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Studies on the Synthesis of Pyridazine Derivatives. IX.[1] Synthesis of 10*H*-Pyridazino(3,2-*b*)quinazolin-10-one and Its Derivatives. (3)[2]

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A structual study of so-called dihydrocompound and tetrahydrocompound of 10*H*-pyridazino(3,2-*b*)quinazolin-10-one (VI) was described. These two compounds were assigned to be 3,4-dihydro- and 1,2,3,4-tetrahydro-10*H* pyridazino(3,2-*b*)quinazolin-10-one (III, IV), respectively. Catalytic hydrogenaytion of VI and III revealed that while the former gave II, III, IV and IX, the later gave II and IX.

In the previous paper[4] of this series, it was reported that the catalytic hydrogenation of 2-chloro-10*H*-pyridazino(3,2-*b*)quinazolin-10-one over palladized charcoal gave two kinds of dihydrocompound (II, mp 243.5° and III, mp 200.5°) and a tetrahydrocompound (IV, mp 166°) of 10*H*-pyridazino(3,2-*b*)quinazolin-10-one (VI). In that paper, dihydrocompounds were assumed to be 2-(2-cyanoethyl)-4(3*H*) quinazolinone (so-called nitrile compound) and 1,2-dihydro-10*H*-pyridazino(3,2-*b*)quinazolin-10-one (so-called dihydrocompound), respectively, by measurement of elemental analysis, infrared and ultraviolet absorption spectra. Previously,[5] the structure of II (so-called nitrile compound) was determined to be 2-(2-cyanoethyl)-4(3*H*) quinazolinone by synthetic method.

This paper describes structural study of the other dihydrocompound (III) and tetrahydrocompound (IV), and catalytic hydrogenation of III and VI.

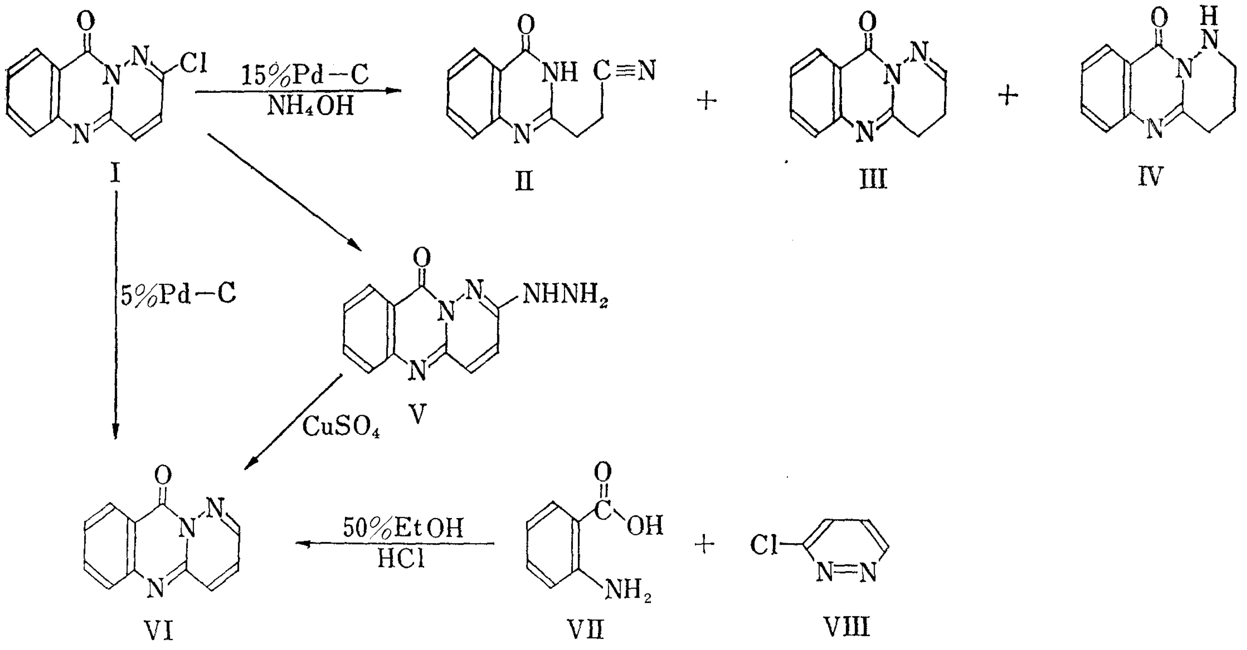

Chart 1

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[1] Part VIII: M. Yanai and T. Kinoshita, *Yakugaku Zasshi*, **87**, 114 (1967).
[2] Part 2: M. Yanai, T. Kinoshita, and S. Nakashima, *Yakugaku Zasshi*, **86**, 69 (1966).
[3] Location: *4-23 Bunkyo-machi, Nagasaki.*
[4] M. Yanai, T. Kinoshita, S. Nakashima, and M. Nakamura, *Yakugaku Zasshi*, **85**, 339 (1965).
[5] M. Yanai, T. Kinoshita, and S. Nakashima, *Yakugaku Zasshi*, **86**, 69 (1966).

The infrared absorption spectrum of III showed characteristic peaks at 1692 cm^{-1} (carbonyl), 770 cm^{-1} (*ortho* disubstitution), and no absorption band owing to N–H, O–H streching vibration. In the nuclear magnetic resonance (NMR) spectrum of III, new signals appeared at δ 7.87, δ *ca.* 3.0 and δ *ca.* 2.7 by comparison with those of VI. The signal of δ *ca.* 2.7 changed into symmetrical pattern of δ *ca.* 3.0 by double irradiation at δ 7.87. Decoupling showed that these signals were coupled to each other, the spin coupling constant is about 3.2 cps. The parts of saturated proton region were probably AA'BB' split, and the signal of δ *ca.* 2.7 was splitted again by coupling with the δ 7.87 proton. Relative intensity of the peaks at δ 7.87, δ *ca.* 3.0 and δ *ca.* 2.7 was about 1:2:2, and those of the parts of unsaturated proton and saturated proton was about 5:4. It was suggested that III had a partial structure of $=CHCH_2CH_2-$. Therefore the structure of III was probably 3,4-dihydro-10*H*-pyridazino (3,2-*b*)quinazolin-10-one.

The infrared absorption spectrum of IV showed absorption bands at 1662 cm^{-1} (carbonyl), 784 cm^{-1} (*ortho* disubstitution), and at 3280 cm^{-1} (secondary N–H stretching vibration). NMR spectrum showed first order pattern in saturated proton region, which consisted of two parts with the relative intensity about 2:1. The lower field part changed into doublet by double irradiation at the higher field, and the small doublet of the lowest triplet disappeared by same treatment at δ 7.13. It was indicated that the lower field consisted of two different signals (δ 3.02, δ 3.36), and their spin coupling constant was about 6.9 cps. Therefore it was explained that the signal of higher field was splitted into a quintet (triplet of triplets) by coupled with the signals of δ 3.02 and δ 3.36. It was suggested that IV had a partial structure of $-CH_2CH_2CH_2NH-$. Therefore the structure of IV was probably 1,2,3,4-tetrahydro-10*H*-pyridazino(3,2-*b*) quinazolin-10-one.

10*H*-Pyridazino(3,2-*b*)quinazolin-10-one (VI) was obtained by following methods, i) by dehydrazination of 2-hydrazino-10*H*-pyridazino(3,2-*b*)-quinazolin-10-one (V) with cupric sulfate, ii) by catalytic dechlorination of 2-chloro-10*H*-pyridazino (3,2-*b*)quinazolin-10-one (I) over 5% palladized charcoal in ammonia alkaline, in 26% yield, iii) by reaction of anthranilic acid (VII) with 3-chloropyridazine (VIII) in ethanolic solution of hydrochloric acid, in 29% yield.

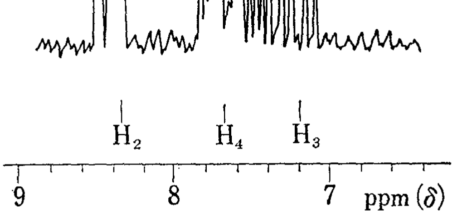

Fig. 1. Nuclear Magnetic Resonance Spectrum of 10*H*-Pyridazino(3,2-*b*)quinazolin-10-one (VI) at 60 Mcps in Dioxane (internal standard, tetramethylsilane)

In order to prove the hydrogenation process, following reactions were examined. Over 15% palladized charcoal, VI was hydrogenated to III in 64% yield. When III was hydrogenated over 25% palladized charcoal for long time, tetrahydrocompound, mp 240° IX ($C_{11}H_{11}ON_3$), was obtained. This compound was different from so-called tetrahydrocompound (IV). Therefore it seemed that III was not a precursor of IV, but IV was prepared by hydrogenation of VI directly. III, IV and IX were obtained, when VI was hydrogenated over palladized charcoal at room temperature, on the other hand, II, IV and III were obtained at elevated temperature. Therefore, it was assumed that III was precursor of II. Indeed, II and IX were obtained, when hydrogenated III over palladized charcoal at elevated temperature.

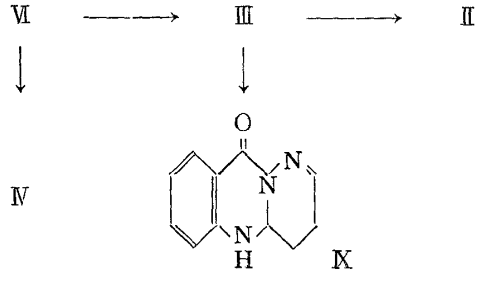

Chart 2

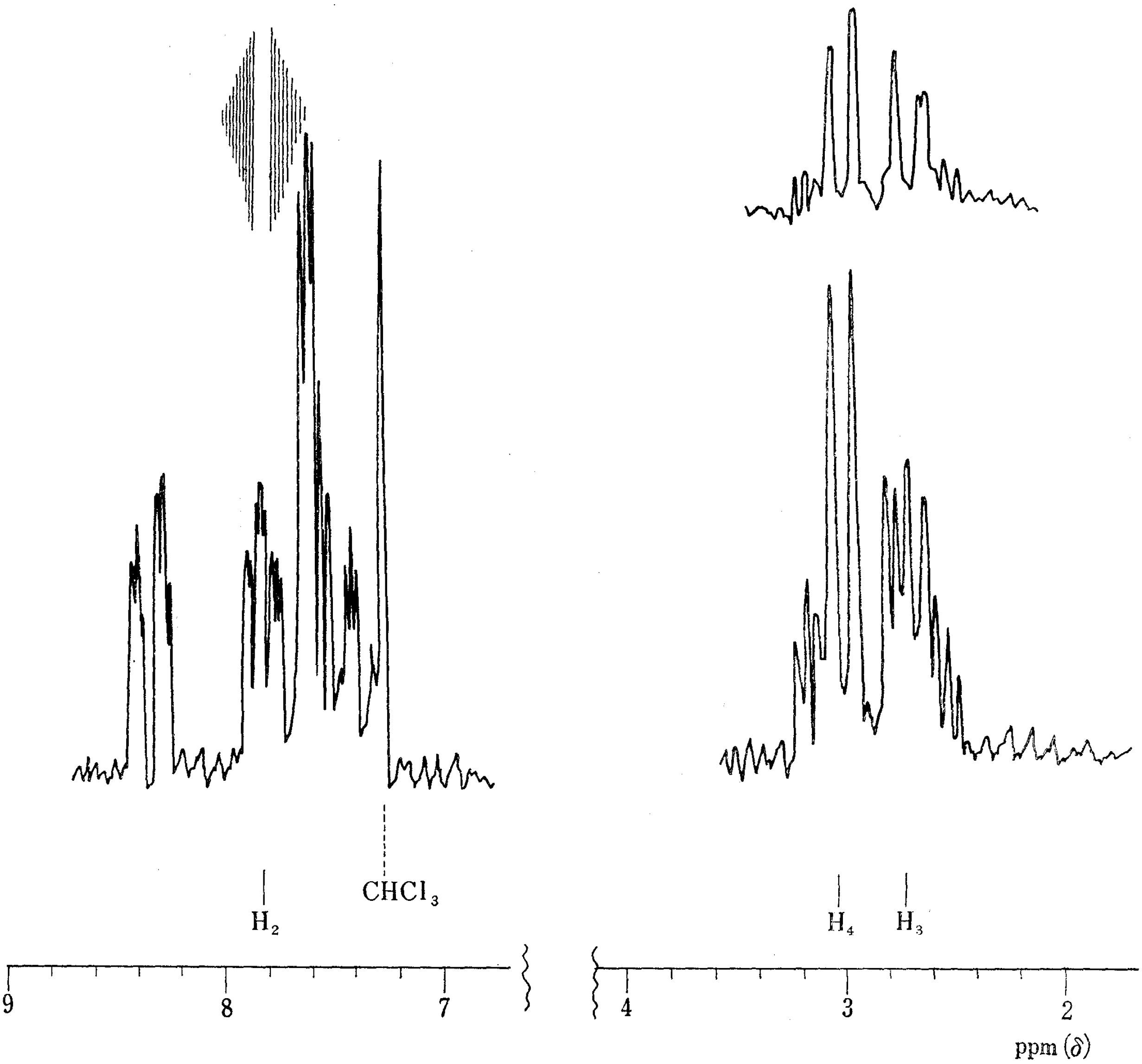

Fig. 2. Nuclear Magnetic Resonance Spectrum of 3,4-Dihydro-10*H*-pyridazino(3,2-*b*)quinazolin-10-one(III) at 60 Mcps in Deuteriochloroform (internal standard, tetramethylsilane)

The structure of IX was assumed to be 3,4,5,6-tetrahydro-10*H*-pyridazino(3,2-*b*)quinazolin-10-one by measurement of elementary analysis and infrared absorption spectrum showing absorption bands at 3280 cm^{-1} (secondary N-H streching vibration), 1650 cm^{-1} (carbonyl), and at 760 cm^{-1} (*ortho* disubstitution).

Experimental

10*H*-Pyridazino(3,2-*b*)quinazolin-10-one (VI)——i) A mixture of I (3.0 g), conc. ammonia (2 ml) and MeOH (400 ml) was hydrogenated at ordinary temperature and pressure over 5% Pd-C (1.8 g). After uptake of 1.05 moles of hydrogen, the catalyst was filtered and washed with hot MeOH, the filtrate and washing were combined and evaporated to dryness. The residue was extracted with acetone, the extract was passed through an alumina column for decoloration. The crude product was recrystallized from AcOEt to yellow needles, mp 213—214°, 1.0 g undepressed on admixture with a sample obtained previously.[4)]

ii) A mixture of VII (3.6 g), VIII (3.0 g) and conc. HCl (3 ml) in 50% EtOH (40 ml) was refluxed for 3 hr and after cooling the deposited crystals were collected. Recrystallization from EtOH afforded pale yellow needles, mp 265° (decomp.), 2.6 g, ($AgNO_3$ positive, it was probably hydrochloride of VI). The crystals were dissolved in 30 ml of water. After alkalized with ammonia, the solution was evaporated to dryness *in vacuo*. The residue was extracted with boiling AcOEt and the extract was concentrated and

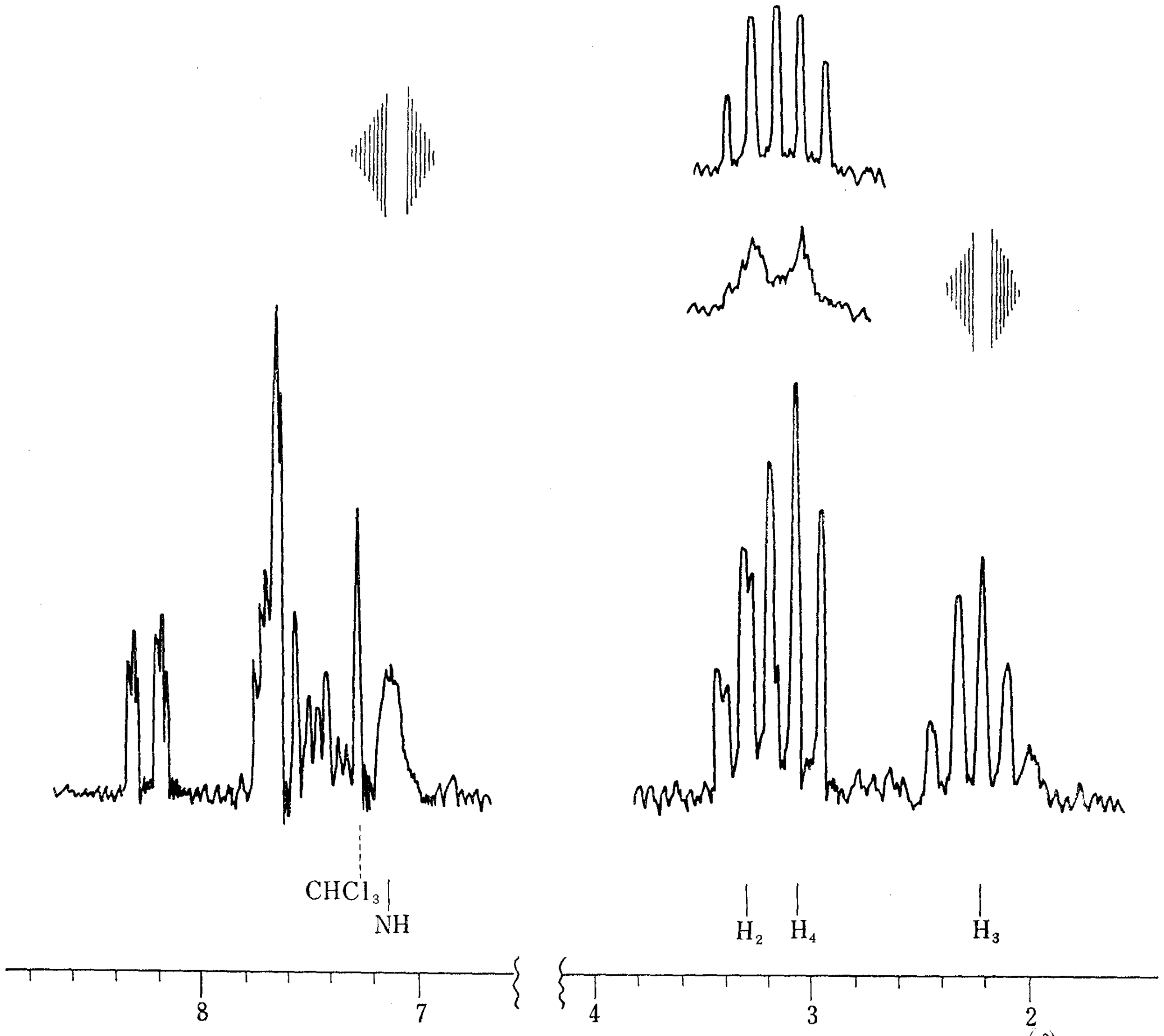

Fig. 3. Nuclear Magnetic Resonance Spectrum of 1,2,3,4-Tetrahydro-10*H*-pyridazino(3,2-*b*)quinazolin-10-one(IV) at 60 Mcps in Deuteriochloroform (internal standard, tetramethylsilane)

chilled. The deposited crystals were collected. Yellow needles, mp 213—214°, 1.5 g. It was not depressed on admixture with a sample obtained above i) method.

Catalytic Reduction of 10*H*-Pyridazino(3,2-*b*)quinazolin-10-one (VI)——i) A mixture of VI (3.0 g) and MeOH (250 ml) was hydrogenated at ordinary temperature and pressure over 15% Pd-C (1.5 g). When absorption became slow, to the mixture was added moreover 15% Pd-C (2.0 g) and was hydrogenated unitl no hydrogen uptake was observed. It took about 5 hr and total hydrogen uptake was *ca.* 1.2 moles. The catalyst was filtered and washed with hot MeOH and the filtrate and washing were combined and evaporated to dryness. The residue was recrystallized from MeOH to pale yellow needles, III mp 200—201°, 1.93 g, undepressed on admixture with a sample obtained before.

ii) A solution of VI (200 mg) in MeOH (50 mg) was hydrogenated at ordinary temperature and pressure over 25% Pd-C (150 mg) until no hydrogen uptake was observed. It took about 5 hr and total hydrogen uptake was *ca.* 1.5 moles. After the catalyst was filtered and washed with hot MeOH, the filtrate and washing were combined and evaporated to dryness. The residue was recrystallized from acetone to pale yellow needles, III mp 200—201°, 15 mg. The mother liquor was poured onto an alumina column for chromatography and eluted with acetone. The initial fraction afforded 15 mg of IV as colorless needles, mp 163°. The following fraction afforded a mixture, which on recrystallization from MeOH gave 15 mg of III as pale yellow neeldes, mp 201° and a small amount of IX.

iii) A mixture of VI (440 mg) and MeOH (100 ml) was hydrogenated at ordinary temperature and pressure over 25% Pd-C for 2.2/3 hr and further 2 hr, the hydrogenation was continued at heated condition. After the catalyst was filtered and washed with hot MeOH, the filtrate and washing were combined and evaporated to dryness. The residue was recrystallized from acetone to colorless neeldes, II mp 243°, 35 mg.

The mother liquor was poured onto an alumina column for chromatography, eluted with acetone. The initial fraction afforded 45 mg of IV mp 166° and the following fraction afforded a small amount of III.

Catalytic Reduction of 3,4-Dihydro-10*H*-pyridazino(3,2-*b*)quinazolin-10-one (III)——i) A mixture of III (600 mg) and MeOH (200 ml) was hydrogenated at ordinary temperature and pressure over 20% Pd–C (500 mg) for 5 hr. The hydrogenation was continued after adding 25% Pd–C (500 mg) (for 2.5 hr) and again adding 20% Pd–C (500 mg) (for 3.5 hr). The reaction mixture fluoresced and the catalyst was filtered and washed with hot MeOH. Then the filtrate and washing were combined and evaporated to dryness. The residue was recrystallized from MeOH to colorless plates, IX mp 238.5—240°, 120 mg. *Anal.* Calcd. for $C_{11}H_{11}ON_3$: C, 65.67; H, 5.51; N, 20.88. Found: C, 65.97; H, 5.61; N, 20.49.

ii) A mixture of III (122 mg) and MeOH (70 mg) was hydrogenated at elevated temperature and ordinary pressure over 25% Pd–C (100 mg). About 1.3 moles of hydrogen was absorbed. After the catalyst was filtered and washed with hot MeOH, the filtrate and washing were combined and evaporated to dryness. The residue was recrystallized from AcOEt–MeOH to colorless plates, IX mp 238—240°, 10 mg. The mother liquor affored 20 mg of II as colorless needles, mp 243°.

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