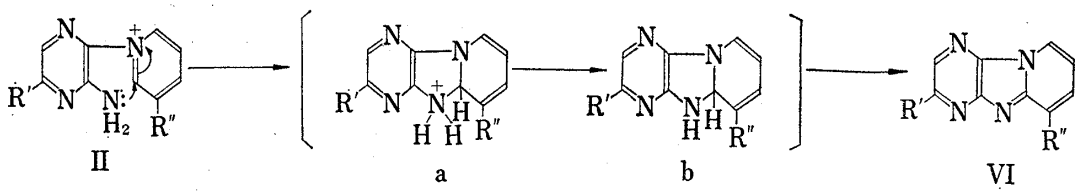

Chart 3

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Synthesis of 3*H*-4,5-Dihydro-3-benzazepine Derivatives from Isoquinolines

Recently, we have been much interested in the formation and application of various kinds of stable dihydro-heteroaromatic amines, prepared ionically[1,2] or photochemically[3] from aromatic N-heterocycles possessing an electron-withdrawing group at the position β to the ring nitrogen, and have achieved the conversion of the stable dihydroquinolines into indole derivatives as reported in a previous paper.[2] We wish to describe here the ring expansion[4] of the isoquinoline system to 3*H*-4,5-dihydro-3-benzazepine derivatives (**2**, **3**, **5**) by utilizing the rearrangement through the carbonium ion initiated at the carbinol function of the photo-addition product (**1**).[3]

Mono-O-mesylation was effected when the photo-induced addition product (**1a**) between 4-cyanoisoquinoline and methanol was treated with mesyl chloride in a benzene-pyridine mixture at room temperature for a short period. The resulting mesylate was warmed, without further purification, with sodium methoxide in methanol at 60° for 2 hr, and comparison of the ultraviolet (UV) absorption spectrum (Table I) of the reaction product (**2a**) with the accumulated UV data of both the photo-addition product (**1**) and Grignard reaction products[1] (**4**) (Table II) suggested that the environment of the conjugated system was different from the original 1,2-dihydroisoquinolines, and the deuterium exchange study of NH in its nuclear magnetic resonance (NMR) spectrum clearly indicated the presence of the partial structure of CH_3O-$\dot{C}$H-CH_2-NH-CH=C$<$ in **2a** by the collapse of the doublet signal at 7.05 δ shown in the Table I to a singlet, as well as the appearance of the AB part of ABX pattern

1) M. Natsume and M. Wada, *Chem. Pharm. Bull.* (Tokyo), **20**, 1589 (1972).
2) M. Natsume and I. Utsunomiya, *Chem. Pharm. Bull.* (Tokyo), **20**, 1595 (1972).
3) M. Natsume and M. Wada, *Tetrahedron Letters*, **1971**, 4503.
4) Ring enlargement of 3,4-dihydroisoquinolinium salt and the 1,2,3,4-tetrahydroisoquinoline derivative was reported. *cf.* H.O. Bernhard and V. Snieckus, *Tetrahedron*, **27**, 2091 (1971); H. Irie, S. Tani, and H. Yamase, *Chem. Commun.*, **1970**, 1713.

signals from the multiplet of 3.34—4.00 δ to be interpreted as H_A: 3.43 δ, dd; H_B: 3.78 δ, dd; H_X: 4.55 δ, dd; J_{AB}=13.5 Hz, J_{AX}=1.5 Hz, J_{BX}=6.0 Hz. Two directions (paths a and b) are anticipated for the rearrangement to the 3-benzazepine derivative from isoquinoline and the nitrogen migration is predominant in the above case. Similar reaction of the mesylate of **1b** was carried out at room temperature which afforded **2b**, and its structure was also found to be an analogous product by examination of its UV, IR, and NMR spectra.

An attempt was made to find a general reaction condition in order to extend the above dihydrobenzazepine synthesis to other nucleophiles and it was concluded that warming the

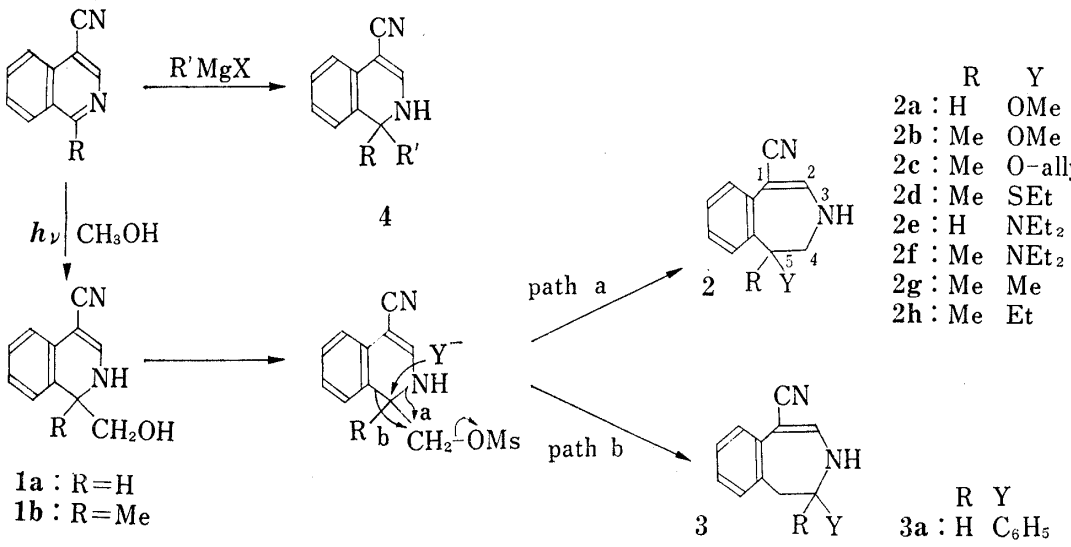

Chart 1

TABLE I

	mp (°C)	Yield (%)	UV λ_{max}^{EtOH}nm(ε)	IR ν_{max}^{KBr}cm^{-1} CN	IR >C=C<	NMR ($CDCl_3$) δ R	NMR C-4 (H)	NMR $NH^{a)}$	NMR C-2 (H)$^{b)}$
2a	160—161	47	215 (16300) 252 (5600) 310 (12600)	2198	1619	4.55 dif. d	3.34—4.00 m	5.62	7.05
2b	141—143	47	218 (18900) 253 (5400) 308 (13300)	2200	1620	1.42 s	3.30, dd[c,d,e] 3.54, dd	5.62	7.01
2c	syrup	72	—	2200	1632 1621	1.48 s	3.47, d[f]	5.56	7.06
2d	syrup	55	—	2205	1638	1.72 s	3.44, dd[c,d,e] 3.53, dd	5.70	7.10
2e	syrup 204—205.5[g]	75	—	2201[g]	1641[g]	4.08 dif. d[h]	3.56 dif. t[f,h]	5.42	7.20
2f	syrup 129.5—131[g]	62	—	2200[g]	1623[g]	1.30 s	3.30, d[f]	5.71	7.05
2g	174—175	71	216 (16100) 253 (4800) 307 (13700)	2190	1623	1.35 s	3.23, d[f]	5.50	7.05
2h	156—157.5	34	217 (16200) 250 (5100) 309 (13000)	2198	1634	1.36 s	3.67, dd[c,d,e] 3.84, dd	5.40	7.01
3a	185—186	23	—	2196	1616	4.64 m	3.26[i], d[h]	5.36	7.08

a) broad multiplet; *b*) doublet, $J_{2,NH}$=7.0—8.0 Hz; *c*) $J_{4A,4B}$=13.0—14.0 Hz; *d*) $J_{4A,NH}$=4.5—5.5 Hz; *e*) $J_{4B,NH}$= 4.0—4.5 Hz; *f*) $J_{4,NH}$=5.0—5.5 Hz; *g*) data of picrate; *h*) $J_{4,5}$=5.0 Hz; *i*) C-5 (H)

Table II. UV Absorption Spectral Data of **1** and **4**

	R	R′	λ_{max}^{EtOH} nm (ε)
1a	H	—	238 (16100), 327 (7800)
1b	Me	—	236 (15900), 328 (7200)
4a	H	Me	235 (14500), 327 (7900)
4b	H	Et	237 (13800), 326 (9000)
4c	Me	Me	236 (14900), 325 (8400)
4d	Me	Et	238 (14700), 326 (7300)

mesylates from **1a** or **1b** in methanol at 65° for 45 min in the presence of potassium hydroxide was sufficient to produce **2a** or **2b** in 54 or 57% yield. Therefore, an analogous ring expansion reaction was accomplished with allyl alcohol, diethylamine, or ethanethiol in place of methanol and its result is summarized in Table I.

The above knowledge was extended to an aprotic nucleophilic reaction and simultaneous formation of a carbon-carbon bond in the dihydro-3-benzazepine system was also possible by the Grignard reaction on the mesylate of **1a** and **1b**, accompanied by a ring rearrangement. Thus, **2g**, **2h**, and **3a** were isolated as major products from a mixture of the substances produced by paths a and b, and it was noted that the benzene migration path was predominant in the case of the phenyl-Grignard. For the second approach to the rearrangement in an aprotic solvent, we next studied the constrained abstraction of sulfonic acid from the O-tosylate of **1b**, mp 117.5—118.5°, and the mesylate of **1c**, by heating in pyridine under reflux[5] and observed the formation of dihydro-3-benzazepine derivatives having an *exo*-methylene double bond; **5a**, mp 132—133°, IR ν_{max}^{KBr} cm^{-1}: 2180, 1635, 1618; UV λ_{max}^{EtOH} nm (ε): 222 (14000), 251 (18300), 306 (9500); NMR ($CDCl_3$) δ: 3.98 (2H, d, J=4.5 Hz, s with the deuterium exchange of NH, -C<u>H</u>$_2$-NH-), 5.19, d and 5.49, d (J=1 Hz, CH_2=C<), 6.08 (br. m, NH), 7.07 (d, J=8 Hz, =C<u>H</u>-NH-), and **5b**, mp 139—140°, IR ν_{max}^{KBr} cm^{-1}: 2183, 1631, 1608; UV λ_{max}^{EtOH} nm (ε): 219 (30300), 246 (sh, 23600), 303 (13300); NMR ($CDCl_3$) δ: 1.12 (3H, d, J=6.5 Hz, C<u>H</u>$_3$-CH<), 4.25 (1H, dif. quintet, q with the deuterium exchange of NH, J=6.5 Hz, CH_3-C<u>H</u>-NH-), 5.13, d and 5.23, d (J=1.5 Hz, C<u>H</u>$_2$=C<), 5.90 (br. m, NH), 6.95 (d, J=7.5 Hz, =CH-NH-). The fundamental structure of **5a** and **5b** was found to be the nitrogen-migrated product, mostly by applying the above argument of their NMR spectra. Further investigation for developing the application of the present ring expansion reaction is in progress and detailed discussion of assumed factors regulating the paths a and b will be reported in a forthcoming full paper.

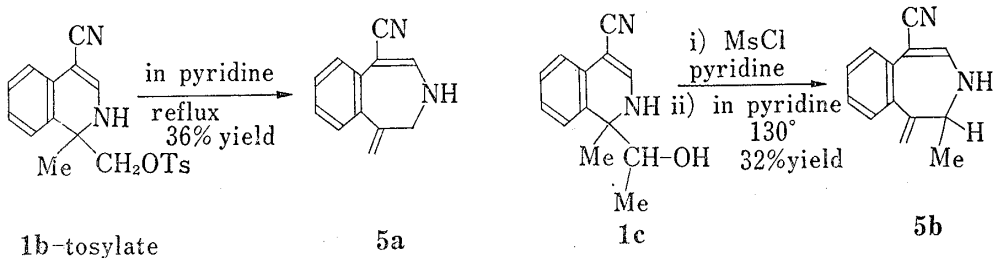

Chart 2

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5) A similar rearrangement was reported in the case of pyridine. T.J. van Bergen and R.M. Kellogg, *J. Org. Chem.*, **36**, 978 (1971).