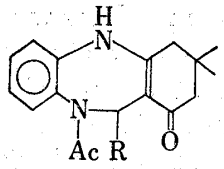
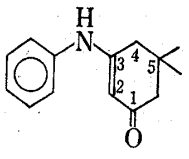


IV



V

3310 cm^{-1} (secondary amine). The NMR spectrum (DMSO-d_6) had signals at τ 1.13 (1H, s, O=C-C=C-NH), 2.81 (5H, s, C_6H_5), 2.85—3.40 (4H, Ar), 3.76 (1H, d, NH), 4.16 (1H, d, N-C<u>H</u>-C_6H_5), 7.38 (2H, s, CH_2), 7.80, 7.83 (2H, CH_2), 8.90, 8.95 (2×3H, s, gem CH_3), two (1.13, 3.76) of which were removed and one (4.16) of which changed to a singlet by D_2O.

The ready formation of 10-acetyl derivative (IV) also supported the structure II. Imino group at 5-position of II or 3-position of III is of vinylogous amide character and reluctant to acetylation. Our attempts to acetylate vinylogous imino group of 3-anilino-5,5-dimethyl-2-cyclohexen-1-one (V) also failed.

The synthesis just outlined is of quite general application since several analogs of II (R=H, CH_3,[9] C_2H_5, and $C_6H_4Cl(p)$) could be prepared with great ease. It also features simple manipulation, ready availability of starting material and excellent yields.

The following procedure for the preparation of II (R=C_6H_5) is illustrative: To a solution of 2.3 g (0.01 mole) of I in 10 ml of ethanol was added 1.06 g (0.01 mole) of benzaldehyde and one drop of acetic acid and the resulting mixture was allowed to stand at room temperature for 1 hr. The deposited crystalline was collected as nearly pure light-yellow plates, mp 258—259°. Yield was 3 g (94.3%). The melting point raised to 258.5—259.5° after one recrystallization from ethanol. *Anal.* Calcd. for $C_{21}H_{22}ON_2$: C, 79.21; H, 6.96; N, 8.80. Found: C, 79.06; H, 6.96; N, 8.86.

Faculty of Pharmaceutical Sciences,
Fukuoka University
Nanakuma, Fukuoka

Seiji Miyano
Nobuhiro Abe

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9) Acetaldehyde diethylacetal was employed as an aldehyde component instead of acetaldehyde.

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The Reaction of 4-Cyanoisoquinolines with the Grignard Reagent and Carbanions

Recently, we reported[1] the photochemical reaction of 4-cyanoisoquinoline and its 1-alkyl derivatives (**1**) in alcohols, esters, ethers, and amides, which was found to result in unusually facile addition of these solvents to C-1 position of **1** from the carbon atom adjacent to the hetero-atoms (Z), giving rise to **2**.

We now wish to describe the chemical behavior of **1** toward the Grignard reagent and also other carbanions mainly affording 1-substituted derivatives (**3**) without any interaction with the cyano function (Table I, Chart 1 and 2). Structure of the products is readily recognized from infrared (IR), ultraviolet (UV), and nuclear magnetic resonance (NMR) spectra, and an example of these data is shown beside the formula of **3h**. There have been a few

1) M. Natsume and M. Wada, *Tetrahedron Letters*, **1971**, 4503.

instances of a similar Grignard reaction in the past, in which dihydro addition products were isolated in the case of 3-pyridyl and 3-quinolyl ketones,[2] and 3,5-dicyano- or dialkoxycarbonyl-pyridine derivatives.[3] However, it is remarkable in our case that the reaction undergoes even with 1-alkylated compounds (**1b**), and consequently 1,1-disubstituted substances (**3e—i**) without alkyl group on the nitrogen of isoquinoline could be produced as fairly stable materials owing to the partial structure of vinylogous N-nitrile, contrary to the known fact that only the quaternary salts can afford *gem*-disubstituted derivatives possessing an N-alkyl group, although they are unstable, reflecting their enamine character.[4] Formation of **3** enables us to elaborate the functionalization of the nitrogen not only with alkyl group but the acyl or sulfonyl substituent to obtain **4**, **7**, and **9**, and this knowledge opens the way to convert **4** to 1,1-dialkyl-1,2,3,4-tetrahydroisoquinolines[5] (**5**) and further to achieve the

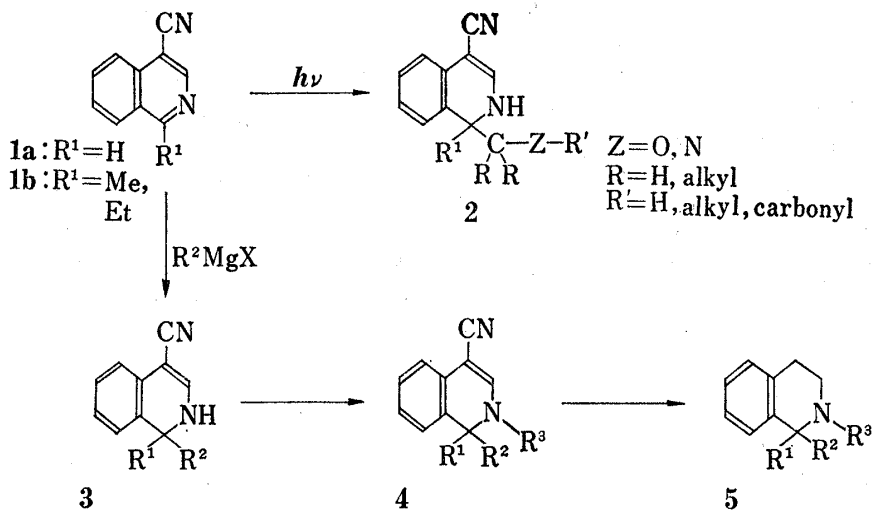

Chart 1

TABLE I

	R¹	R²	mp (°C)	Yield (%)		R³	mp (°C)	Yield (%)
3a	H	Me	95—96	82	**4a**	Me	80—81	80 (from **3a**)
					4a'	Ts	152—153	44 (from **1a**)
3b	H	Et	96—96.5	64.5				
3c	H	C_6H_5	195—196	50				
3d	H	$CH_2C_6H_5$	156—158	76				
3e	Me	Me	133—134	38	**4e**	Me	syrup	91 (from **3e**)
					4e'	Ts	146—147	47 (from **1b**)
3f	Me	Et	syrup	32	**4f**	Me	syrup	43 (from **1b**)
3g	Me	allyl	syrup	—	**4g**	Me	syrup	40 (from **1b**)
3h	Me	$CH_2C_6H_5$	118—120	29	**4h**	Me	113.5—114	75 (from **3h**)
					4h'	Ts	159—159.5	43 (from **1b**)
3i	Et	$CH_2C_6H_5$	syrup	40	**4i**	Me	174	

2) R.C. Fuson and J.J. Miller, *J. Am. Chem. Soc.*, **79**, 3477 (1957); R.E. Lyle and D.A. Nelson, *J. Org. Chem.*, **28**, 169 (1963).
3) R. Lukeš and J. Kuthan, *Coll. Czech. Chem. Commun.*, **26**, 1422, 1845 (1961); J. Kuthan, E. Janečková and M. Havel, *ibid.*, **29**, 143 (1964); J. Paleček, L. Ptáčková and J. Kuthan, *ibid.*, **34**, 427 (1969).
4) J. Knabe and K. Detering, *Arch. Pharm.*, **300**, 97 (1967); S.F. Dyke, G. Kinsman, J. Knabe and H.D. Holtje, *Tetrahedron*, **27**, 6168 (1972). Special example such as phthalazine derivatives afforded the product corresponding to **3** with *gem*-dialkyl group; A. Marxer, F. Hofer and U. Salzmann, *Helv. Chim. Acta*, **52**, 1376 (1969).
5) M. Natsume, S. Kumadaki and K. Kiuchi, *Chem. Pharm. Bull.* (Tokyo), **20**, 1592 (1972).

synthesis of indole derivatives from the corresponding quinolines.[6]

Conversion of **3** to **4** could be carried out by making the sodium salt with sodium hydride in dimethylformamide, followed by the addition of alkyl halide or tosyl chloride. In order to improve the total yield of **4** from **1**, some device was introduced here on the basis of the observation that (i) no N-alkylation took place even if an excess of alkyl halide was present, as long as ether or benzene–ether mixture was employed for medium of the Grignard reaction, and that (ii) when dimethyl sulfoxide (DMSO) was added to this mixture, partial N-alkylation proceeded, implying that the magnesium salt (**6**) can be alkylated in dipolar aprotic solvents. Therefore, the method was modified by evaporating the solvent after the Grignard reaction before decomposition with water, followed by addition of alkyl halide in DMSO in nitrogen atmosphere. Thus, **4e** and **4h** were obtained directly from **1b** in respective yields of 49% and 48%, which are better than by the two step method shown in Table I. Another modification was the use of hexamethylphosphoric triamide (HMPT) for the Grignard reaction,[7] and the reaction mixture between the HMPT solution of **1b** and the ether suspension of benzylmagnesium halide (Mg excess) was treated with tosyl chloride, resulting in the formation of **4h'** in 43% yield. Similar reaction of **1a** with phenyllithium and subsequent tosylation furnished **7**, mp 138—139°, in 45% yield.

When an acetonitrile solution of **1a** was stirred with sodium hydride at room temperature, a single and neutral substance (**8**), mp 148—149°, was obtained in 67% yield after

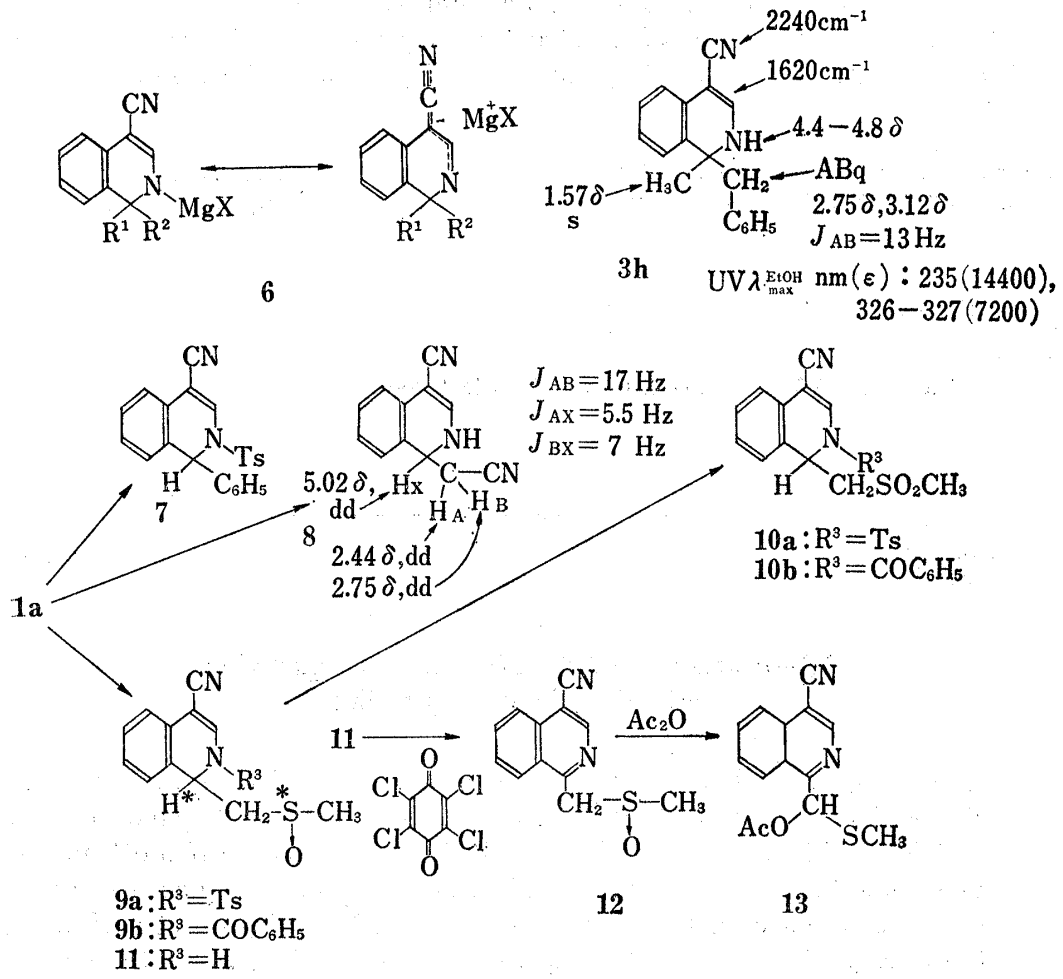

Chart 2

6) M. Natsume and I. Utsunomiya, *Chem. Pharm. Bull.* (Tokyo), **20**, 1595 (1972).
7) H. Normant, *Angew. Chem.* (*Int. Engl. Ed.*), **6**, 1046 (1967).

a simple work-up. Its IR spectrum showed the presence of two kinds of nitrile group at 2256 and 2202 cm^{-1}, and also a characteristic band for -NH-CH=C-CN was observed at 1616 cm^{-1}, suggesting that the product was the dihydro addition derivative. The structure of **8** for the neutral product was definitely established from the NMR pattern of ABX type, whose proton of X part could be assigned to C-1 (H) from the comparison of its chemical shifts (5.02 δ) to those of the corresponding Grignard products (**3a**: 4.79 δ; **3b**: 4.58 δ; **3d**: 4.76 δ). This reaction clearly suggests that **1a** is very susceptible to the nucleophile and a carbanion derived from acetonitrile interacts with **1a** under a very mild condition, so that we next turned our interest to the reaction of **1a** with sodium methylsulfinylmethide for the purpose of isolating the intermediate (**11**), corresponding to the first step proposed for Russel's methylation reaction of isoquinoline.[8]

1a was reacted with methylsulfinylcarbanion in DMSO at room temperature, and for the convenience of ready isolation, the adduct was directly converted to its N-tosylate (**9a**) or N-benzoate (**9b**), either of which was a mixture of diastereoisomers originating from the sulfoxide and C-1 position of 1,2-dihydroisoquinoline. **9a** was successfully separated into each isomer in pure state; $\mathbf{9a_1}$, mp 186° (10% yield from **1a**) and $\mathbf{9a_2}$ as a syrup (17% yield), whereas **9b**, mp 201—204°, obtained in 33% yield from **1a**, remained to be a mixture even after careful preparative thin-layer chromatography, and yet it was oxidized to a single sulfone (**10b**) with *m*-chloroperbenzoic acid. Similar oxidation of each isomer of the tosylates, $\mathbf{9a_1}$ and $\mathbf{9a_2}$, produced the same compound (**10a**), demonstrating their diastereoisomeric nature. Hydrolysis of **9b** with methanolic potassium hydroxide gave the desired compound (**11**), mp 204—207°, in 70% yield, whose structure was proved by its transformation to the Pummerer rearrangement product (**13**), mp 117—118°, by way of **12**, mp 159—159.5°.

Research Foundation ITSUU Laboratory
Tamagawa 2-28-10, Setagaya-ku, Tokyo

MITSUTAKA NATSUME
MORITAKA WADA

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8) G.A. Russel and S.A. Weiner, *J. Org. Chem.*, **31**, 248 (1966).

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UDC 547.833.3.057

1,1-Disubstituted 1,2,3,4-Tetrahydroisoquinoline Derivatives from Isoquinolines

In the preceding paper,[1] one of us reported the preparation of various kinds of 1,1-disubstituted isoquinolines (**2**) starting from the readily available 4-cyanoisoquinolines (**1**). When this fact is considered with previous finding[2] concerning the photochemical reaction of **1**, we can conclude that the cyano function in **1** behaves as a strong activating group over isoquinolines, due to the accumulation of the electron-withdrawing effect both of the cyano group and the nitrogen in the aromatic ring toward C-1 position, where the nucleophilic or photochemical addition reaction takes place quite easily, and furthermore, the presence of

1) M. Natsume and M. Wada, *Chem. Pharm. Bull.* (Tokyo), **20**, 1589 (1972).
2) M. Natsume and M. Wada, *Tetrahedron Letters*, **1971**, 4503.