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°.

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

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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.

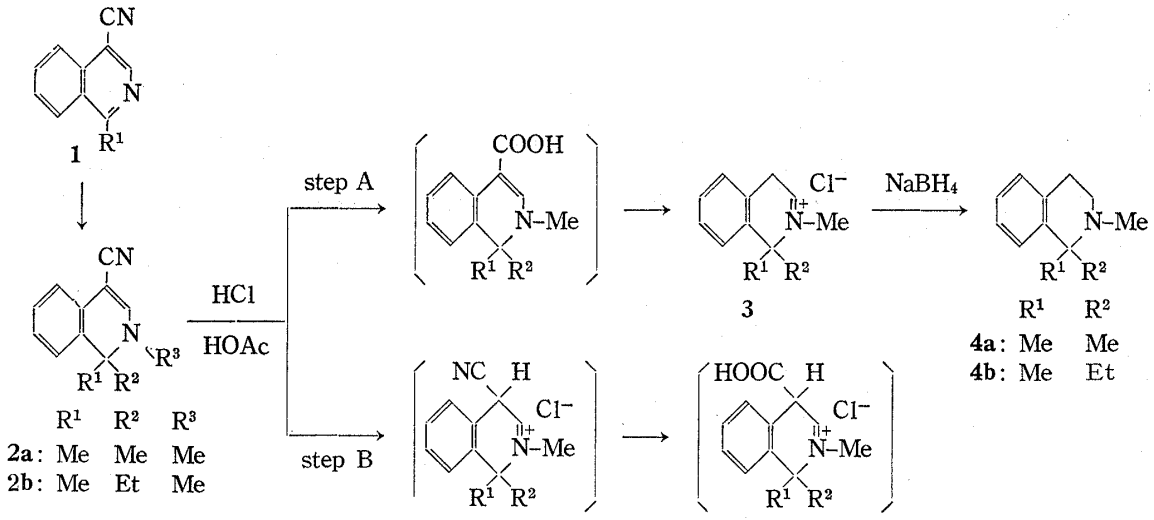

Chart 1

the cyano group enables production of a number of substances otherwise inaccessible, whose 1,2-dihydro structure is stabilized by the vinylogous cyanamide character, and the undesirable reaction can be avoided and isolation of the product made possible. Now, in this paper, we wish to report the removal of the activating function from the reaction product by two different ways, furnishing a route for the synthesis of the title compounds.

In the case of **2** with the N-alkyl function, a solution of **2a** or **2b** in a 1:1 mixture of conc. hydrochloric acid and glacial acetic acid was treated under reflux condition for several hours, on the assumption that the acid hydrolysis of the cyano group (step A) might predominate over the preliminary protonation (step B), and induce the spontaneous decarboxylation and protonation of the resulting enamine to end up with the formation of the quaternary salt (**3**). Without any purification, the salt was subjected to reduction with sodium borohydride in methanol and the tertiary amine (**4a**) or (**4b**) was obtained as an oil in 47% or 40% yield, whose structure was established as the desired 1,1-dialkyltetrahydroisoquinoline from its nuclear magnetic resonance (NMR) spectra together with the elemental analysis data of the respective picrates, **4a**-picrate, mp 146.5—147.5° and **4b**-picrate, mp 160—161°.

Another series of reaction for elimination of the cyano group originated from the model experiment, where the alkaline hydrolysis of 4-cyano-2-tosyl-1,2-dihydroisoquinoline (**2c**) was the key reaction. While Yamada and his co-workers[3] announced the formation of 4-cyano-1,2-dihydroisoquinoline (**5**) by the sodium borohydride reduction of **1** (R^1=H) in pyridine, we achieved the same partial reduction to **5** by carrying out the catalytic hydrogenation of **1** over 10% palladium-carbon at 20° under atmospheric pressure, keeping mind on the previous work[4] relating to the partial hydrogenation of 3-acetyl-, 3-alkoxycarbonyl-, and other 3-substituted pyridines. Tosylation or mesylation of **5** was effected by treatment with sodium hydride in dimethylformamide, followed by the addition of tosyl chloride or mesyl chloride, affording **2c**, mp 142—143°, and **2d**, mp 130.5—131°, in 63% and 59% yields, respectively.

2c was heated in a solution of *ca.* 15% potassium hydroxide in aqueous ethylene glycol in an oil bath of 160—170° for a few hours and after acidification, a carboxylic acid (**6c**: R^1=R^2=H, R^3=Ts), IR ν_{CO}^{KBr} 1702 cm^{-1}, was obtained as a sole reaction product (Table I). Treatment of **6c** with diazomethane in a short period converted the acid into its methyl ester (**7**),

3) S.-I. Yamada, H. Kikugawa, I. Saito, M. Kuramoto, and H. Watanabe, *Abstr. Papers, 2nd Symp. Heterocyclic Chemistry*, **1969**, 54.

4) M. Frifelder, *J. Org. Chem.*, **29**, 2895 (1964); P.M. Quan and L.D. Quinn, *ibid.*, **31**, 2487 (1966); E. Wenkert, K.G. Dave, F. Haglid, R.G. Lewis, T. Oishi, R.V. Stevens, and M. Terashima, *ibid.*, **33**, 747 (1968).

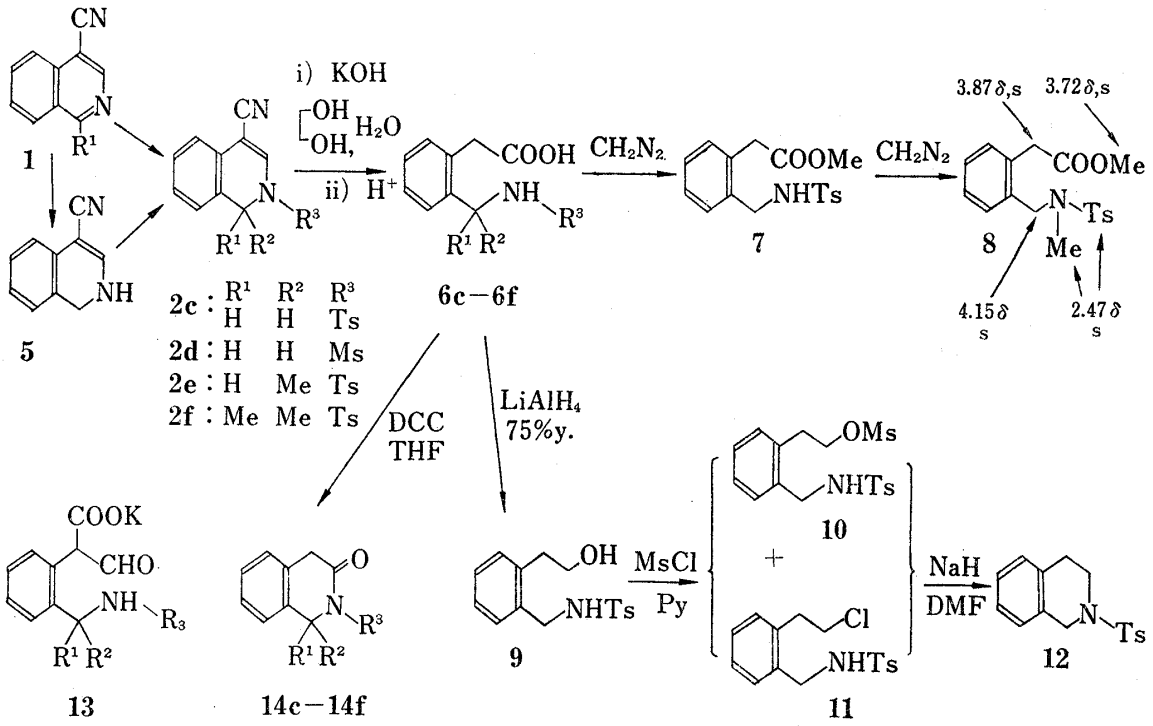

Chart 2

mp 104—105°, IR ν_{CO}^{KBr} 1739 cm^{-1}, in 90% yield. A singlet signal of two protons at 3.58 δ, a doublet signal of two protons at 4.12 δ (J=6 Hz), and a diffuse triplet between 5.2 and 5.6 δ are visible in its NMR spectrum, in addition to the expected methyl proton signals of the ester (3.67 δ) and the tosyl group (2.27 δ); and it is characteristic of noticing that the diffuse triplet signal was exchangeable with deuterium and at the same time the doublet at 4.12 δ collapsed to a singlet by the addition of deuterium oxide, implying the presence of a partial structure of -CH_2-NH-. The NH group was methylated with diazomethane by prolonged treatment to afford **8**, mp 84.5—85.5°, in 76.5% yield and its NMR signals described beside the formula support the assumed structure not only of **8** but of **6c**.

The conclusive evidence for the structure of **6c** was obtained by its transformation to the known substance[5] (**12**), mp 145—146°, *via* **9**, mp 97—98°, **10**, mp 86.5—87.5°, and **11**, mp 87—87.5°. Mesylation of **9** always gave rise to a mixture of **10** and **11**, but the ring closure to **12** was best effected by the direct treatment of the mixture with a strong base, in an overall yield of 78.5%. The same alkaline hydrolysis of **2d** produced the mesyl derivative (**6d**: R^1=R^2=H, R^3=Ms), IR ν_{CO}^{KBr} 1726 cm^{-1}, NMR (10% CD_3OD–$CDCl_3$) δ: 2.82 (3H, s, -SO_2CH_3), 3.73 (2H, s, -$C\underline{H}_2COOH$), 4.32 (2H, s, -$C\underline{H}_2NHMs$), and now the preparation of

Table I. Preparation of **6c—6f** from **2c—2f** and Their Conversion to **14c—14f**

	mp (°C)	Yield (%)		mp (°C)	Yield (%)
6c	157—158.5	65	**14c**	198—199	77
6d	128—129	65	**14d**	98—99.5	71
6e	166—167	31	**14e**	173—174	59
6f	174—175	36	**14f**	157.5—158.5	65

c: R^1=R^2=H, R^3=Ts; d: R^1=R^2=H, R^3=Ms; e: R^1=H, R^2=Me, R^3=Ts; f: R^1=R^2=Me, R^3=Ts

5) F.G. Holliman and F.G. Mann, *J. Chem. Soc.*, **1942**, 737; G.R. Proctor and R.H. Thompson, *ibid.*, **1957**, 2302; G. Hazebroucq and J. Gardart, *C.R.*, **257**, 923 (1963).

other acids (**6e**: R^1=H, R^2=Me, R^3=Ts; and **6f**: R^1=R^2=Me, R^3=Ts) was analogously possible from the corresponding Grignard products (**2e** and **2f**), the intermediate such as **13** being conceivable during the course of the hydrolysis. Synthesis of the N-sulfonyl-1,2,3,4-tetrahydroisoquinoline derivatives (**14**) from **6** was accomplished by means of dicyclohexylcarbodiimide as shown in Table I, and among them, **14d** (R^1=R^2=H, R^3=Ms) was the model compound for the successful Wittig reaction on the N-sulfonyl lactam grouping,[6] aiming at the functionalization of the lactam-carbonyl in the six-membered ring.

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6) M. Natsume, M. Takahashi, K. Kiuchi, and H. Sugaya, *Chem. Pharm. Bull.* (Tokyo), **19**, 2648 (1971).

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Formation of 3-Cyano-1,4-dihydroquinolines and Their Conversion to Indole Derivatives

In order to extend our knowledge about the formation of stable dihydro heteroaromatic amines and to develop their application to the field of synthetic chemistry, we have taken up the quinoline series and at first refer to the Grignard reaction of 3-cyanoquinoline[1] (**1a**) and its alkyl derivative (**1b**), position of the cyano group in which corresponds to that of 4-cyanoisoquinolines reported in another paper.[2]

Two reaction sites, C-2 and C-4 positions, are conceivable in the quinolines, but the Grignard reaction proceeded exclusively at C-4 to afford a single product, though the dihydro addition product (**2**) was not so stable as that of isoquinoline derivatives, and it was necessary to convert **2** immediately either to the alkylated quinolines (**1b**,[3] mp 144—144.5°; **1c**, mp 77—78°; 68% and 72% yields from **1a**) by dehydrogenation with chloranil or to the N-tosyl derivatives (**3a**, mp 130—131°, 30% from **1a**; **3b**, mp 174—175.5°, 8% yield from **1b**), the latter being obtainable only by tosylation with powdered potassium hydroxide in hexamethylphosphoric triamide.[4] The position where the reaction took place was proved by the transformation of **1b** to lepidine (**4**) by alkaline hydrolysis of the cyano function, followed by decarboxylation. In contrast to obtaining **3b** in a poor yield due to the extremely unstable character of **2b**, it was quite surprising and inexplicable at the present time to realize that the dihydro product (**2c**), mp 140—141° was stable enough to be isolated in 57% yield and further methylated, benzoylated, or tosylated in a usual manner to form **3c**, mp 80—81.5°, **3d**, mp 126—126.5°, or **3e**, mp 125—126°, in respective yield of 63%, 60.5%, or 53%. The structure of 1,4-dihydroquinoline derivatives thus synthesized was supported by the

1) H.E. Jansen and J.P. Wibaut, *Rec. Trav. Chim.*, **56**, 709 (1937); H. Gilman and S.M. Spatz, *J. Am. Chem. Soc.*, **63**, 1553 (1941); F. Zymalkowski and P. Tinapp, *Ann.*, **699**, 98 (1966).
2) M. Natsume and M. Wada, *Chem. Pharm. Bull.* (Tokyo), **20**, 1589 (1972).
3) L. Marion and R.H.F. Manske, *Can. J. Chem.*, **24B**, 224 (1946).
4) F.L. Hahn and H. Walter [*Ber.*, **54B**, 1531 (1921)] prepared alcohol tosylates by using powdered potassium hydroxide in ether.