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.

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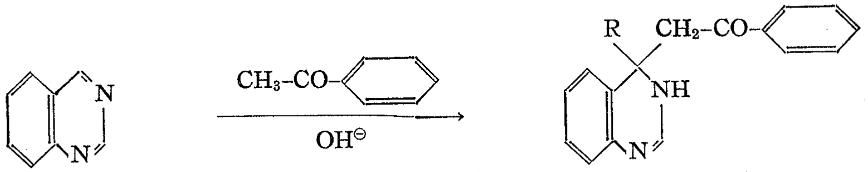
In the previous paper[1] of this series we have reported that the 4-position in quinazoline (I), owing to the overlapping of -M and -E effects of the nitrogen atoms of the ring and the effect of the fused benzene-ring, is very reactive to nucleophilic reagents. Especially we attended to the formation 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 Chart 1. Ⅱ

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).

III shows the absorption bands for hydroxyl and carbonyl group in its infrared spectrum as in Table II and gives monosemicarbazone (VI) on being made to react with semicarbazide. In the ultraviolet spectrum, the absorption peaks of III approximate to those of 3,4-dihydroquinazoline as shown in Table I.

Table I*[2]

Compounds	UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε)		
3,4-Dihydroquinazoline	290 (3.77)		223.5 (4.06)
III	303 (3.92)	232.5 (4.12)	226.5 (4.19)
IV	305 (3.90)	234 (4.09)	227.5 (4.16)
V	300 (3.95)	234.5 (4.20)	227.5 (4.25)

Table II.*[3]

Compounds	IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}		
	>NH	>C=O	-OH
3,4-Dihydroquinazoline	3180		
III		1610	3460
IV		1605	3480
V		1600	3540
Diacetone alcohol[2)]		1712	3484
2-(Hydroxylcyclohexyl)cyclohexanone		1700	3500

Those data indicate that III should be 4-substituted-3,4-dihydroquinazoline, and not 2,4-disubstituted-1,2,3,4-tetrahydroquinazoline, and also the substituent in the 4-position of I contains carbonyl and hydroxyl groups one by one.

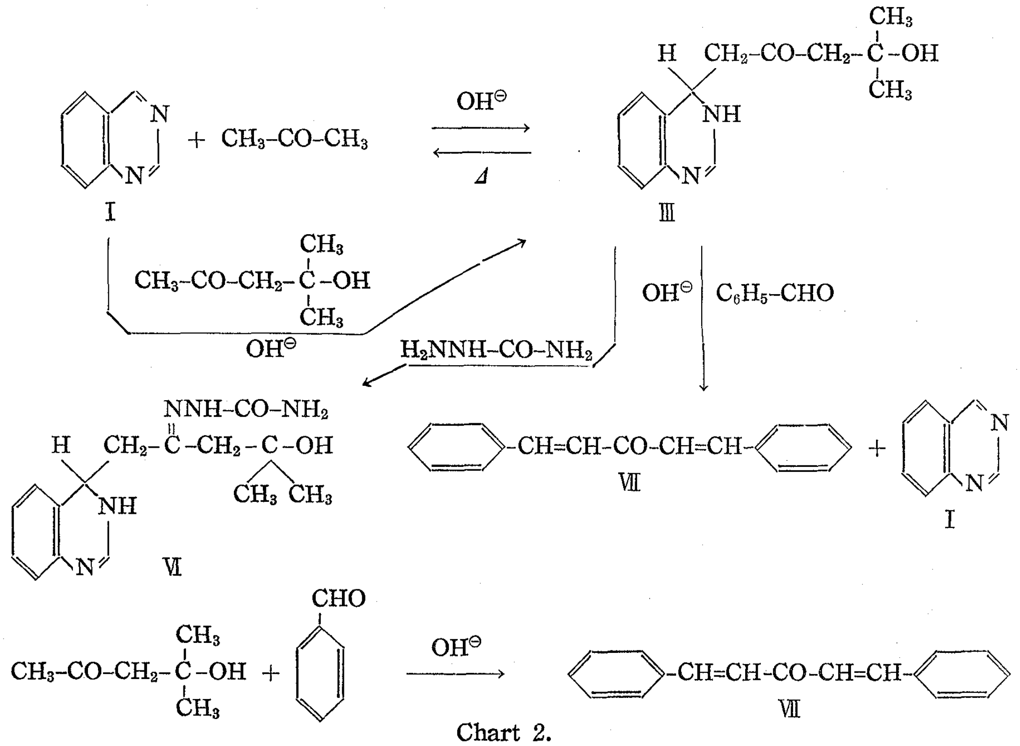


Chart 2.

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*[2] Ultraviolet spectra were measured in 99% EtOH on a Hitachi UV-Spectrophotometer Model ESP-2U.

*[3] Infrared spectra were recorded with a Nippon Bunko IR-Spectrophotometer Model IR-S.

2) R.S. Rasmussen, D.D. Tunnicliff, R.R. Brattain: J. Am. Chem. Soc., **71**, 1068 (1945).

In practice, when I is made to react with diacetone alcohol in the presence of hydroxide anion at room temperature, the same reaction product with Ⅲ in its melting point, analytical values, ultraviolet spectrum and infrared spectrum, is obtained.

On the other hand, thermal decomposition of Ⅲ involves to give acetone and quinazoline. Moreover the reaction of Ⅲ with benzaldehyde in the presence of hydroxide anion gives 1,5-diphenyl-3-pentadienone (Ⅶ) and quinazoline. Similar reaction proceeds in the interaction between diacetone alcohol and benzaldehyde to give Ⅶ.

On those bases, the structure of Ⅲ should be 1-(3,4-dihydro-4-quinazolinyl)-4-hydroxy-4-methyl-2-pentanone.

Considering the formation of Ⅳ and V in the reaction of I with 2-butanone or cyclohexanone may be similar to that of Ⅲ through the following data, the structures of those compounds are postulated to be 1-(3,4-dihydro-4-quinazolinyl)-4-hydroxy-3,4-dimethyl-2-hexanone (Ⅳ) and 2-(3,4-dihydro-4-quinazolinyl)-6-(1-hydroxycyclohexyl)-cyclohexanone (V).

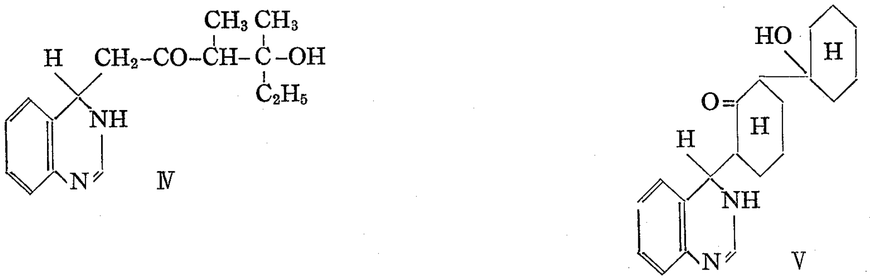

Chart 3.

i) The analytical values of Ⅳ aud V agreed with $C_{16}H_{22}O_2N_2$ and $C_{20}H_{26}O_2N_2$ respectively.

ii) The ultraviolet and infrared absorption spectra of Ⅳ and V well approximate to those of Ⅲ, as shown in Table I and Ⅱ.

iii) Especially, on the structure of Ⅳ, similar reaction does not proceed as I is made to react with 3-pentanone.

The possible mechanism for this reaction is that the carbanion as nucleophilic reagents, which may be formed by treating acetone with sodium hydroxide, may attack the 4-position in I susceptible to nucleophilic reagents to form an intermediate such as A_2 type, followed by reaction of aldol condensation between A_2 and acetone to give Ⅲ.

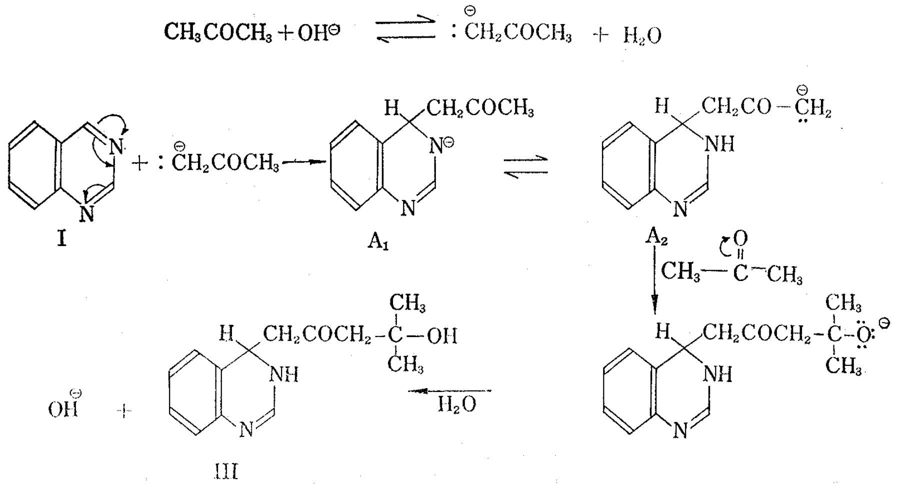

Chart 4.

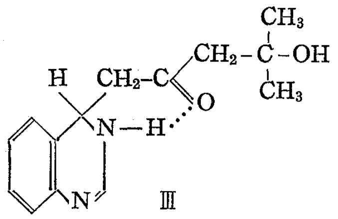
Ⅲ

Chart 5.

In general, it is known that the intramolecular hydrogen bonding effect induces the carbonyl absorption to a low-frequency shift in infrared absorption band such as 2-hydroxyacetophenone[3] and 2-aminoacetophenone.[4] Similarly, it may be assumed that low frequency shifts of carbonyl group in Ⅲ, Ⅳ and Ⅴ in contrast with those of diacetone alcohol and 2-(1-hydroxycyclohexyl)cyclohexanone[5] from Table Ⅱ are contributed to intramolecular hydrogen bonding effects as shown in Chart 5.

Also it may be seemed that low frequency shifts and decreasing intensities of the secondary amine stretching bands of Ⅲ, Ⅳ, and Ⅴ in contrast with that of 3,4-dihydroquinazoline attribute to intramolecular hydrogen bonding effects to result in the elimination of NH band of the material, and it is concluded that they are coincident with the CH stretching bands near 3000 cm^{-1}.

Experimental[*4]

1-(3,4-Dihydro-4-quinazolinyl)-4-hydroxy-4-methyl-2-pentanone Semicarbazone (VI)——In a small amount of MeOH, 0.5 g. of 1-(3,4-dihydro-4-quinazolinyl)-4-hydroxy-4-methyl-2-pentanone (Ⅲ) was dissolved. A quantity of H_2O was added until the solution is faintly turid, and the turbidity was removed with few further drops of MeOH. Then 0.4 g. of semicarbazide hydrochloride and 0.5 g. of AcONa were added. The mixture was warmed on a water bath for 10 min. with vigorous shaking. After removing MeOH under a reduced pressure, the residue was solidefied by the stimulation with a glass rod. The crystals (Ⅵ) were collected by filtration, and recrystallised from MeOH aq. The hygroscopic colorless needles (0.54 g., 84%), m.p. 131°(decomp.), were obtained. *Anal.* Calcd. for $C_{15}H_{21}O_2N_5 \cdot H_2O$ (1-(3,4-dihydro-4-quinazolinyl)-4-hydroxy-4-methyl-2-pentanone semicarbazone monohydrate) : C, 56.06; H, 7.21; N, 21.79. Found : C, 56.35; H, 7.42; N, 21.86.

Reaction of Quinazoline (I) with Diacetone Alcohol——To a mixture of 1.3 g. of I, 1.3 g. of diacetone alcohol and NaOH solution (0.5 g. of NaOH dissolved in 0.5 ml. of H_2O), a quantity of MeOH was added to make an uniform solution. After having been allowed to stand overnight at room temperature, the reaction mixture was poured into 50 ml. of ice water. The organic layer was extracted with $CHCl_3$, and the $CHCl_3$ extract was dried over anhyd. Na_2SO_4, and concentrated to dryness. The residual solid was washed with benzene and recrystallised from MeOH, giving Ⅲ as a white crystal (1.5 g., 61%), m.p. 167~168°(decomp.). *Anal.* Calcd. for $C_{14}H_{18}O_2N_2$ (1-(3,4-dihydro-4-quinazolinyl)-4-hydroxy-4-methyl-2-pentanone) : C, 68.27; H, 7.37; N, 11.37. Found : C, 68.34; H, 7.40; N, 11.43.

The UV and IR spectra of this compound well agreed with those of the reaction product (Ⅲ) obtained in the interaction between acetone and I in Table I and Ⅱ.

Thermal Decomposition of III——When 5.0 g. of Ⅲ was heated at 167~172° for 30 min., acetone (1.7 g., 83%) was distilled off and identified by the admixture of its 2,4-dinitrophenylhydrazone with an authentic sample, m.p. 125°.

Benzene solution of the residue was passed through a column of activated alumina. The evaporation of the eluate gave a colourless liquid (1.2 g., 54%) which was identical with quinazoline, on mixed melting point method as picrate, m.p. 188~189°.

Reaction of III with Benzaldehyde——To a solution of 4.0 g. of Ⅲ in 15 ml. of MeOH, 15 ml. of 10% NaOH was added to make a uniform solution, followed by adding 8.0 g. of benzaldehyde. The solution was warmed at 70° on a water bath for 2~3 min., and cooled in an ice bath. Pale yellow crystals separated were collected by filtration. Recrystallisation from MeOH afforded a yellow plate crystal (4.6 g., 61%), m.p. 112°, which was identical with 1,5-diphenyl-3-pentadienone by admixture with an authentic sample.

After adding 30 ml. of H_2O to the filtrate, the oily material was extracted with $CHCl_3$. The $CHCl_3$ layer was extracted with 2*N* HCl several times. The HCl layer was neutralized and saturated with K_2CO_3. This solution was again extracted with benzene, and the benzene layer was dried over anhyd. K_2CO_3 and passed through a column of activated alumina. The evaporation of the eluate gave the colourless liquid

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[*4] All melting points are uncorrected.

[3] M. Yamaguchi : Nippon Kagaku Zasshi, **78**, 1236 (1957).

[4] *Idem* : Daiyūkikagaku, Separate Volume 2 (The Asakura Publishing Company, Ltd.), p. 324 (1963).

[5] J. Stanek : Chem. Listy., **46**, 110 (1952).

(0.6 g., 29%) which was identical with quinazoline by admixture of its picrate with an authentic sample, m.p. 188~189°.

Reaction of Diacetone Alcohol with Benzaldehyde——A solution of 1.0 g. of diacetone alcohol, 4 ml. of 10% NaOH and 4.0 g. of benzaldehyde in 4 ml. of MeOH was treated similarly as described above. 1,5-Diphenyl-3-pentadienone (Ⅶ) (2.4 g., 61%) was obtained.

Reaction of I with 3-Pentanone——A solution of 1.3 g. of I, 1.4 g. of 3-pentanone and NaOH solution (0.5 g. of NaOH in 0.5 ml. of H_2O) in MeOH was treated similarly as described in the reaction of I with acetone, already reported.[1] I (0.6 g.) was recovered.

The authors are indebted to Mr. K. Narita and Miss N. Yamazaki for microanalytical data and to Miss K. Asahina for ultraviolet spectral measurements in this college.

The expenses for this work was defrayed by a Grant-in-Aid for Individual Research in 1963 from the Ministry of Education, for which is gratefully acknowledged.

Summary

The structures of the reaction products, Ⅲ, Ⅳ, and V, obtained in the interaction between quinazoline and acetone, 2-butanone and cyclohexanone in the presence of hydroxide anion at room temperature, were determined to be 1-(3,4-dihydro-4-quinazolinyl)-4-hydroxy-4-methyl-2-pentanone (Ⅲ), 1-(3,4-dihydro-4-quinazolinyl)-4-hydroxy-3,4-dimethyl-2-hexanone (Ⅳ) and 2-(3,4-dihydro-4-quinazolinyl)-6-(1-hydroxycyclohexyl)-cyclohexanone (V).

The possible mechanism for this reaction was suggested in Chart 4 in the text.

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UDC 615.782-012

37. Tetsuji Kametani, Kazuo Kigasawa, Mineharu Hiiragi,[*1] and Haruhide Ishimaru[*2]: Azabenzomorphane and Related Compounds. II.[*3] A Synthesis of 1,2,3,4-Tetrahydro-6*H*-1,5-methanobenzo[*f*][1,4]diazocine.[*4]

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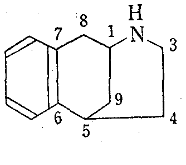
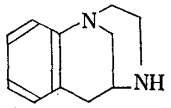
In a previous paper[*3] 3,4,5,6-tetrahydro-2*H*-1,5-methanobenzo[*e*][1,4]diazocine (Ⅱ), into which one nitrogen was introduced instead of tertiary carbon atom at 5 position of benzomorphane ring (I), was synthesized using a quinoline as a starting material. The purpose of the present investigation was to synthesize 1,2,3,4-tetrahydro-6*H*-1,5-methanobenzo[*f*][1,4]diazocine (Ⅲ) in order to test its analgesic activity.



I



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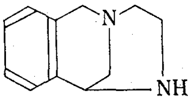

III

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[*2] Shinmachi-3-chome, Setagaya-ku, Tokyo (石丸春秀).

[*3] Part I. T. Kametani, K. Kigasawa, M. Hiiragi, T. Hayasaka, T. Iwata: Yakugaku Zasshi, 84, 405 (1964).

[*4] This forms Part CVI of "Studies on the Syntheses of Heterocyclic Compounds" by Tetsuji Kametani.