Aroylsemicarbazides——A hot solution of aroylhydrazine (10 mmole) in H_2O (20 ml) and AcOH (20 ml) was added to a stirred and ice-cooled solution of potassium cyanate (11 mmole) in H_2O (5 ml). The mixture was stirred overnight at room temperature. The precipitates were collected and washed with EtOH and ether to give the product. 4-Hydroxybenzoylsemicarbazide had mp 219—221° (lit.[8] mp 230°). *Anal.* Calcd. for $C_8H_9O_3N_3$: C, 49.23; H, 4.65; N, 21.53. Found: C, 49.52; H, 4.67; N, 21.15. 4-Aminobenzoylsemicarbazide had mp 230—232° (decomp.). *Anal.* Calcd. for $C_8H_{10}O_2N_4$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.25; H, 4.97; N, 28.27.

3-Aryl-Δ^2-1,2,4-triazolin-5-ones (38—55)——Method D: 5-Alkoxy-3-aryl-1H-1,2,4-triazole (1 g) was heated under reflux with concd. HCl (25 ml) for few hours. After cooling, the precipitates were collected, washed, and recrystallized.

Method E: After refluxing the solution of aroylsemicarbazide (25 mmole) in 10% NaOH (100 ml) for 10 hr, the undissolved material was removed while hot. The filtrate was acidified by addition of AcOH and cooled. The precipitates were collected, washed, and recrystallized.

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UDC 547.895.04 : 547.831.6.04

Heteroaromatic Analogs of Benzomorphan. III.[1] Synthesis of 1,2,3,4,5,6-Hexahydro-2,6-methano-3-methylpyrido[3,2-*d*]azocine

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6-Acetamido-5,6,7,8-tetrahydroquinoline N-oxide (VI) was derived to the 8-oxo derivative (IX) *via* the acetoxy compound (VII). Introduction of carboxymethyl group by a Wittig reaction of IX and catalytic hydrogenation afforded the amido ester (XI). The title compound (XVI) was synthesized from the amino acid ester (XII) by intramolecular cyclization and the subsequent lithium aluminum hydride reduction of the resulting lactam.

In the course of our study on analgesics, we were interested in the synthesis of heteroaromatic analogs of benzomorphan. Previously we reported the synthesis of 1,2,3,4,5,6-hexahydro-1,5-methanopyrido[2,3-*c*]azocine and -[3,2-*c*]azocine (I and II), and 1,2,3,4,5,6-hexahydro-2,6-methanopyrido[2,3-*d*]azocine (III) derivatives.[1,3] These compounds were synthesized by the formation of pyridine ring fused to the corresponding 2-azabicyclo[3.3.1]-nonane intermediates. This paper deals with the synthesis of 1,2,3,4,5,6-hexahydro-2,6-methano-3-methylpyrido[3,2-*d*]azocine (XVI) starting from a pyridine derivative.

According to the method for preparation of 5,6,7,8-tetrahydroquinoline derivative,[4] 4-acetamidocyclohexanone (IV) was heated with 3-aminoacrolein in triethylamine to give the

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2) Location: *a) Gofuku, Toyama, 930, Japan; b) Sakado-cho, Saitama, 350-02, Japan.*
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corresponding tetrahydroquinoline (V) in 32% yield. In order to obtain 8-oxo derivative of V, direct oxidations of V with selenium dioxide[5] and with chromium trioxide[6] were attempted. These reactions, however, resulted in recovery of V and/or formation of unidentified products. So, we attempted to synthesize the desired ketone by an application of acetoxylation of pyridine N-oxide and oxidation of the resulting alcohol.[7] Treatment of V with 30% hydrogen peroxide and acetic acid at 80° gave the corresponding N-oxide (VI). When *m*-chloroperbenzoic acid was used in this reaction,[8] the reaction proceeded at room temperature in a short time to give almost pure VI in high yield. On heating in acetic anhydride, VI yielded the acetate (VII) quantitatively. This product showed two spots on thin-layer chromatography (TLC), and its nuclear magnetic resonance (NMR) spectrum showed that VII consisted of a mixture of *trans*- and *cis*-isomers concerning with acetamido and acetoxy functions in a ratio of 1:1.[9] When VII was treated with potassium carbonate in aqueous methanol at room temperature, hydrolysis of only the ester group occurred to afford the alcohol (VIII). Separation of the two stereoisomers of VIII, though it had no concern with the next step, could be achieved by chromatography on silica gel. On the NMR spectra, both of the signals of C-8 methine protons of these isomers appeared at δ 4.7 ppm and splitted into doublet of

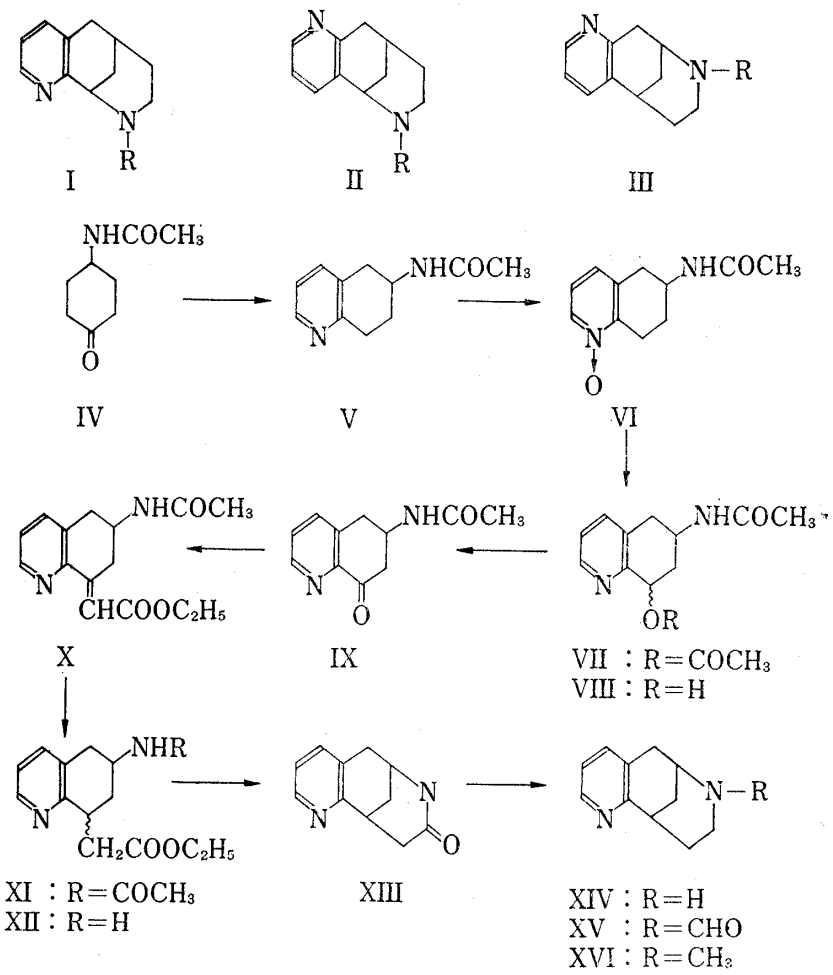

Chart 1

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9) As well as this case, the terms "*cis*" and "*trans*" are used for indication of stereoisomers concerning with the substituents at C-6 and C-8 of tetrahydroquinoline skeleton.

doublet. Their coupling constants were as follows; *cis*-VIII, J=10 and 6 Hz, *trans*-VIII, J=7 and 4 Hz. The above observation suggested that the acetamido function of VIII would exist in mainly equatorial conformation. Oxidation of VIII with active manganese dioxide[10] gave the ketone (IX).

A modified Wittig reaction of IX using triethyl phosphonoacetate and sodium hydride in N,N-dimethylformamide (DMF) afforded the olefinic ester (X) in 61% yield. Catalytic hydrogenation of X gave the amido ester (XI), which was also a mixture of *cis*- and *trans*-isomers (1:1). It was considered that only the *cis*-isomer would have possibility of intramolecular cyclization in the subsequent steps. As attempts to isolate the *cis*-isomer from the above product were unsuccessful, XI was submitted to hydrolysis with hydrochloric acid and followed by esterification to yield the amino acid ester (XII). The compound (XII) was then heated at 150° to give the lactam (XIII). The overall yield of XIII from XI was 45%. Lithium aluminum hydride reduction of XIII afforded the amine (XIV), which was derived to the formamide (XV) by treatment with acetic formic anhydride. In the NMR spectrum of XV, the signals of the methine proton being adjacent to nitrogen atom and formyl proton appeared at δ 4.1, 5.0 ppm and 8.0, 8.2 ppm respectively, and all of them had equal intensity. Thus, the compound (XV) consisted of a 1:1 mixture of two rotamors concerning with the C-N bond of amido function. The desired compound (XVI) was obtained by reduction of XV with lithium aluminum hydride in 66% yield.

Experimental

Melting points were determined with Yanagimoto micro melting point apparatus and uncorrected. All boiling points were indicated by bath temperatures. NMR spectra were taken with a JEOL JNM-C-60H or PMX-60 spectrometer using TMS as internal standard. Mass spectra were taken on a JEOL JMS-01SG-2 instrument at 75 eV ionization potential.

4-Acetamidocyclohexanone (IV)——A mixture of 4-acetamidocyclohexanol (91 g) and CrO_3 (43 g) in AcOH (500 ml) was stirred at room temperature for 3 hr. After removal of the AcOH *in vacuo*, the residue was triturated with acetone and filtered. The filtrate was concentrated *in vacuo*, and the residue in benzene–$CHCl_3$ (1:1) was passed through on a column of basic alumina (150 g). Elution with the same solvent gave crystalline mass of IV, which was recrystallized from benzene to afford 51 g (56%) of colorless cubes, mp 139—141°. *Anal.* Calcd. for $C_8H_{13}O_2N$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.86; H, 8.52; N, 8.85.

6-Acetamido-5,6,7,8-tetrahydroquinoline (V)——A mixture of IV (31 g), 3-aminoacrolein[11] (20 g), NH_4-OAc (0.5 g) and triethylamine (200 ml) was heated with stirring at 120° for 27 hr. After concentration of the mixture *in vacuo*, the residue was dissolved in $CHCl_3$, washed with water, dried over Na_2SO_4, and concentrated. The residue was chromatographed on neutral alumina (100 g). Elution with benzene–$CHCl_3$ (1:1) gave 12.3 g (32 %) of V as an oil. IR ν_{max}^{film} cm^{-1}: 3220, 3030 (NH), 1640 (C=O). NMR ($CDCl_3$) δ: 1.6—2.3 (2H, m), 1.95 (3H, s, $-COCH_3$), 2.6—3.2 (4H, m), 4.0—4.5 (1H, m), 7.0 (1H, d.d, J=7.5, 4.5 Hz, arom.), 7.3 (1H, broad d, J=7.5 Hz, arom.), 8.3 (1H, broad d, J=4.5 Hz, arom.), 7.0—7.5 (1H, broad peak, –CONH–). Picrate of V: yellow needles, mp 190—192° (MeOH). *Anal.* Calcd. for $C_{11}H_{14}ON_2 \cdot C_6H_3O_7N_3$: C, 48.69; H, 4.09; N, 16.69. Found: C, 48.52; H, 3.81; N, 16.86.

6-Acetamido-5,6,7,8-tetrahydroquinoline 1-Oxide (VI)——To a solution of V (1.5 g) in $CHCl_3$ (5 ml) was added a solution of *m*-chloroperbenzoic acid (1.29 g) in $CHCl_3$ (10 ml) at 0—5° with stirring. After the addition was completed, the stirring was continued at room temperature for 5 hr. The reaction mixture was then passed through on a column of basic alumina (56 g). Elution with $CHCl_3$ and then with $CHCl_3$–MeOH (3:1) gave 1.27 g (78%) of VI as a crystalline mass, mp 220—223°. This product showed one spot on TLC, and was used for next step without further purification. IR ν_{max}^{KBr} cm^{-1}: 3150, 3050 (NH), 1670 (C=O), 1240 (N–O). NMR ($CDCl_3$) δ: 2.0 (3H, s, $-COCH_3$), 6.0 (1H, broad peak, –NHCO–), 7.0 (2H, d, J=4 Hz, arom.), 8.1 (1H, t, J=4 Hz, arom.).

6-Acetamido-8-acetoxy-5,6,7,8-tetrahydroquinoline (VII)——A mixture of VI (2.9 g) and Ac_2O (20 ml) was heated on an oil bath at 60° with stirring for 2 hr. The mixture was concentrated *in vacuo*, and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was worked up as usual to give 3.2 g (92%) of colorless oil of VII, bp 150—160° (0.07 mmHg). IR ν_{max}^{film} cm^{-1}: 3250, 3050 (NH), 1735, 1650 (C=O). NMR ($CDCl_3$) δ: 1.95 (3/2H) and 2.0 (3/2H, s, $-NHCOC\underline{H}_3$), 2.1 (3/2H) and 2.15 (3/2H, s, $-OCOCH_3$), 4.0—4.6 (1H, m, $>C\underline{H}-NH-$), 5.9—

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6.2 (1H, m, >CH–OCO–). *Anal.* Calcd. for $C_{13}H_{16}O_3N_2$: C, 62.89; H, 6.50; N, 11.28. Found: C, 63.06; H, 6.51; N, 11.44.

6-Acetamido-5,6,7,8-tetrahydro-8-hydroxyquinoline (VIII)——A mixture of VII (3.2 g) in MeOH (40 ml) and 10% K_2CO_3 (20 ml) was stirred at room temperature for 40 hr, and then extracted with $CHCl_3$. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave 2.54 g of crystalline VIII. A part of the above product was chromatographed on silica gel. Elution with $CHCl_3$ gave *cis*-VIII, mp 140—141° (acetone). IR ν_{max}^{KBr} cm^{-1}: 3300 (NH), 3200—2600 (OH), 1660 (C=O). NMR (d_6-DMSO) δ: 4.7 (1H, d.d, J=10, 6 Hz >CH–OH) 8.1 (1H, d, J=7 Hz, –NHCO–). *Anal.* Calcd. for $C_{11}H_{14}O_2N_2$: C, 64.06;H, 6.84; N, 13.58. Found: C, 64.22; H, 7.03; N, 13.50.

Further elution with $CHCl_3$–MeOH (4: 1) gave *trans*-VIII, mp 210—212° (acetone). IR ν_{max}^{KBr} cm^{-1}: 3300—3000 (NH, OH), 1625 (C=O). NMR (d_6-DMSO) δ: 4.7 (1H, d.d, J=7, 4 Hz, >CH–OH), 7.9 (1H, broad d, J=7 Hz, –NHCO–). *Anal.* Calcd. for $C_{11}H_{14}O_2N_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.81; H, 6.92; N, 13.55.

6-Acetamido-5,6,7,8-tetrahydro-8-oxoquinoline (IX)——A mixture of VIII (2.7 g) and active MnO_2 (7.8 g)[10] in acetone (300 ml) was stirred at room temperature for 10 hr. The mixture was filtered, and the filtrate was concentrated *in vacuo* to give crystalline residue. Recrystallization from acetone gave 1.08 g (40%) of colorless prisms of IX, mp 242—245°. IR ν_{max}^{KBr} cm^{-1}: 3240, 3050 (NH), 1700, 1660 (C=O). *Anal.* Calcd. for $C_{11}H_{12}O_2N_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.92; H, 5.87; N, 13.77.

6-Acetamido-8-ethoxycarbonylmethylene-5,6,7,8-tetrahydroquinoline (X)——A mixture of NaH (216 mg) and triethyl phosphonoacetate (1.66 g) in benzene (10 ml) was refluxed for 10 min. The benzene was then removed *in vacuo*. The solid residue was dissolved in DMF (10 ml), and mixed with a solution of IX (1.4 g) in DMF (20 ml). The mixture was stirred at room temperature for 7 hr. After removal of the solvent *in vacuo*, the residue was dissolved in $CHCl_3$. Usual working up of the $CHCl_3$ solution gave 1.15 g (61%) of X, bp 115° (0.15 mmHg), mp 202—206°. For analysis recrystallization from benzene gave colorless needles, mp 206—207°. IR ν_{max}^{KBr} cm^{-1}: 3240, 3050 (NH), 1720, 1650 (C=O). NMR ($CDCl_3$) δ: 1.9 (3H, s, $-COCH_3$), 5.9 (1H, s, >C=CH–), 6.2 (1H, broad peak, –NHCO–). *Anal.* Calcd. for $C_{15}H_{18}O_3N_2$: C, 65.67; H, 6.61; N, 10.21. Found: C, 65.38; H, 6.67; N, 10.06.

Ethyl (6-Acetamido-5,6,7,8-tetrahydro-8-quinolyl)acetate (XI)——A solution of X (2.15 g) in EtOH (40 ml) was hydrogenated at room temperature in the presence of 10% Pd-C (1 g) in the usual manner for 5 hr. The mixture was worked up as usual to give 1.99 g (92%) of XI as a colorless viscous oil, bp 130° (5×10^{-5} mmHg). IR ν_{max}^{film} cm^{-1}: 3250, 3050 (NH), 1725, 1640 (C=O). NMR ($CDCl_3$) δ: 1.95 (3/2H) and 2.0 (3/2H, s, $-COCH_3$), 5.9 (1H, broad peak, –NHCO–). *Anal.* Calcd. for $C_{15}H_{20}O_3N_2$: C, 65.19; H, 7.30; N, 10.14. Found: C, 65.47; H, 7.49; N, 9.88.

Ethyl (6-Amino-5,6,7,8-tetrahydro-8-quinolyl)acetate (XII)——A mixture of XI (1.1 g) and concd. HCl (10 ml) was refluxed for 7 hr. After concentration *in vacuo* to dryness, the residue was dissolved in abs. EtOH (30 ml) and saturated with dry HCl. The reaction mixture was refluxed for 1.5 hr, and then concentrated *in vacuo*. To the residue was added water and made alkaline with K_2CO_3. Extraction with $CHCl_3$ and usual working up of the extract gave 550 mg of the crude XII as an oil. IR ν_{max}^{film} cm^{-1}: 3250, 3200 (NH_2), 1725 (C=O). Dipicrate of XII: yellow cubes, mp 186—188° ($CHCl_3$–MeOH). *Anal.* Calcd. for $C_{13}H_{18}O_2N_2\cdot2C_6H_3O_7N_3$: C, 43.36; H, 3.49; N, 16.18. Found: C, 43.45; H, 3.64; N, 15.90.

1,2,3,4,5,6-Hexahydro-2,6-methanopyrido[3,2-*d*]azocin-4-one (XIII)——The crude XII (550 mg) was heated at 150° (20 mmHg) for 3.5 hr. The resulting solid product was then sublimed at 120° (5×10^{-4} mmHg) to give 340 mg (45% based on XI) of XIII, colorless crystals, mp 190—195°. Recrystallization from ether–$CHCl_3$ gave the analytical sample, colorless cubes, mp 196—198°. IR ν_{max}^{KBr} cm^{-1}: 3150, 3010 (NH), 1650 (C=O). NMR ($CDCl_3$) δ: 2.1—3.0 (6H, m), 3.4 (1H, m), 4.0 (1H, m, >CH–N<). Mass Spectrum *m/e*: 188 (M^+). *Anal.* Calcd. for $C_{11}H_{12}ON_2$: C, 70.18; H, 6.43; N, 14.88. Found: C, 69.92; H, 6.26; N, 14.60.

3-Formyl-1,2,3,4,5,6-hexahydro-2,6-methanopyrido[3,2-*d*]azocine (XV)——To a stirred suspension of $LiAlH_4$ (289 mg) in dioxane (15 ml) was added dropwise a solution of XIII (285 mg) in dioxane (35 ml) at room temperature. The mixture was heated on an oil bath at 90° for 7 hr, and then refluxed for 10 min. After decomposition of the excess of $LiAlH_4$ by addition of saturated potassium sodium tartrate solution, the dioxane was removed *in vacuo*. The residue was extracted with $CHCl_3$, and the extract was worked up as usual to give 256 mg of the crude XIV as an oil. A mixture of Ac_2O (408 mg) and HCOOH (184 mg) was heated on an oil bath at 50° for 2 hr, cooled to room temperature, and dissolved in benzene (1.5 ml). To this solution was added a solution of the above crude XIV (256 mg) in benzene (1.5 ml) with stirring at room temperature. The mixture was stirred for 1 hr, diluted with $CHCl_3$, and washed with water. The organic solution was dried over Na_2SO_4, and concentrated. Distillation of the residue afforded 188 mg (61% based on XIII) of a colorless oil of XV, bp 100° (2×10^{-4} mmHg). IR ν_{max}^{film} cm^{-1}: 1660 (C=O). NMR ($CDCl_3$) δ: 1.7—3.7 (9H, m), 4.1 (1/2H) and 5.0 (1/2H, m, >CH–N<), 8.0 (1/2H) and 8.2 (1/2H, s, –CHO). *Anal.* Calcd. for $C_{12}H_{14}ON_2$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.29; H, 7.08; N, 13.57.

1,2,3,4,5,6-Hexahydro-2,6-methano-3-methylpyrido[3,2-*d*]azocin (XVI)——A mixture of XV (332 mg) and $LiAlH_4$ (250 mg) in tetrahydrofuran (20 ml) was refluxed on an oil bath for 40 min. After cooling, to the mixture was added saturated potassium sodium tartrate solution. Extraction with $CHCl_3$ and usual working up of the extract gave 205 mg (66%) of a colorless oil of XVI, bp 80° (0.09 mmHg). IR ν_{max}^{film} cm^{-1}: 2800 (NMe).

NMR ($CDCl_3$) δ: 2.4 (3H, s, $>NCH_3$), 7.0 (1H, d.d, $J=7.5$, 4.5 Hz, arom.), 7.4 (1H, broad d, $J=7.5$ Hz, arom.), 8.3 (1H, broad d, $J=4.5$ Hz, arom.). Mass Spectrum *m/e*: 188 (M^+). *Anal.* Calcd. for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88. Found: C, 76.38; H, 8.63; N, 14.59.

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Reaction of Ethoxymethylenemalononitrile with Hydrazine Hydrate

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The reaction of ethoxymethylenemalononitrile (EMMN) with hydrazine hydrate in the presence of ethanol at room temperature gave 3-amino-4-cyanopyrazole (I) and a novel pyrazole derivative, 3-amino-4-cyano-2-hydrazonomethylpyrazole (II). When this reaction was carried out under reflux, II was not obtained. The result of various solvents for the preparation of II was found at present acetonitrile as a solvent most suitable. The reaction of EMMN with hydrazine hydrate in water at room temperature gave I in good yield. On the other hand, the reaction of hydrazine hydrate with excess EMMN afforded 7-amino-3,6-dicyanopyrazolo[1,5-*a*]pyrimidine.

In our recent publication, we have reported that the reaction of ethoxymethylenemalononitrile (EMMN) with hydrazine hydrate in ethanol at room temperature gave 3-amino-4-cyanopyrazole (I) and a novel pyrazole derivative, 3-amino-4-cyano-2-hydrazonomethylpyrazole (II).[2] The 3-amino-4-cyanopyrazole ring system was first described in 1956 by Robins,[3] who obtained only compound I by the reaction of EMMN with hydrazine hydrate in the absence of a solvent. Similarly, refluxing of EMMN with hydrazine hydrate in anhydrous ethanol or ethanol gave only compound I.[4]

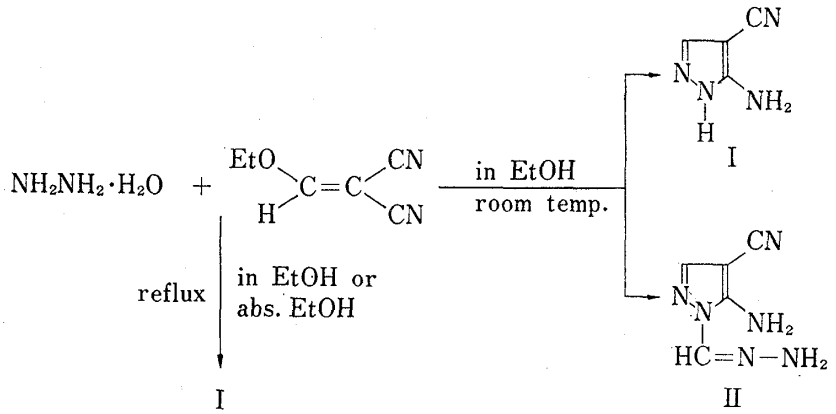

Chart 1

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