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Reaction of 1-Alkyl-3,4-dihydroisoquinolines with 4-Nitrobenzoyl Cyanide and Diketene[1,2]

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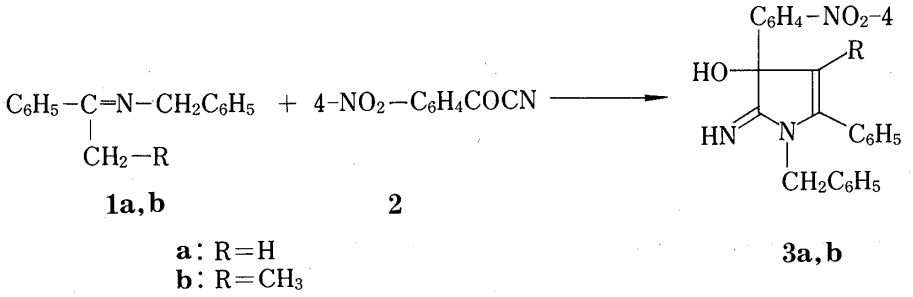
The reactions of 1-alkyl-3,4-dihydroisoquinolines (**4a—d**) with 4-nitrobenzoyl cyanide (**2**) gave the indolizine derivatives **5a—c** and **6d**, respectively. Compounds **4a** and **4b** also reacted with diketene (**8**) to give the quinolizinone derivatives **9a**, **b**, respectively.

Keywords——enamine-imine prototropy; 1-alkyl-3,4-dihydroisoquinoline; 4-nitrobenzoyl cyanide; diketene; cyclization

In the previous paper,[3] we reported the reaction of *N*-(1-phenylalkylidene)benzylamine (**1a**, **b**) with 4-nitrobenzoyl cyanide (**2**) to give 4,5-dihydropyrrole derivatives, **3a**, **b**, respectively. The reaction involves the cyclization of **2** with the active methyl or methylene group of **1** accompanied with prototropy to give 4,5-dihydropyrrole derivatives. The reactivity of the active methyl or methylene group of cyclic compounds such as 1-alkyl-3,4-dihydroisoquinolines also has some precedents.[4] The subject of the present paper is thus the reaction of 1-alkyl-3,4-dihydroisoquinolines (**4a—d**) with **2** and diketene (**8**).



1a,b **2** **3a,b**

a: R=H
b: R=CH_3

Chart 1

First, the reaction of 1-ethyl-3,4-dihydroisoquinoline (**4b**) with **2** in benzene afforded 3-imino-1-methyl-2-(4-nitrophenyl)-2,3,5,6-tetrahydrobenzo[*g*]indolizin-2-ol (**5b**) in 49% yield. The structure of **5b** was confirmed by comparison of its spectral data with those of **3b**,[3] whose structure was determined by X-ray crystallographic analysis (see Table I).

In particular, the chemical shifts in the ^{13}C-nuclear magnetic resonance (NMR) spectrum of **5b** are similar to those of **3b**: a singlet peak at 83.6 ppm due to the quaternary carbon, a singlet peak at 115.1 ppm due to the olefinic carbon, and a singlet peak at 174.1 ppm due to the imino carbon. Compound **5b** was converted to the benzoylate (**7**) by treatment with benzoyl chloride.

Similar reactions of 1-methyl-3,4-dihydroisoquinoline (**4a**) and 1-benzyl-3,4-dihydroisoquinoline (**4c**) with **2** afforded 2,3,5,6-tetrahydrobenzo[*g*]indolizin-2-ols, **5a** (69%) and **5c** (58%), respectively. The reaction of 1-propyl-3,4-dihydroisoquinoline (**4d**) with **2** under the same conditions gave rise to **6d** *via* the adduct **5d**. The structures of the products **5a**, **c**,

TABLE I. Spectral Data for **3b** and **5b**

Compd.	UV $\lambda_{max}^{EtOH}(\varepsilon)$ [$\lambda_{shoulder}^{EtOH}(\varepsilon)$]	IR ν_{max}^{KBr} cm^{-1}	^{1}H-NMR δ (in $CDCl_3$)	^{13}C-NMR δ (in $CDCl_3$)
3b[a]	270 (7300)	3390 (O–H)	1.39 (s, CH_3)	8.4 (s, CH_3)
		3290 (N–H)	6.12 (NH, OH)	82.2 (s, C–OH)
		1638 (C=N)		117.0 (s, =C–CH_3)
		1130 (C–O)		175.6 (s, C=NH)
5b	240 (14200)	3390 (O–H)	1.83 (s, CH_3)	9.9 (s, CH_3)
	[270 (7900)]	3290 (N–H)	5.19 (NH, OH)	83.6 (s, C–OH)
		1655 (C=O)		115.1 (s, =C–CH_3)
		1159 (C–O)		174.1 (s, C=NH)

a) This compound has been reported in the literature.[3]

and **6d** were fully supported by comparison of their spectral data (see "Experimental") with those of 4,5-dihydropyrrole derivatives (**3a, b**).[3]

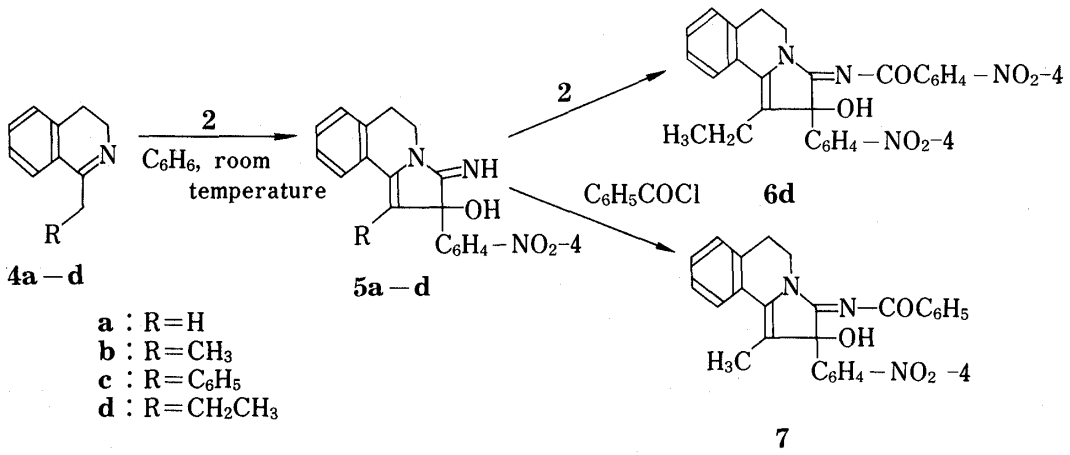


Chart 2

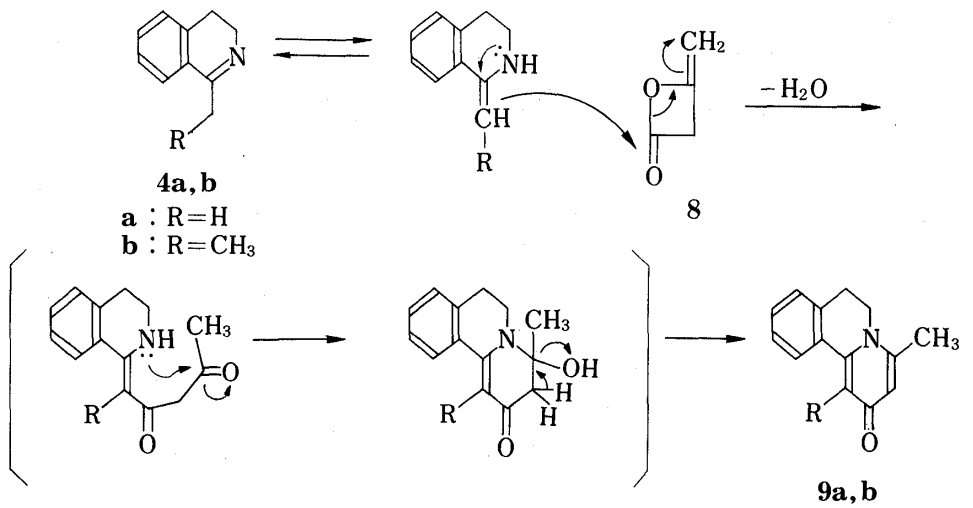


Chart 3

It has been reported that diketene (**8**) reacts with ketimines possessing an active methyl or methylene group such as ketone anils[5] to give heterocyclic compounds. Similarly, the reaction of **8** with 2-pyridyl acetonitrile[6] and 2-alkyl-2-imidazolines[7] gives pyridine derivatives. Thus, we investigated the reaction of **4a**, **b** with **8**. Heating of **4a** with **8** gave a tricyclic compound, 2*H*-6,7-dihydro-4-methylbenzo[*a*]quinolizin-2-one (**9a**) in 37% yield. Similar reaction of **4b** with **8** gave 2*H*-6,7-dihydro-1,4-dimethylbenzo[*a*]quinolizin-2-one (**9b**) in 44% yield.

The strucrure of **9a** was ascertained from spectral data. In particular, the infrared (IR) band at 1628 cm^{-1} indicates a 4-pyridone system. This is also supported by a characteristic coupling constant ($J=3$ Hz) between hydrogens in the α-position with respect to the carbonyl group in the ^{1}H-NMR spectrum, and by the two doublet peaks at 114.0 and 118.7 ppm corresponding to the carbons of the 4-pyridone system in the ^{13}C-NMR spectrum.

Further work using conjugated nitriles for the preparation of other heterocyclic compounds is in progress.

Experimental

All melting points were measured with a Yanaco MP-3 apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on JEOL PS-100 and JEOL FX-60 spectrometers, respectively. Chemical shifts are given in δ-values referred to internal tetramethylsilane. Mass and IR spectra were taken on JEOL D-300 and JASCO DS-701G instruments, respectively.

Reaction of 1-Methyl-3,4-dihydroisoquinoline (4a) with 4-Nitrobenzoyl Cyanide (2)——A mixture of 0.83 g (5.72 mmol) of **4a** and 1.00 g (5.68 mmol) of **2** in 20 ml of dry benzene was stirred for 4 h at room temperature, then the precipitate was collected by filtration. Recrystallization from MeOH gave 1.25 g (69%) of 3-imino-2-(4-nitrophenyl)-2,3,5,6-terahydrobenzo[*g*]indolizin-2-ol (**5a**) as yellow plates, mp 149—150 °C. *Anal.* Calcd for $C_{18}H_{15}N_3O_3$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.13; H, 4.64; N, 13.01. UV λ_{max}^{EtOH} (ε): 247 (26000), 270 (sh, 13100). IR ν_{max}^{KBr} cm^{-1}: 3410 (br, O–H), 3290 (N–H), 1645 (C=C and C=N), 1514 and 1344 (NO_2), 1155 (C–O). ^{1}H-NMR (in DMSO-d_6): 2.98 (2H, m with t-character, $J=6$ Hz, 2H–C (6)), 3.28 (1H, br, OH, D_2O-erasable), 3.39 (1H, dt, $J_1=12$ Hz, $J_2=6.5$ Hz, H–C (5)), 3.76 (1H, dt, $J_1=12$ Hz, $J_2=6$ Hz, H–C (5)), 5.78 (1H, s, H–C (1)), 6.53 (1H, s, NH, D_2O-erasable), 7.20—7.85 (4H, m, H–C (7), H–C (8), H–C (9), and H–C (10)), 7.67 and 8.20 (4H, each d, $J=9$ Hz, 4H in a phenyl group). ^{13}C-NMR (in DMSO-d_6): 28.1 (t, C (6)), 37.3 (t, C (5)), 80.4 (s, C (2)), 103.2 (d, C (1)), 123.3, 125.1, 126.4, 126.7, 128.7, and 129.4 (6d, 8C in aromatic rings), 125.9, 134.8, 141.2, 146.6, and 150.4, (5s, C (6a), C (10a), C(10b), 2C in a phenyl group), 173.2 (s, C (3)). MS *m/e*: 321 (M^+), 199 ($M^+-C_6H_4NO_2$).

Reaction of 1-Ethyl-3,4-dihydroisoquinoline (4b) with 2——A mixture of 1.81 g (11.4 mmol) of **4b** and 2.00 g of (11.4 mmol) of **2** in 50 ml of dry benzene was stirred for 4 h at room temperature, then the precipitate was collecred by filtration. Recrystallization from EtOH gave 1.87 g (49%) of 3-imino-1-methyl-2-(4-nitrophenyl)-2,3,5,6-tetrahydrobenzo[*g*]indolizin-2-ol (**5b**) as yellow crystals, mp 256—258 °C. *Anal.* Calcd for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 67.95; H, 5.00; N, 12.60. UV λ_{max}^{EtOH} (ε): 240 (14200), 270 (sh, 7900). IR ν_{max}^{KBr} cm^{-1}: 3390 (br, O–H), 3290 (N–H), 1655 (C=C and C=N), 1511 and 1343 (NO_2), 1159 (C–O). ^{1}H-NMR (in $CDCl_3$): 1.83 (3H, s, H_3C–C (1)), 2.96 (2H, m with t-character, $J=6$ Hz, 2H–C (6)), 3.48—3.87 (2H, m, 2H–C (5)), 5.19 (2H, br, NH and OH, D_2O-erasable), 7.22—7.70 (4H, m, H–C (7), H–C (8), H–C (9), and H–C (10)), 7.45 and 7.98 (4H, each d, $J=$ 9 Hz, 4H in a phenyl group). ^{13}C-NMR (in $CDCl_3$): 9.9 (q, CH_3), 30.0 (t, C (6)), 38.4 (t, C (5)), 83.6 (s, C (2)), 115.1 (s, C (1)), 123.7, 126.2, 126.9, and 128.9 (4d, C (7), C (8), C (9), C (10), and 4C in a phenyl group), 127.6, 134.0, 135.7, 147.6, and 148.1 (5s, C (6a), C (10a), C (10b), and 2C in a phenyl group), 174.1 (s, C (3)). MS *m/e*: 335 (M^+), 320 (M^+-CH_3), 213 ($M^+-C_6H_4NO_2$).

Benzoylation of 5b——A solution of 1.00 g (3.0 mmol) of **5b** in 50 ml of Et_2O was poured into 50 ml of 10% sodium bicarbonate solution, then a solution of 0.42 g (3.0 mmol) of benzoyl chloride in 20 ml of Et_2O was added. The reaction mixture was shaken thoroughly for several minutes. The precipitate was collected by filtration, yielding 1.09 g (84%) of 3-benzoylimino-1-methyl-2-(4-nitrophenyl)-2,3,5,6-tetrahydrobenzo[*g*]indolizin-2-ol (**7**) as yellow crystals, mp 205—206 °C. *Anal.* Calcd for $C_{26}H_{21}N_3O_4$: C, 71.06; H, 4.82; N, 9.56. Found: C, 71.36; H, 4.71; N, 9.67. IR ν_{max}^{KBr} cm^{-1}: 3400 (br, O–H), 1578 (C=O), 1543 (C=N), 1520 and 1345 (NO_2). ^{1}H-NMR (in DMSO-d_6): 1.79 (3H, s, H_3C–C (1)), 3.00—3.22 (3H, m, 2H–C (6) and OH), 3.82—4.18 (2H, m, 2H–C (5)). MS *m/e*: 439 (M^+), 334 ($M^+-C_6H_5CO$), 105 ($C_6H_5CO^+$).

Reaction of 1-Benzyl-3,4-dihydroisoquinoline (4c) with 2——A mixture of 2.20 g (10 mmol) of **4c** and 1.85 g (10.5 mmol) of **2** in 100 ml of dry Et_2O was stirred for 3 h at room temperature. After cooling of the reaction mixture, the precipitate was collected by filtration. Recrystallization from EtOH gave 2.30 g (58%) of 3-imino-2-(4-nitrophenyl)-1-phenyl-2,3,5,6-tetrahydrobenzo[*g*]indolizin-2-ol (**5c**) as yellow crystals, mp 174—175 °C. *Anal.* Calcd

for $C_{24}H_{19}N_3O_3$: C, 72.53; H, 4.82; N, 10.57. Found: C, 72.75; H, 4.69; N, 10.63. IR ν_{max}^{KBr} cm^{-1}: 3400 (br, O–H), 3280 (N–H), 1642 (C=C and C=N), 1514 and 1343 (NO_2), 1153 (C–O). ^{1}H-NMR (in $CDCl_3$): 2.82—3.12 (2H, m, 2H–C (6)), 3.25—3.58 and 3.77—4.05 (2H, 2m, 2H–C (5)), 5.8—6.6 (1H, br, OH, D_2O-erasable), 6.88—7.40 (9H, m, H–C (7), H–C (8), H–C (9), H–C (10), and 5H in a phenyl group), 7.36 (1H, s, =NH, D_2O-erasable), 7.38 and 7.94 (4H, each d, J=10 Hz, 4H in a 4-nitrophenyl group). ^{13}C-NMR (in $CDCl_3$): 29.9 (t, C (6)), 38.3 (t, C (5)), 83.8 (s, C (2)), 119.2 (s, C (1)), 123.5, 126.4, 126.6, 127.7, 128.6, and 129.6 (6d, 13C in aromatic rings), 126.4, 128.6, 133.1, 136.2, 147.4, and 148.0 (6s, C (6a), C (10a), C (10b), and 3C in aromatic rings), 174.0 (s, C (3)). MS *m/e*: 397 (M^+), 320 ($M^+ - C_6H_5$), 275 ($M^+ - C_6H_4NO_2$).

Reaction of 1-Propyl-3,4-dihydroisoquinoline (4d) with 2——A mixture of 0.99 g (5.72 mmol) of **4d** and 1.00 g (5.68 mmol) of **2** in 20 ml of dry benzene was stirred for 4 h at room temperature, then the precipitate was collected by filtration. Recrystallization from dimethylformamide (DMF) gave 0.80 g (57%) of 1-ethyl-3-(4-nitrobenzoyl)imino-2-(4-nitrophenyl)-2,3,5,6-tetrahydrobenzo[*g*]indolizin-2-ol (**6d**) as colorless prisms, mp 200—202 °C. *Anal.* Calcd for $C_{27}H_{22}N_4O_6$: C, 65.05; H, 4.45; N, 11.24. Found: C, 64.81; H, 4.48; N, 11.06. IR ν_{max}^{KBr} cm^{-1}: 3400 (br, O–H), 1584 (C=O), 1543 (C=N), 1518 and 1343 (NO_2), 1158 (C–O). ^{1}H-NMR (in $CDCl_3$): 0.97 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.75 (1H, br, OH, D_2O-erasable), 2.35 and 2.55 (2H, each dq, J_1=15 Hz, J_2=7.5 Hz, $C\underline{H}_2CH_3$), 3.24 (2H, m with t-character, J=7 Hz, 2H–C (6)), 4.12 and 4.39 (2H, each dt, J_1=14 Hz, J_2=7 Hz, 2H–C (5)). MS *m/e*: 498 (M^+), 376 ($M^+ - C_6H_4NO_2$), 348 ($M^+ - O_2NC_6H_4CO$), 150 ($O_2NC_6H_4CO^+$).

Reaction of 1-Methyl-3,4-dihydroisoquinoline (4a) with Diketene (8)——Diketene (**8**) (4.20 g, 50 mmol) was added dropwise to 1.45 g (10 mmol) of **4a** at room temperature, and then the mixture was refluxed for 1 h. After removal of excess diketene (**8**) by evaporation, the oily residue was solidified with a small amount of EtOH. Recrystallization from acetone gave 0.78 g (37%) of 2*H*-6,7-dihydro-4-methylbenzo[*a*]quinolizin-2-one (**9a**) as colorless needles, mp 176—178 °C. *Anal.* Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.60; H, 6.14; N, 6.57. IR ν_{max}^{KBr} cm^{-1}: 1628 (C=O). ^{1}H-NMR (in $CDCl_3$): 2.44 (3H, s, H_3C–C (4)), 3.10 (2H, t, J=6 Hz, 2H–C (7)), 4.09 (2H, t, J=6 Hz, 2H–C (6)), 6.31 (1H, d, J=3 Hz, H–C (3)), 6.85 (1H, d, J=3 Hz, H–C (1)), 7.20—7.48 and 7.63—7.74 (4H, 2m, aromatic-H). ^{13}C-NMR (in $CDCl_3$): 20.8 (q, CH_3), 28.5 (t, C (7)), 44.5 (t, C (6)), 114.0 and 118.7 (2d, C (1) and C (3)), 125.7, 127.6, 127.9, and 130.3 (4d, C (8), C (9), C (10), and C (11)), 129.3 and 134.2 (2s, C (7a) and C (11a)), 145.6 and 147.9 (2s, C (4) and C (11b)), 178.9 (s, C (2)). MS *m/e*: 211 (M^+), 183 ($M^+ - CO$).

Reaction of 1-Ethyl-3,4-dihydroisoquinoline (4b) with 8——Diketene (**8**) (4.20 g, 50 mmol) was added dropwise to 1.59 g (10 mmol) of **4b** at room temperature, and then the mixture was refluxed for 1 h. After evaporation of excess diketene (**8**), the brown oily residue was solidified with a small amount of EtOH. Recrystallization from acetone gave 0.99 g (44%) of 2*H*-6,7-dihydro-1,4-dimethylbenzo[*a*]quinolizin-2-one (**9b**) as colorless needles, mp 60—62 °C. *Anal.* Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.83; H, 6.67; N, 6.18. IR ν_{max}^{KBr} cm^{-1}: 1620 (C=O). ^{1}H-NMR (in $CDCl_3$): 2.36 and 2.42 (6H, 2s, H_3C–C (1) and H_3C–C (4)), 2.99 (2H, t, J=6 Hz, 2H–C (7)), 4.00 (2H, t, J=6 Hz, 2H–C (6)), 6.33 (1H, s, H–C (3)), 7.20—7.44 and 7.52—7.67 (4H, 2m, aromatic-H). MS *m/e*: 225 (M^+), 197 ($M^+ - CO$).

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References and Notes

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