synthesized by Clauson-Kaas, *et al.* from furan, bromine and methanol in the presence of potassium acetate.¹²⁾



Clauson-Kaas, *et al.* separated this *cis* and *trans* mixture into pure isomers by fractional distillation¹³⁾ however, the dipole moment of each isomer was unfortunately almost the same and whether the higher boiling isomer corresponded to *cis* or *trans* compound could not be determined. We reinvestigated this mixture by nuclear magnetic resonance. A *cis* and *trans* mixture of 2,5-dimethoxy-2,5-dihydrofuran prepared according to the known method¹⁴⁾ gave the nuclear magnetic resonance spectrum shown in Fig. 2. Subsequently this mixture was fractionally distilled using a 70 cm. column packed with glass spheres affording four fractions. In the spectrum of the first fraction the intensity of the peak B decreased

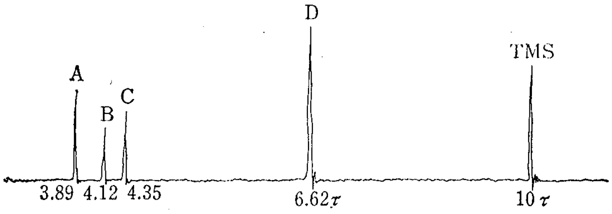


Fig. 2.

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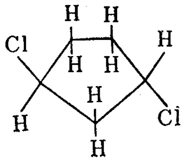
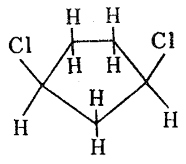
9) K. B. Wiberg, B. J. Nist: J. Am. Chem. Soc., 83, 1226 (1961).
10) P. R. Jefferies, R. S. Rosich, D. E. White: Tetrahedron Letters, **1963**, 1853.
11) J. A. Elividge, R. G. Foster: J. Chem. Soc., **1964**, 981.
12) N. Clauson-Kaas, *et al.*: Acta. Chem. Scand., **2**, 109 (1948).
13) *Idem*: *Ibid.*, **12**, 63 (1958).
14) J. Fakstorp, D. Raleigh, L. E. Schniepp: J. Am. Chem. Soc., **72**, 869 (1950); J. C. Sheehan, B. M. Bloom: *Ibid.*, **74**, 3825 (1952).

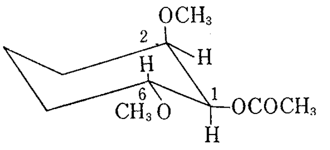
remarkably and in the last fraction peak C had almost disappeared. From these result it is apparent that the peak A is due to olefinic hydrogens, and the peaks B and C arise from acetal hydrogens. It is now necessary to determine which peak of B and C corresponds to that of *cis* or *trans* isomer. In the steroid field the nuclear magnetic resonance peak of 19-methyl group is known to shift to lower field when chloro, hydroxy or cyano group is introduced at the 6β-position.$^{15)}$ This paramagnetic shielding by hydroxy or halogeno group is observed when those groups are located at 1,3-diaxial position to the methyl substituent. A similar result has been obtained in the case of *cis*- and *trans*-1,3-dichlorocyclopentane.$^{16)}$ In XV C_1-H and C_3-Cl are located in a quasi 1,3-diaxial position to each other (The precise conformation of the above compounds has not been stated in the litelature). The signals of C_1-H and C_3-H of XV appeared at lower field (5.5 τ) as compared with those of the *cis* compound (XVI) (5.8 τ). Further examples of this 1,3-diaxial paramagnetic shielding effect is observed in compounds (XVII) and (XVIII).$^{17)}$



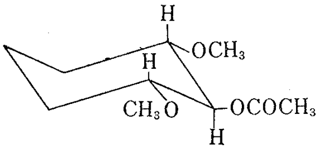
XV *trans*



XVI *cis*



XVII

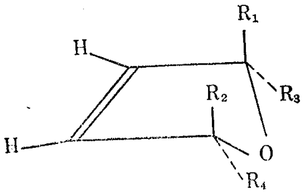


XVIII

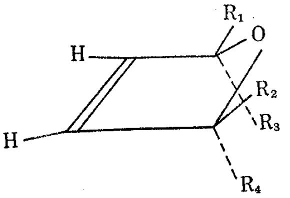
As expected the C_6-hydrogen peak of isomer XVII appeared at lower field as compared with that of XVIII, namely C_6-H of compound (XVII) exhibits a 1,3-diaxial paramagnetic effect by the C_2-methoxy group. From these data it can be concluded that acetal hydrogens of compound (XIII) give signals at lower field as compared with those of compound (XIV). Thus peak B in Fig. 2 is due to acetal hydrogens of *trans*-2,5-dimethoxy-2,5-dihydrofuran having the higher boiling point and peak C corresponds to acetal hydrogens of *cis*-2,5-dimethoxy-2,5-dihydrofuran which has lower boiling point as compared with that of *trans* isomer.

2. Conformational Analysis

Tetrahydrofuran ring has either an envelope or half-chair conformation,$^{18)}$ however, if a double bond is introduced between C_3 and C_4 only an envelope conformation



XIX-A : $R_1=R_4=OCH_3$, $R_2=R_3=H$
XIX-B : $R_1=R_2=OCH_3$, $R_3=R_4=H$



XX-A : $R_1=R_4=OCH_3$, $R_2=R_3=H$
XX-B : $R_1=R_2=OCH_3$, $R_3=R_4=H$

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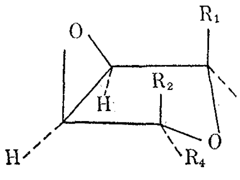
15) Y. Kawazoe : The abstracts of the 82nd Annual Meeting of the Pharmaceutical Society of Japan (1961), p. 85.

16) G. A. Russell, A. Ito : J. Am. Chem. Soc., **85**, 2984 (1963).

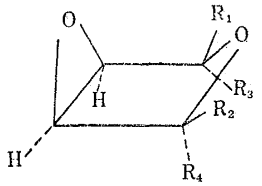
17) R. V. Lemieux, *et al.* : *Ibid.*, **80**, 2237 (1960). They did not assign the signals of C_2 and C_6-H hydrogens because of their overlapping with those of C_2 and C_6-methoxy groups; however, from the signals determined at high gain it is possible to obtain the above conclusion. In this case it should be kept in mind that axial hydrogens generally give signals at higher field as compared with those of equatorial hydrogens.

18) E. L. Eliel : "Stereochemistry of Carbon Compounds," McGraw-Hill Book Company, Inc., New York (1962) p. 249.

becomes possible for 2,5-dihydrofuran ring. In this conformation C_2, C_3, C_4, and C_5 lie in one plane and oxygen atom is either above or below the plane of the carbon atoms. The situation is very similar to 3,4-epoxytetrahydrofuran derivatives.



XXI



XXII

Taking the example of *cis*-2,5-dimethoxy-2,5-dihydrofuran (XIX-B : $R_1=R_2=OCH_3$, $R_3=R_4=H$), conformer (XX-B) would be more stable than that of XIX-B because in the former two bulky groups are located in a quasi diequatorial position whereas in the later those groups are located in a quasi diaxial position. In the case of *trans*-2,5-dimethoxy-2,5-dihydrofuran both conformers, XIX-A and XX-A are thermodynamically equivalent and this *trans* derivative is considered to be equilibrated between both conformers. This interconversion between two conformers is supported by the fact that the nuclear magnetic resonance peak of non-equivalent C_2 and C_5 hydrogens of *trans*-2,5-dimethoxy-2,5-dihydrofuran appeared as sharp singlet which implied that the interchange is so rapid that the shielding of two protons is averaged to a single value. In the case of *cis* isomer, the interconversion might be also rapid at room temperature in solution on the following grounds : nuclear magnetic resonance spectrum of the *cis* compound was measured at high temperature (122°) and in this case no marked shift of acetal hydrogens (signal-C in Fig. 2) from the peak of ethylenic hydrogens (signal A in Fig. 2) was observed as compared with the case measured at room temperature. If the *cis* compound has the thermodynamically stable conformation of XX-B at room temperature, high temperatures might cause equilibrium between the two conformers and this would effect a shift of acetal hydrogens in the spectrum. Since it is known that the chemical shift of axial and equatorial hydrogens differs.[19]

The situation is similar to the case of XXI and XXII. If compounds (I$\sim$XII) have a specific conformation, either XXI or XXII at room temperature, heating may cause an equilibrium between two conformers in which the dihedral angle between C_1-H and C_2-H is different each other and this difference can be clarified by examining the coupling constant $J_{1,2}$. In practice the nuclear magnetic resonance spectrum of compound (I) was measured in dimethylsulfoxide solution at a high temperature (140°); however, I decomposed in this solution at such high temperature and the spectrum subsequently measured at 85°. At this temperature the coupling constant $J_{1,2}$ was almost the same as measured at room temperature. This suggests that I exists at room temperature in both forms, (XXI and XXII) which interconvert rapidly. This is reasonable since in compound (I) two bulky substituents are located in *trans* positions, and conformers (XXI) and (XXII) are almost thermodynamically same neglecting the interaction between ring O and epoxide oxygen. However in the case of compounds (III) and (IV) in which two bulky groups are located in *cis* positions, the situation is different because the conformer with two bulky substituents in diequatorial positions is thermodynamically more stable than the other conformer. With these compounds the conformational analysis was not carried out due to the small coupling constant between C_1-H and C_2-H.

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[19] L. M. Jackman : "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," p. 115. Pergamon Press, London.

Generally speaking the height of the potential barrier required for the interconversion between XIX-A and XX-A might be smaller than that between dihydro XIX-A and dihydro XX-A, because the deviation of the oxygen atom of XIX-A and XX-A from the plane including C_2, C_3, C_4, and C_5 is smaller than that of the oxygen atom of dihydro XIX-A and dihydro XX-A. This difference of bending of ring oxygen is clearly seen from wire molecular models.

The authors are indebted to Drs. O. Yamamoto and T. Suzuki of the Government Chemical Industrial Research Institute of Tokyo and Mr. C. Fujimura of this laboratory for measuring the NMR spectra. They are also grateful to Dr. Y. Arata for reading the manuscript and providing useful suggestions.

Summary

The nuclear magnetic resonance spectra of fourteen anhydro and dihydrofuranose derivatives were measured and it was found that in these compounds the coupling between anomeric C_1 hydrogen and C_2 hydrogen was very small. This does not coincide with the Karplus equation. The conformational structures of these compounds were discussed.

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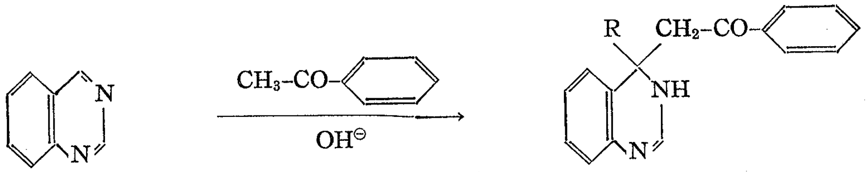
UDC 547.856.07

36. **Eisaku Hayashi and Takeo Higashino**: On the Reaction of Quinazoline with Ketones.

(*Shizuoka College of Pharmacy*[*1])

In the previous paper[1] of this series we have reported that the 4-position in quinazoline (I), owing to the overlapping of -M and -E effects of the nitrogen atoms of the ring and the effect of the fused benzene-ring, is very reactive to nucleophilic reagents. Especially we attended to the formation of 2-(3,4-dihydro-4-quinazolinyl)acetophenone (Ⅱ) on the reaction of I with acetophenone in the presence of hydroxide anion at room-temperature. Similarly prepared are the reaction products of I with acetone, 2-butanone and cyclohexanone and agreeded with $C_{14}H_{18}O_2N_2$ (Ⅲ), $C_{16}H_{22}O_2N_2$ (Ⅳ), and $C_{20}H_{26}O_2N_2$ (V) in those analytical values.



I Ⅱ

Chart 1.

In this paper, our interests are focused to determine the structures of the reaction products, Ⅲ, Ⅳ, and V.

[*1] Oshika, Shizuoka (林 英作, 東野武郎).

[1] E. Hayashi, T. Higashino: This Bulletin, **12**, 1111 (1964).