mmol) of trimethylchlorosilane and 10 mL of anhydrous acetonitrile. After 1 h, the reaction mixture was poured into 100 mL of water and extracted several times with chloroform. The combined organic extracts were dried (Na_2SO_4) and evaporated in vacuo. The solid residue was recrystallized from methanol and gave 150 mg (70%) of **16d** as a colorless compound: IR (KBr) 3180, 1675, 1650, 1615 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 169.94 (Sd, C-3), 168.94 (Sm, C=O), 137.15 (Dm, C-7), 134.32 (Dd, C-5), 133.28 (St, Cs), 131.32 (Dt, *p*-C), 128.49 (D, *o*-C), 128.45 (D, C-4), 128.40 (D, *m*-C), 122.07 (Ddd, C-6).

1-(4′-Methoxybenzoyl)-1,2-dihydro-1,2-diazepin-3-one (16b). This was prepared according to the general procedure and recrystallized from ethanol: yield 60%; IR (KBr) 3180, 1675, 1650, 1615 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 170.17 (Sdd, C-3), 168.17 (Ss, C=O), 161.93 (Sm, *p*-C), 137.74 (Dm, C-7), 134.46 (Ddd, C-5), 130.91 (Dd, *o*-C), 128.54 (D, C-4), 125.03 (St, Cs), 121.52 (Ddd, C-6), 113.87 (Dd, *m*-C), 55.52 (Qs, OCH_3).

1-(4′-Ethoxybenzoyl)-1,2-dihydro-1,2-diazepin-3-one (16c). This was prepared according to the general procedure and recrystallized from ethanol: yield 65%; IR (KBr) 3200, 1660, 1620 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 170.12 (Sd, C-3), 168.07 (Sm, C=O), 161.15 (Stt, *p*-C), 137.69 (D, C-7), 134.37 (Dd, C-5), 130.86 (Dd, *o*-C), 128.49 (D, C-4), 124.80 (St, Cs), 121.43 (Ddd, C-6), 114.24 (Dd, *m*-C), 63.54 (Tq, CH_2), 14.48 (Qt, CH_3).

1-[4′-(Dimethylamino)benzoyl]-1,2-dihydro-1,2-diazepin-3-one (16a). This was prepared according to the general procedure and recrystallized from ethanol: yield 78%; IR (KBr) 3160, 1670, 1650, 1605 cm^{-1}.

1-(4′-Chlorobenzoyl)-1,2-dihydro-1,2-diazepin-3-one (16e). This was prepared according to the general procedure and recrystallized from ethanol: yield 63%; IR (KBr) 3220, 1670, 1650, 1615 cm^{-1}.

Acknowledgment. This investigation was supported by the Centre National de la Recherche Scientifique (Ph.D. Grant to J.L.S. and ATP Grant No. 3810), by the Délégation Générale à la Recherche Scientifique et Technique (Ph.D. Grant to J.C.S.), and by a NAITO Research Grant (to T.K. for 1978). We thank H. Strub for the determination and interpretation of ^{13}C NMR spectra, Mrs. M. Martigneaux for the large-scale diazepine synthesis, and Mrs. C. Strehler for analytical high-pressure LC separations. Last, but not least, we thank Dr. F. Bellamy for some fruitful discussions and especially Dr. G. Jolles and Dr. J. C. Blondel from the Rhone-Poulenc Co. for their kind collaboration.

Registry No. 7, 109-09-1; 8, 39996-52-6; **10a**, 75283-95-3; **10b**, 75283-97-5; **10c**, 75283-99-7; **10d**, 27392-03-6; **10e**, 75284-01-4; **10f**, 75284-03-6; **11a**, 75267-77-5; **11b**, 75267-78-6; **11c**, 75284-04-7; **11d**, 75267-79-7; **11e**, 75284-05-8; **11f**, 75267-80-0; **12a**, 75267-81-1; **12b**, 75267-82-2; **12c**, 75267-83-3; **12d**, 75267-84-4; **12e**, 75284-06-9; **12f**, 75267-85-5; **13**, 75267-86-6; **15a**, 75267-87-7; **15b**, 75267-88-8; **15c**, 75267-89-9; **15d**, 75267-90-2; **15d** $Fe(CO_3)$ complex, 75283-87-3; **15e**, 75267-91-3; **16a**, 75267-92-4; **16b**, 75267-93-5; **16c**, 75267-94-6; **16d**, 75267-95-7; **16e**, 75267-96-8; *p*-(dimethylamino)benzoyl chloride, 4755-50-4; *p*-methoxybenzoyl chloride, 100-07-2; *p*-ethoxybenzoyl chloride, 16331-46-7; benzoyl chloride, 98-88-4; *p*-chlorobenzoyl chloride, 122-01-0; *p*-cyanobenzoyl chloride, 6068-72-0.

Preparation of New Nitrogen-Bridged Heterocycles. Synthesis and Some Reactions of 2,3-Dihydroindolizin-2-one Derivatives

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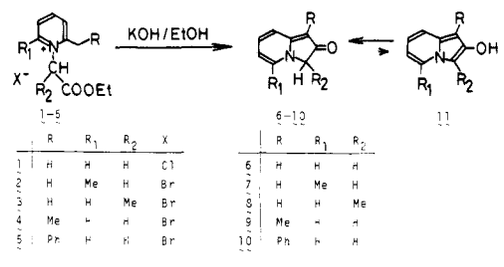
Alkaline treatment of 1-[(ethoxycarbonyl)methyl]-2-picolinium halides **1–5** in ethanol afforded the intramolecular condensation products, 2,3-dihydroindolizin-2-one derivatives **6–10**, with the formation of the pyridine base. The possibility of the aromatic enol tautomer for the structures of **6–10** was excluded completely by the inspection of their IR and NMR spectra. The reactions of dihydroindolizinones **9** and **10** and pyridinium salts **1–5** with some alkylating and acylating agents in the presence of alkali gave 3,3-dialkyl- (**19–40**) and 3-spiro-2,3-dihydroindolizin-2-ones (**45–50**) and 2-alkoxy- (**52, 53**, and **57–63**) and 2-(acyloxy)indolizines (**64** and **65**), while those with a bifunctional reagent such as diethyl (ethoxymethylene)malonate afforded tricyclic 2*H*-pyrano[2,3-*b*]indolizin-2-one derivatives **67–69**. The mechanisms of the alkylation and the acylation could be well explained by the application of the HSAB principle to the ambident anion generated by the alkaline treatment of 2,3-dihydroindolizin-2-ones **6–10**.

In recent papers[1] from our laboratory we described the first preparation of 3-methylene-2,3-dihydroindolizin-2-one derivatives by the intramolecular condensation of 1-[1-(ethoxycarbonyl)vinyl]-2-picolinium halides under basic conditions. We have been especially interested in the facile interaction between the ester carbonyl and the 2-methylene group; therefore, the possibility of replacing the 1-(ethoxycarbonyl)vinyl by an (alkoxycarbonyl)methyl group as the 1-substituent in these pyridinium salts was considered important since a similar reaction mechanism was expected to lead to the unknown parent and simple 2,3-dihydroindolizin-2-ones. Condensations between a keto group and an active methylene group in many pyridinium salts under

Scheme I



	R	R_1	R_2	X
1	H	H	H	Cl
2	H	Me	H	Br
3	H	H	Me	Br
4	Me	H	H	Br
5	Ph	H	H	Br

	R	R_1	R_2
6	H	H	H
7	H	Me	H
8	H	H	Me
9	Me	H	H
10	Ph	H	H

(1) (a) Kakehi, A.; Ito, S.; Nakanishi, K.; Kitagawa, M. *Chem. Lett.* **1979**, 297. (b) Kakehi, A.; Ito, S.; Nakanishi, K.; Watanabe, K.; Kitagawa, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1115.

0022-3263/80/1945-5100$01.00/0

basic conditions have been well established,[2] but the similar participation of an ester group instead of the keto group is less well-known. In this paper we describe the first preparation of some simple 2,3-dihydroindolizin-2-ones and their reactions with various alkylating and acylating agents leading to dihydroindolizinone and aromatic indolizine derivatives.

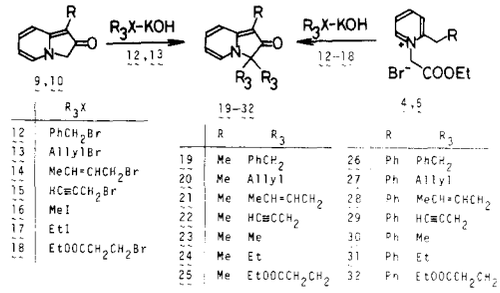
Results and Discussion

Preparations of Simple 2,3-Dihydroindolizin-2-ones. The treatment of 1-[(ethoxycarbonyl)methyl]-2-picolinium chloride (1) with aqueous potassium hydroxide in ethanol at room temperature afforded an oily compound (**6**) in only 3% yield (Scheme I) together with the formation of considerable amounts of 2-picoline (detected by TLC and its odor). Similar alkaline treatment of 1-[(ethoxycarbonyl)methyl]-2,6-lutidinium bromide (**2**), 1-[1-(ethoxycarbonyl)ethyl]-2-picolinium bromide (**3**), 1-[(ethoxycarbonyl)methyl]-2-ethylpyridinium bromide (**4**), and 1-[(ethoxycarbonyl)methyl]-2-benzylpyridinium bromide (**5**) gave the corresponding products (**7–10**) in 18–74% yield along with some pyridine bases.

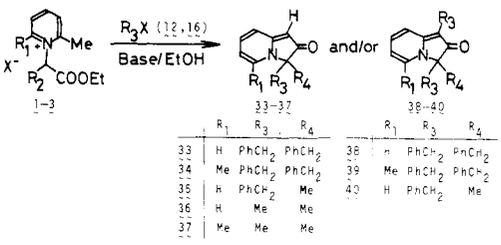
These compounds (**6–10**) were fairly stable in the cold or in ethanol but decomposed rapidly in chloroform or on standing at room temperature. The fact that **6–10** are intramolecularly condensed products was clearly shown by the molecular formulas of **9** and **10** and the disappearance of both proton signals due to the ethoxycarbonyl and 2-methyl or 2-methylene groups in the NMR spectra[3] and in part by the elemental composition analyses of crystalline products **9** and **10**.

For the structure of **6–10** an aromatic enol structure such as **11** is possible. However, the aromatic indolizine structure was excluded by the comparisons of the IR and NMR spectral data of **6–10** with those of known 3-methylene-2,3-dihydroindolizin-2-ones and aromatic indolizines.[1,4] For example, the IR spectra of **6–10** showed a very strong absorption band at 1572–1590 cm^{-1} due to a highly delocalized carbonyl group, and the NMR spectra exhibited a two-proton singlet at δ 4.06–4.36 or a quartet at δ 4.08 due to an active methylene (**6**, **7**, **9**, and **10**) or methine (**8**; exchanged by deuterium oxide), respectively. The chemical shifts (δ 4.9–7.9) of the unsaturated ring protons in **6–10** were obviously higher than those (below δ 6.5) of aromatic indolizine derivatives.[1,4] In particular, these spectral properties of **6–10** are very similar to those of 3-bis(alkylthio)methylene-2,3-dihydroindolizin-2-ones[1] but are not parallel to those of 2-(acyloxy)indolizines[4,5] and 2-alkoxyindolizines synthesized in subsequent reactions. In contrast to the exclusive aromatic enol structure in the analogous 1,2-dihydropyrazolo[1,5-*a*]pyridin-2-one,[6] these products (**6–10**) exist in only the keto form. From these results we concluded compounds **6–10** are the parent 2,3-dihydroindolizin-2-one and its 5-methyl, 3-methyl, 1-methyl, and 1-phenyl derivatives, respectively.

Scheme II



Scheme III



Reactions of 2,3-Dihydroindolizin-2-ones or Pyridinium Salts with Various Alkylating and Acylating Agents. Since the 3-methylene or 3-methine proton in dihydroindolizionones **6–10** was exchanged smoothly with deuterium oxide and since the environment of the group resembles that of the active methylene group in indoxyl, we attempted reactions of **6–10** with various alkylating and acylating agents.

The reactions of dihydroindolizonones **9** and **10**, readily obtainable in good yields in the crystalline state, with 3–4 equimolar amounts of benzyl bromide (**12**) and allyl bromide (**13**) in ethanol in the presence of potassium hydroxide afforded the corresponding reddish crystals (**19** and **26**; **20** and **27**) in 79–97% yields. The same compounds (**19**, **26**, **20**, and **27**) were also obtained by the reactions of pyridinium salts **4** and **5** with **12** and **13**, respectively. Similarly, alkaline treatment of salts **4** and **5** and 1-bromo-*trans*-2-butene (**14**), propargyl bromide (**15**), methyl iodide (**16**), ethyl iodide (**17**), and ethyl 3-bromopropionate (**18**) yielded the corresponding orange to red crystalline compounds **21–25** and **28–32** in 29–91% yields (Scheme II). In these reactions the reactivity of allylic halides such as **12**, **13**, and **15** was particularly high,[7] and the yields of products **19**, **20**, **22**, **26**, **27**, and **29** were generally good (>70%). The use of an equimolar amount of alkyl halide in these reactions gave the same products and dihydroindolizinones **9** and **10**, both in low yields. On the other hand, secondary and tertiary alkyl halides such as 2-bromopropane, 2-bromopentane, and 2-bromo-2-methylpropane did not react with pyridinium salts **4** and **5** and dihydroindolizionones **9** and **10** under the conditions employed here.

In the same way, reactions of pyridinium salts **1–3** with benzyl bromide (**12**) and methyl iodide (**16**) in ethanol in the presence of potassium hydroxide afforded the compounds **33** and **38**, **34** and **39**, **35** and **40**, **36**, **37**, and **36** in low yields, respectively (Scheme III). On the other hand, the same reactions in the presence of potassium carbonate each gave only one product (**38**, **39**, **40**, **36**, **37**, and **36**, respectively).

(2) This reaction is well-known as the Tschitschibabin reaction, and, in particular, 2-alkyl- and 2-arylindolizine derivatives are prepared smoothly by this and modified methods. See the following recent review: Uchida, T.; Matsumoto, K. *Synthesis* **1976**, 209.

(3) Full NMR data for these compounds are given in the supplementary material.

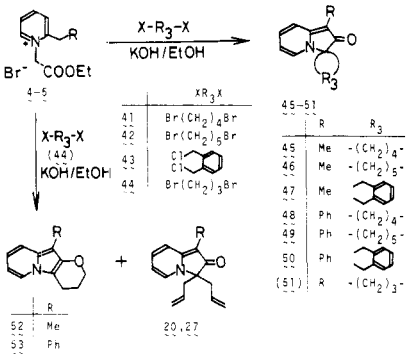
(4) (a) Sasaki, T.; Kanematsu, K.; Kakehi, A.; Ito, G. *Tetrahedron* **1972**, *28*, 4947. (b) Tamura, Y.; Sumida, Y.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2091. (c) Sasaki, T.; Kanematsu, K.; Kakehi, A.; Ito, G. *Ibid.* **1973**, 2089. (d) Kakehi, A.; Ito, S. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 938. (e) Tamura, Y.; Sumida, Y.; Haruki, S.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1575.

(5) (a) Kakehi, A.; Ito, S.; Maeda, T.; Takeda, R.; Nishimura, M.; Yamaguchi, T. *Chem. Lett.* **1978**, 59. (b) Kakehi, A.; Ito, S.; Maeda, T.; Takeda, R.; Nishimura, M.; Tamashima, M.; Yamaguchi, T. *J. Org. Chem.* **1978**, *43*, 4837.

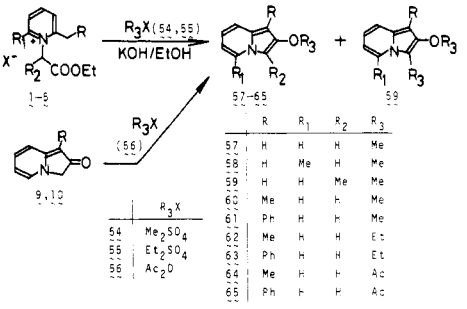
(6) Ochi, H.; Miyasaka, T.; Kanada, K.; Arakawa, K. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1980.

(7) These reactions were faster than the others and ceased completely within 10 min.

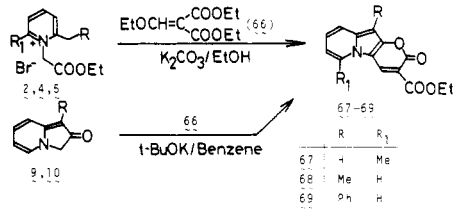
Scheme IV



Scheme V



Scheme VI



These compounds (19–40) are very stable substances under the usual conditions (below 100 °C). The structures of 19–40 are based on the composition and spectra. In particular, the IR spectra of all compounds (19–40) have the same delocalized carbonyl absorption at 1581–1606 cm^{-1} as seen in dihydroindolizinones 6–10 and 3-methylenedihydroindolizinones,[1] and the NMR spectra,[3] except for the signals due to the two alkyl groups derived from the alkylating agents, are very similar to those of dihydroindolizinones 6–10. For example, the NMR spectrum of 23 showed signals at δ 6.30 (1 H, dt, J = 7.0, 7.0, 1.5 Hz, 6-H), 6.83 (1 H, br d, J = 9.0 Hz, 8-H), 7.33 (1 H, br t, J = 9.0, 7.0 Hz, 7-H), and 7.55 (1 H, br d, J = 7.0 Hz, 5-H) due to the protons on the pyridine ring and at δ 1.42 (6 H, s) and 1.77 (3 H, s) due to the 3,3-dimethyl and the 1-methyl protons, respectively. Evidently, all the chemical shifts except the 3,3-dimethyl signal (δ 1.42) are parallel to those in 1-methyl-2,3-dihydroindolizin-2-one (9).[3] The structures of 1-benzyl derivatives 38–40 were determined similarly in view of the absence of the one-proton singlet near δ 5.0 and the presence of the three benzyl signals in the NMR spectra. From these facts the structures of 19–40 were assigned to be 3,3-dialkyl-2,3-dihydroindolizin-2-one derivatives.

The smooth introduction of two alkyl groups in these dihydroindolizinones prompted us to examine the possibility of the preparation of 3-spirodihydroindolizinone using dihalides. Treatment of an equimolar mixture of pyridinium salt 4 or 5 and 1,4-dibromobutane (41), 1,5-dibromopentane (42), or α,α'-dichloro-*o*-xylene (43) with potassium hydroxide gave the expected 3-spiro-2,3-dihydroindolizin-2-ones (45–50) as reddish crystals (Scheme IV). On the other hand, the reactions of 4 and 5 with 1,3-dibromopropane (44) did not afford the corresponding 3-spiro compound (51) but gave 3,4-dihydro-2*H*-pyrano[2,3-*b*]indolizines 52 and 53 together with 3,3-diallyl-2,3-dihydroindolizin-2-ones 20 and 27.

The structural assignment of these spirodihydroindolizinones (45–50) was achieved in a manner similar to that described above. Pyranoindolizines 52 and 53 were identified by the following information: in the IR spectra, the delocalized carbonyl absorption at near 1600 cm^{-1} was absent, and, in the NMR spectra,[3] a triplet signal at δ 4.27 (52) or 4.30 (53) attributable to the *O*-methylene protons appeared.

Reactions of pyridinium salts 1–5 with dimethyl (54) and diethyl sulfate (55) in the presence of alkali gave colorless to pale yellow oils or crystals (57 and 59 and 58–63) in 10–35% yields, respectively (Scheme V). Similarly, reactions of dihydroindolizinones 9 and 10 with acetic anhydride (56) in benzene afforded the corresponding products (64 and 65) in 23% and 28% yields.

In contrast to 3,3-disubstituted 2,3-dihydroindolizin-2-ones 19–40 and 45–50, these compounds (57–65) were unstable and decomposed even at room temperature. The IR spectra of 57–65 did not show the characteristic absorption band near 1600 cm^{-1} due to the delocalized carbonyl group as seen in dihydroindolizinones, and the NMR spectra showed comparatively low absorptions of the skeletal protons (δ 6.2–8.0) and methyl protons (δ 2.2–2.5), and methoxy signals [δ 3.8–4.0, (3 H, s)] in 57–61 and ethoxy signals [δ near 1.4 (3 H, t, J = 7.0 Hz) and 4.0 (2 H, q, J = 7.0 Hz)] in 62 and 63 were also indicated. In particular, the low values of the skeletal protons and methyl protons coincided well with those of aromatic indolizines but not of dihydroindolizines. From these results the compounds were assigned to be 2-alkoxy- (57–63) and 2-acetoxyindolizine derivatives (64 and 65).

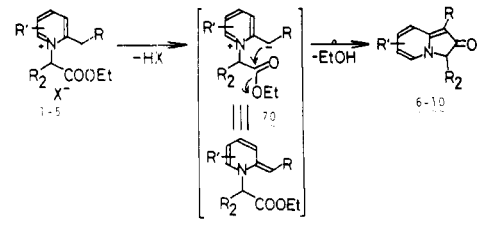
Reactions of Pyridinium Salts and Dihydroindolizinones with Diethyl (Ethoxymethylene)malonate. The reaction of the pyridinium salt or dihydroindolizinone with a vinylating agent such as diethyl (ethoxymethylene)malonate (66) was also examined, and a new reaction which led to a 2*H*-pyrano[2,3-*b*]indolizin-2-one derivative was found. When an equimolar mixture of salt 2, 4, or 5 and 66 was treated with potassium carbonate in ethanol at room temperature, a very strongly fluorescent substance (67, 68, or 69) was isolated in low yield (Scheme VI). The same products (68 and 69) were also obtained by the reactions of dihydroindolizinones 9 and 10 with 66 in benzene in the presence of potassium *tert*-butoxide. On the other hand, the reactions of salts 1 and 3 with 66 and of dihydroindolizinones 9 and 10 with ethyl (ethoxymethylene)cyanoacetate afforded complex mixtures, and the isolations of any identifiable substances from them were unsuccessful.

The assignment of the 2*H*-pyrano[2,3-*b*]indolizin-2-one structure for compounds 67–69 was achieved by the comparison of the physical and spectral data with those of similar pyranoindolizinones described recently by us.[1]

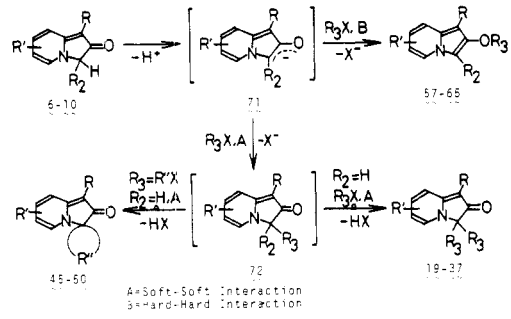
Reaction Mechanism. The formation of 2,3-dihydroindolizin-2-ones 6–10 can be explained reasonably by the dehydrohalogenation of pyridinium salts 1–5 followed by intramolecular neucleophilic attack of the resulting intermediate (70) with the elimination of ethanol (Scheme VII).

In the transformations from pyridinium salts 1–5 to 3,3-dialkyl- (19–40) and 3-spiro-2,3-dihydroindolizin-2-ones (45–50), 2-alkoxy- (57–63) and 2-acetoxyindolizines (64 and 65), and 2*H*-pyrano[2,3-*b*]indolizin-2-ones (52, 53, and

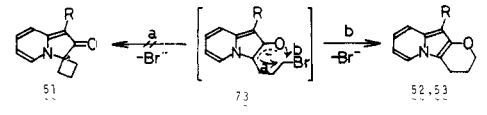
Scheme VII



Scheme VIII

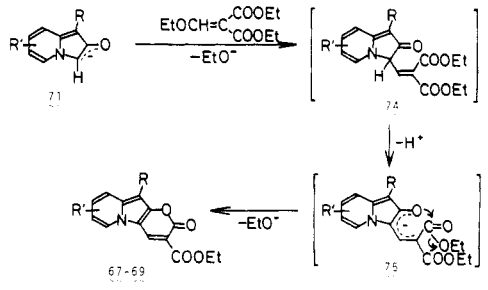


Scheme IX



67–69), the intermediacy of dihydroindolizinones **6–10** seems to be certain for the following reasons: (a) the same products were actually obtained by using **6–10**, which were isolated or generated in situ;[8] (b) **6–10** were not only detected in the reaction solutions by TLC at the early stage but also isolated in some cases when the reactions were stopped before completion; (c) the cyclizations of **1–5** were very fast, and **6–10**, thus formed, have less hindered structures, while the alkylations of 2-picolinium 1-methylides, which are possible intermediates in the alternative process to **19–40**, **45–50**, **52**, **53**, **57–65**, and **67–69**, should lead to unfavorably crowded pyridinium salts.[9] Possible mechanisms for the formation of dihydroindolizinones **19–37** and **45–50** and indolizines **57–65** are summarized in Scheme VIII. In particular, the soft–soft and hard–hard interactions[10] of the ambident anions **71** generated in situ by the hydrogen abstraction from **6–10** are key steps in these reactions. On the other hand, the formation of 3,4-dihydro-2*H*-pyrano[2,3-*b*]indolizines **52** and **53** can be interpreted as the result of the hard–soft interaction of ambident anion **73**, in which less hindered products (**52** and **53**) rather than strained spiro[2,3-dihydroindolizin-2-one-3,1'-cyclobutane] (**51**, R = H) were formed (Scheme IX). The 1-benzyl derivatives **38–40** must be generated by the alkylation of initially formed 1-unsubstituted 3,3-dialkyl-2,3-dihydroindolizin-2-ones (**33–35**), since the conversion of **35** to **40** was actually confirmed. Similarly, the formation mechanism of pyranoindolizinones **67–69** seems to proceed via the soft–soft interaction of the anion **71** with diethyl (ethoxymethylene)malonate (**66**) and the hydrogen abstraction from the corresponding 3-vinyldihydroindolizinones (**74**), followed by the hard–hard interaction of the resulting

Scheme X



anion (**75**; Scheme X). Recently, we have suggested a similar mechanism for the reactions of 3-methylene-2,3-dihydroindolizin-2-ones with acetates in the presence of alkali.[1]

Experimental Section

Melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. Microanalyses were carried out on a Perkin-Elmer 240 elemental analyzer. The NMR spectra were determined with a Varian EM360A spectrometer in deuteriochloroform with tetramethylsilane as an internal standard. The chemical shifts are expressed as δ values. The IR spectra were taken with a Hitachi 260-10 infrared spectrophotometer.

Preparations of 2,3-Dihydroindolizin-2-ones 6–10. General Method. To an ethanolic solution (100 mL) of pyridinium salt[1] (**1–5**, 5 mmol) was added aqueous potassium hydroxide (6 mmol in 1 mL of water) dropwise with stirring at room temperature. After the disappearance of the salt (detected by TLC) the excess base was neutralized carefully with dilute hydrochloric acid, and the reaction solution was filtered to remove inorganic substances. The filtrate was then concentrated at reduced pressure, and the residue was separated by column chromatography (alumina). Compounds **6–8** were obtained as pale yellow oils and **9** and **10** as orange prisms (from chloroform–hexane at −5 °C). These results and some properties are listed in Table I.[3]

Reactions of 2,3-Dihydroindolizin-2-ones 9 and 10 with Benzyl Bromide (12) and Allyl Bromide (13). General Method. A mixture of dihydroindolizinone (**9** or **10**, 2 mmol) and bromide (**12** or **13**, 6–8 mmol) was treated with aqueous potassium hydroxide (4.5 mmol in 1 mL of water) in ethanol (40 mL) at room temperature for 10 min. The reaction mixture was neutralized with dilute hydrochloric acid and then filtered. The filtrate was worked up by the usual manner described above. Recrystallizations from chloroform–hexane gave the corresponding 3,3-dibenzyl- (**19** and **26**) and 3,3-diallyl-2,3-dihydroindolizin-2-one derivatives (**20** and **27**) as reddish crystals. These results and some properties are summarized in Table I.[3]

Reactions of Pyridinium Salts 1–5 with Some Alkylating Agents (12–18). Method A. To an ethanolic solution (100 mL) of pyridinium salt (5 mmol) and halide (20 mmol) was added aqueous potassium hydroxide (18 mmol in 3 mL of water) dropwise with stirring at room temperature. The reaction mixture was allowed to react until the disappearance of 2,3-dihydroindolizin-2-one (**6–10**) was confirmed by TLC (5 min–12 h). The usual workups gave the corresponding 3,3-disubstituted 2,3-dihydroindolizin-2-ones **19–40** as yellow to red crystals.

In these reactions the use of an equimolar amount of an alkylating agent afforded diminished yields of products (**19–40**) together with small amounts of dihydroindolizinones **6–10**. In the reactions of **1–3** with benzyl bromide (**12**) mixtures of 1-unsubstituted (**33–35**) and 1-benzyl derivatives (**38–40**) were obtained, and only **35** could be isolated by fractional crystallization.

Method B. In the reactions of salts **1–5** with benzyl bromide (**12**) and methyl iodide (**16**), a large excess of potassium carbonate instead of potassium hydroxide was used as a base. In the cases of **1–3** with **12** only one product (**38–40**) was formed.

Compound **40** was also prepared by the reactions of 1-unsubstituted derivative **35** with **12** under the conditions described in method B (54%). These data are listed in Table I.[3]

Reactions of Salts 4 and 5 With Dihalides. General Method. An equimolar mixture of pyridinium salt (5 mmol) and dihalide (5 mmol) was treated with aqueous potassium hydroxide

(8) In these reactions an alkylating or acylating agent was added after the generation of dihydroindolizinones **6–10**.

(9) (a) Kakehi, A.; Ito, S.; Uchiyama, K.; Kondo, K. *J. Org. Chem.* **1978**, *43*, 2896. (b) Kakehi, A.; Ito, S.; Watanabe, K.; Ono, T.; Miyajima, T. *J. Chem. Res. (S)* **1980**, 18; *J. Chem. Res. (M)* **1980**, 401–425.

(10) Ho, T.-L. "Hard and Soft Acids and Bases Principle in Organic Chemistry"; Academic Press: New York, 1977.

Table I. Some Results and Properties of Indolizine Derivatives

compd[a]	reactants	yield, %	mp, °C	$\nu_{C=O}$ (KBr), cm^{-1}
6	1	3	oil	1585[b]
7	2	21	oil	1585[b]
8	3	18	oil	1590[b]
9[c]	4	67	126-128	1587
10	5	74	136-138	1572
19	9, 12	79	191-193	1595
	4, 12	71		
20	9, 13	92	107-108	1581
	4, 13	81		
21[d]	4, 14	31	155-158	1600
22	4, 15	72	217-219	1600
23	4, 16	58	144-146	1595
24[c]	4, 17	29	57-58	1600
25	4, 18	45	128-130	1603
26	10, 12	97	209-212	1592
	5, 12	89		
27	10, 13	86	144-146	1594
	5, 13	72		
28	5, 14	80	57-58	1603
29	5, 15	71	120-122	1591
30	5, 16	78	166-168	1590
31	5, 17	60	138-140	1599
32	5, 18	91	110-111	1598
33 + 38	1, 12	trace	mixture	
34 + 39	2, 12	ca. 15	mixture	
35 + 40	3, 12	ca. 21 + 5	178-181[e]	1608[e]
36	1, 16	1	oil	1600[b]
	3, 16	12	oil	
37	2, 16	18	185-188[f]	1591[b]
38[d]	1, 12[g]	15	92-93	1602
39	2, 12[g]	25	116-117	1608
40	3, 12[g]	21	160-162	1603
45	4, 41	35	141-143	1600
46[c]	4, 42	23	76-78	1580
47	4, 43	58	189-191	1595
48	5, 41	42	68-83[h]	1597
49	5, 42	50	70-82[h]	1600
50	5, 43	77	203-205	1600
52 + 20	4, 44	5 + 12	141-143[f,i]	
53 + 27	5, 44	42 + 10	154-156[j]	
57 + 59	1, 54	ca. 10	mixture	
58	2, 54	17	126-127[f]	
59	3, 54	26	165-167[f]	
60	4, 54	35	63-65	
61	5, 54	33	105-107	
62	4, 55	30	130-132[f]	
63	5, 55	32	81-83	
64	4, 56	23	107-109[f]	1760[b]
65	5, 56	28	74-75	1760
67	2, 66	38	190-192	1719, 1668
68	4, 66	4	239-241	1730, 1660
	9, 66	20		
69	5, 66	6	212-213	1747, 1680
	10, 66	17		

[a] Satisfactory analytical data (±0.32% for C, H, and N) were obtained for all new compounds listed in the table except 6-8, 33, 34, 36, and 57. [b] Neat. [c] Hemihydrate. [d] Monohydrate. [e] Compound 35. [f] Its picrate. [g] Reaction in ethanol in the presence of potassium carbonate. [h] Its melting point was not indicated definitely. [i] Compound 52. [j] Compound 53.

(18 mmol in 3 mL of water) with stirring at room temperature. After the disappearance of dihydroindolizinones 6-10 was confirmed by TLC, the reaction mixture was treated in the usual manner described in the preparation of 6-10.

From the reactions of 4 and 5 with 1,4-dibromobutane (41), 1,5-dibromopentane (42), and α,α'-dichloro-o-xylene (43) were obtained the corresponding spiro[2,3-dihydroindolizin-2-one-3,1'-cyclopentanes] (45 and 48), -cyclohexanes] (46 and 49), and -2'-indans] (47 and 50), respectively. On the other hand, the reactions of 4 and 5 with 1,3-dibromopropane (44) did not give the expected spiro[2,3-dihydroindolizin-2-one-3,1'-cyclobutane] (51) but gave 3,4-dihydro-2*H*-pyrano[2,3-*b*]indolizines 52 and 53 together with 3,3-diallyl-2,3-dihydroindolizin-2-ones 20 and 27. These results are listed in Table I.[3]

Preparations of 2-Alkoxyindolizines 57-63. General Method. An equimolar mixture of pyridinium salt (2 mmol) and dimethyl (54) or diethyl sulfate (55) was treated with aqueous potassium hydroxide (4.4 mmol in 1 mL of water) in ethanol (30 mL) at room temperature for 10 min, and the resulting mixture was immediately extracted with ether (100 mL). The ether extract was dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure. Column separation of the residual substances with ether gave the corresponding 2-alkoxyindolizine derivatives (57-63).

Since these reactions were very fast and the resulting products (57-63) are very unstable under the conditions employed here, the prolonged reaction time (over 30 min) and the severe procedure for compound isolation gave rise always to unsatifactory results. These results and some properties are summarized in Table I.[3]

Preparations of 2-Acetoxyindolizines 64 and 65. General Method. A benzene solution (30 mL) of 2,3-dihydroindolizin-2-one (9 or 10, 2 mmol) was treated with acetic anhydride (56, 2.2 mmol) at room temperature for 15 min, and the reaction mixture was immediately separated by column chromatography (alumina) using benzene as an eluent.

The same products (64 and 65) were also obtained by the reactions of salts 4 and 5 with acetic anhydride (56) in the presence of base, but the yields were very low (below 5%). These results and some properties are listed in Table I.[3]

Preparations of 2*H*-Pyrano[2,3-*b*]indolizin-2-ones 67-69. Method A. A mixture of pyridinium salt (3 mmol) and diethyl (ethoxymethylene)malonate (66, 3 mmol) was treated with potassium carbonate (10 g) in ethanol (50 mL) at room temperature for about 1 week. The reaction mixture was filtered to removed inorganic substances and concentrated at reduced pressure. The usual separation of the residue by column chromatography (alumina) afforded strongly fluorescent, orange crystals of 67-69.

Method B. A benzene solution of 2,3-dihydroindolizin-2-one (9 or 10, 2 mmol) was allowed to react with 66 in the presence of potassium *tert*-butoxide (2 mmol) at room temperature for 3 days. The reaction mixture was neutralized carefully with dilute hydrochloric acid and then filtered. The filtrate was concentrated at reduced pressure, and the residue was separated by column chromagography (alumina) and then by preparative TLC. Recrystallizations from chloroform–hexane gave the corresponding pyranoindolizinones (68 and 69).

Generally these reactions gave very complex mixtures, and the isolations of any significant products except 68 and 69 were unsuccessful. Compounds 68 and 69 were also obtained by the reactions of 9 and 10 with 66 in the absence of base or in the presence of potassium carbonate, but the isolated yields were extremely low (below 1%). These results and some properties are summarized in Table I.[3]

Registry No. 1, 58963-28-3; 2, 31778-09-3; 3, 67988-76-5; 4, 70257-97-5; 5, 74360-64-8; 6, 75247-95-9; 7, 75247-96-0; 8, 75247-97-1; 9, 75247-98-2; 10, 75247-99-3; 12, 100-39-0; 13, 106-95-6; 14, 29576-14-5; 15, 106-96-7; 16, 74-88-4; 17, 75-03-6; 18, 539-74-2; 19, 75266-17-0; 20, 75248-00-9; 21, 75248-01-0; 22, 75266-18-1; 23, 75248-02-1; 24, 75248-03-2; 25, 75248-04-3; 26, 75248-05-4; 27, 75248-06-5; 28, 75248-07-6; 29, 75248-08-7; 30, 75248-09-8; 31, 75248-10-1; 32, 75248-11-2; 33, 75248-12-3; 34, 75266-19-2; 35, 75248-13-4; 36, 75248-14-5; 37, 75248-15-6; 38, 75248-16-7; 39, 75266-20-5; 40, 75248-17-8; 41, 110-52-1; 42, 111-24-0; 43, 612-12-4; 44, 109-64-8; 45, 75248-18-9; 46, 75248-19-0; 47, 75248-20-3; 48, 75248-21-4; 49, 75248-22-5; 50, 75266-21-6; 52, 75248-23-6; 53, 75248-24-7; 54, 77-78-1; 55, 64-67-5; 56, 108-24-7; 57, 75248-25-8; 58, 75248-26-9; 59, 75248-27-0; 60, 75266-22-7; 61, 75248-28-1; 62, 75248-29-2; 63, 75248-30-5; 64, 75248-31-6; 65, 75248-32-7; 66, 87-13-8; 67, 75248-33-8; 68, 75248-34-9; 69, 75248-35-0.

Supplementary Material Available: Full NMR data for all compounds (6-10, 19-40, 45-50, Table I; 57-65, Table II; 52, 53, 67-69, Table III) (5 pages). Ordering information is given on any current masthead page.