Photochemical Syntheses of 1,2-Diazepines. 11.[1] Regiospecific Synthesis of 1,2-Dihydro-1,2-diazepin-3-ones

Toshiko Kiguchi,[2] Jean-Luc Schuppiser, Jean-Claude Schwaller, and Jacques Streith*

Ecole Nationale Supérieure de Chimie,[3] Université de Haute-Alsace, 68093 Mulhouse, Cedex, France

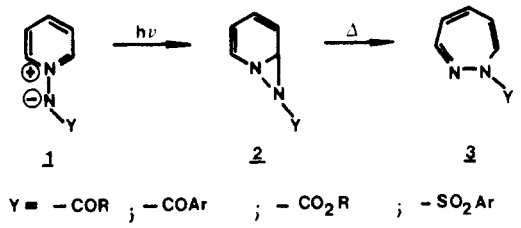
Received June 20, 1980

Starting from 2-chloropyridine 1, a series of 1,2-diazepin-3-ones 16 was prepared by a five-step synthesis. The key intermediates were the bicyclic oxadiazolium salts 10 which led, through a methoxide ion induced ring opening, to the expected 2-methoxypyridinium ylides 11. The photoinduced ring enlargement of ylides 11 proved to be regiospecific and led to 3-methoxy-1,2-diazepines, the immediate precursors of the final diazepinones 16.

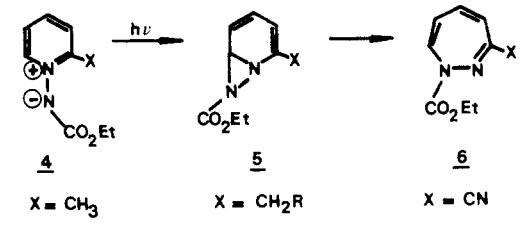
The photoinduced ring enlargement of 1-iminopyridinium ylides 1 to the corresponding isomeric 1*H*-1,2-diazepines 3 has been well documented during the last decade.[4] Although the overall quantum yield of these rearrangement processes is low, chemical yields are generally excellent, so that 1,2-diazepines can be obtained in large amounts, provided that powerful UV lamps are used.[5] The 1,7-diazanorcaradiene isomers 2 were first postulated and later proved to be short-lived intermediates in the conversion of the singlet excited state of the ylides 1 to the photoproducts 3[6,7] (Scheme I). In contrast the triplet excited state leads to the cleavage of the N–N bond.[18] The directing effects of ring substituents at C-2 or C-3 upon the photoinduced ring enlargement of 1-iminopyridinium ylides to the corresponding 1,2-diazepines have already been described.[1,8-11] The substituents attached at C-3 were found to lead either regiospecifically to one diazepine or to both possible diazepines, depending on their electronic properties.[1] As to substituents at C-2, they induced a regiospecific ring enlargement to the corresponding 3-substituted 1,2-diazepines regardless of their electronic properties. For example, pyridinium ylides 4 having either an alkyl or a cyano group attached to carbon atom C-2[11] lead to the same regiospecific ring enlargement.[8-10] It was therefore assumed that this regiospecific ring enlargement observed in high yield with these 2-alkyl and 2-cyano ylides 4 was mainly due to a steric rather than an inductive or orbital factor. Nonbonding interactions between X and N–Y groups must therefore prevent photoinduced ring closure from occurring toward C-2[12] (Scheme II).

In view of the important role played by benzo-annelated diazepines as tranquilizers in modern medicine,[14,15] it appeared desirable to develop an approach toward the synthesis of the 1,2-dihydro-1,2-diazepin-3-one ring system. To our knowledge only one set of these latter structural types has been synthesized so far, by Kisch,[13] who started from cyclic diazenes and used an organometallic route. Kisch's compounds were bicyclic and fully substituted by alkyl and phenyl groups on the diazepinone ring. We now report a simple five-step, and, in part, photochemical synthesis of this ring system.

Scheme I



Scheme II



Our general scheme for the synthesis of 1,2-diazepin-3-ones was based on the known photoinduced ring enlargement of 1-iminopyridinium ylides and on the expected effect of an alkoxy group attached to the C-2 position of these ylides on the regiospecificity of the rearrangement process. Since alkyl and cyano groups led in high yield to the corresponding 3-methyl-1,2-diazepines[8,9] (Scheme II), it seemed reasonable to expect that an alkoxy group would behave similarly. Along these lines we undertook the synthesis of 1,2-dihydro-1,2-diazepin-3-ones 16 according to Schemes III and IV.

Our first goal was the synthesis of 2-methoxy(benzoylimino)pyridinium ylides 11, starting from 2-chloropyridine (7). It was achieved as follows. Reaction of 7 with mesitylsulfonylhydroxylamine (MSH) in methylene chloride led in 70% yield to the expected *N*-aminopyridinium salt 8. Sequential treatment of 8 with benzoyl chloride and with perchloric acid in methanol gave the bicyclic salt 10 (Scheme III). Its structure was based in particular on IR spectroscopy which confirmed the absence of N–H and C=O bands. The formation of the bicyclic oxadiazolium

(1) Part 10: H. Fritz, R. Gleiter, M. Nastasi, J. L. Schuppiser, and J. Streith, *Helv. Chim. Acta*, 61, 2887 (1978).
(2) Lecturer on leave from Kobe Women's College of Pharmacy, Kobe, Japan.
(3) Laboratoire Associé au Centre National de la Recherche Scientifique (LA 135).
(4) M. Nastasi, *Heterocycles*, 4, 1509 (1976).
(5) For a description of the 2000-W "falling film" type photoreactor used in our laboratory, see F. Bellamy and J. Streith, *J. Chem. Res.* (S), 18 (1979).
(6) H. Kwart, D. A. Benko, J. Streith, D. J. Harris, and J. L. Schuppiser, *J. Am. Chem. Soc.*, 100, 6501 (1978).
(7) H. Kwart, D. A. Benko, J. Streith, and J. L. Schuppiser, *J. Am. Chem. Soc.*, 100, 6502 (1978).
(8) A. Balasubramanian, J. M. McIntosh, and V. A. Snieckus, *J. Org. Chem.*, 35, 433 (1970).
(9) T. Sasaki, K. Kanematsu, A. Kakehi, I. Ichikawa, and K. Hayakawa, *J. Org. Chem.*, 35, 426 (1970).
(10) A. Frankowski and J. Streith, *Tetrahedron*, 33, 427 (1977).
(11) J. Streith and J. M. Cassal, *Bull. Soc. Chim. Fr.*, 2175 (1969).
(12) J. Streith, *Pure Appl. Chem.*, 49, 305 (1977).
(13) B. Ulbrich and H. Kisch, *Angew. Chem., Int. Ed. Eng.*, 17, 369 (1978).
(14) A. Marxer and O. Schier, *Prog. Drug Res.*, 20, 385 (1976).
(15) L. H. Sternbach, *J. Med. Chem.*, 22, 1 (1979).

0022-3263/80/1945-5095$01.00/0

Table I. Physical and Spectral Properties of Ylides 11

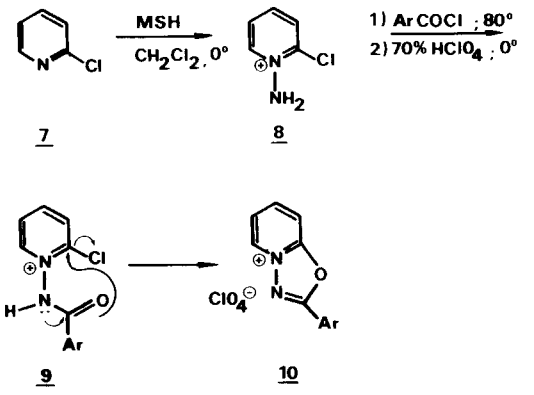
	mp, °C	UV (EtOH), λ_{max} (ϵ)	IR (KBr), cm^{-1}	^1H NMR ($CDCl_3$), δ (J, Hz)					
				H-3	H-4	H-5	H-6	*o*-H	*m*-H
11a	161-163	285 (10 600), 322 (3250)	1610, 1580, 1570	7.4-7.0 (m)	7.9 (td, $J_{4,5}$ = 7.5, $J_{4,3}$ = 7.5, $J_{4,6}$ = 2.0)	7.4-7.0 (m)	8.3 (dd, $J_{6,5}$ = 7.0, $J_{6,4}$ = 2.0)	8.1 (d, J = 8.0)	6.7 (d, J = 8.0)
11b	161-162	250 (17 300), 282 (9400), 303 (5500)	1630, 1600 1590	7.4-7.0 (m)	7.9 (td, $J_{4,5}$ = 8.0, $J_{4,3}$ = 8.0, $J_{4,6}$ = 2.0)	7.4-7.0 (m)	8.3 (dd, $J_{6,5}$ = 8.0, $J_{6,4}$ = 2.0)	8.1 (d, J = 9.0)	6.9 (d, J = 9.0)
11c	149-151	250 (16 300), 283 (8800), 303 (5500)	1620, 1575, 1560	7.5-7.0 (m)	7.9 (td, $J_{4,5}$ = 8.0, $J_{4,3}$ = 8.0, $J_{4,6}$ = 2.0)	7.5-7.0 (m)	8.4 (dd, $J_{6,5}$ = 7.0, $J_{6,4}$ = 2.0)	8.1 (d, J = 9.0)	6.9 (d, J = 9.0)
11d	122-123	230 (11 000), 286 (7500), 308 (3700)	1620, 1590, 1545	7.6-7.0 (m)	7.9 (td, $J_{4,5}$ = 7.5, $J_{4,3}$ = 7.5, $J_{4,6}$ = 2.0)	7.6-7.0 (m)	8.3 (dd, $J_{6,5}$ = 6.0, $J_{6,4}$ = 2.0)	8.1 (m)	7.6-7.0 (m, including *p*-H)
11e	141-142	230 (12 200), 285 (6400), 303 (3700)	1620, 1590	7.5-7.0 (m)	7.9 (td, $J_{4,5}$ = 8.0, $J_{4,3}$ = 8.0, $J_{4,6}$ = 2.0)	7.5-7.0 (m)	8.3 (dd, $J_{6,5}$ = 7.0, $J_{6,4}$ = 2.0)	8.1 (m)	7.5-7.0 (m)
11f	182-183	230 (13 500), 280 (8000), 305 (4250)	2230, 1620, 1580	7.35 (m)	8.05 (td, $J_{4,5}$ = 8.0, $J_{4,3}$ = 8.0, $J_{4,6}$ = 1.5)	7.35 (m)	8.4-8.2 (m)	8.4-8.2 (m)	7.65 (d, J = 9.0)

Table II. Physical and Spectral Properties of α-Pyridones 12

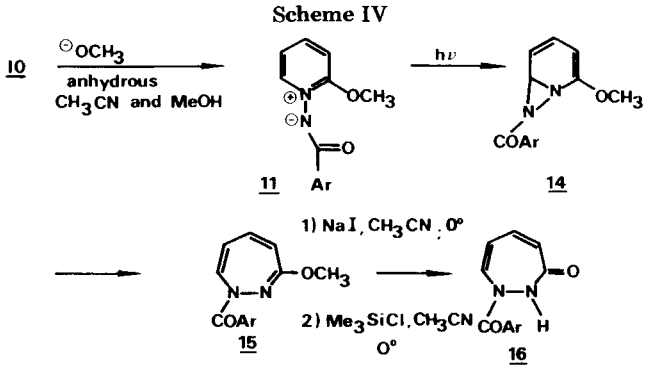
	physical state	IR ($CHCl_3$), cm^{-1}	^1H NMR ($CDCl_3$), δ (J, Hz)					
			H-3	H-4	H-5	H-6	*o*-H	*m*-H
12a	oil	1660, 1610	6.8-6.4 (m)	7.5-7.0 (m)	6.2 (td, $J_{5,4}$ = 7.0, $J_{5,6}$ = 7.0, $J_{5,3}$ = 3.0)	7.5-7.0 (m)	7.5-7.0 (m)	6.8-6.4 (m)
12b	oil	1630, 1600	6.5 (dd, $J_{3,4}$ = 8.0, $J_{3,5}$ = 2.0)	7.4-7.0 (m)	6.1 (td, $J_{5,4}$ = 8.0, $J_{5,6}$ = 8.0, $J_{5,3}$ = 2.0)	7.4-7.0 (m)	7.4-7.0 (m)	6.8 (d, J = 9.0)
12c	oil	1660, 1650	6.3 (dd, $J_{3,4}$ = 8.0, $J_{3,5}$ = 2.0)	7.3-7.1 (m)	6.1 (td, $J_{5,4}$ = 8.0, $J_{5,6}$ = 8.0, $J_{5,3}$ = 2.0)	7.3-7.1 (m)	7.4-7.0 (m)	6.8 (m)
12d	oil	1665, 1655	6.3 (dd, $J_{3,4}$ = 8.0, $J_{3,5}$ = 2.0)	7.4-7.0 (m)	6.1 (td, $J_{5,4}$ = 8.0, $J_{5,6}$ = 8.0, $J_{5,3}$ = 2.0)	7.4-7.0 (m)	7.4-7.0 (m)	7.4-7.0 (m, including *p*-H)
12e	oil	1655	6.4 (dd, $J_{3,4}$ = 10.0, $J_{3,5}$ = 2.0)	7.4-7.2 (m)	6.1 (td, $J_{5,4}$ = 7.0, $J_{5,6}$ = 7.0, $J_{5,3}$ = 2.0)	7.4-7.2 (m)	7.4-7.2 (m)	7.4-7.2 (m)
12f	solid (mp 140-142 °C)	2230,[a] 1660, 1620	6.4 (dd, $J_{3,4}$ = 10.0, $J_{3,5}$ = 2.0)	7.8-7.4 (m)	6.2 (td, $J_{5,4}$ = 7.0, $J_{5,6}$ = 7.0, $J_{5,3}$ = 2.0)	7.8-7.4 (m)	7.8-7.4 (m)	7.8-7.4 (m)

[a] In KBr.

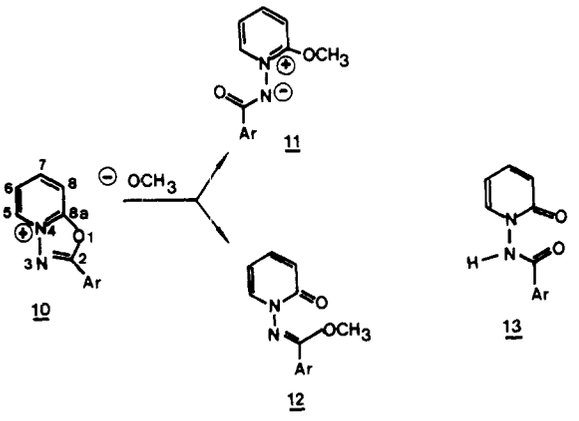
Scheme III



Scheme IV



Scheme V



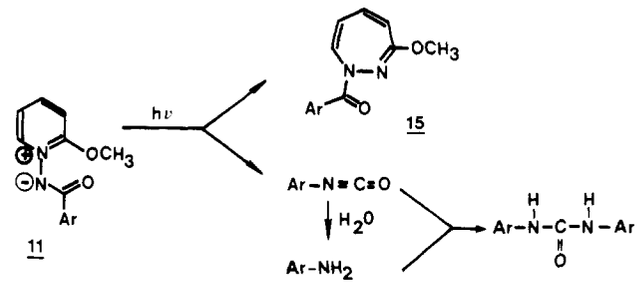
salt 10 is mechanistically straightforward: *N*-benzoylation of 8 leads to the salt 9 whose oxygen atom triggers the intramolecular nucleophilic displacement of a chloride ion. This process was not unexpected since 2-halogeno- and 2-alkoxypyridinium salts were known[16] to react easily even with poor nucleophiles, as was shown in particular by Mukaiyama for analogous intermolecular reactions.[17] It follows that intramolecular nucleophilic substitutions of 2-alkoxy pyridinium salts should be even more facile.

As expected, the anhydrous perchlorate salts 10 led to the 2-methoxypyridinium ylides 11 when treated with methoxide ion in dry acetonitrile solution (Table I). The α-pyridone imino ether isomers 12 were also isolated; their formation obviously results from a competing methoxide ion attack upon carbon atom C-2 (Scheme V and Table II). The presence of even trace amounts of water invariably resulted in the formation of α-pyridones 13. Therefore moisture had to be rigorously excluded from the reaction medium. Since the α-pyridones 12 were of no direct use for our planned synthesis of diazepinones, it was thought that methoxide attack at carbon atom C-8a should be favored when electron-donating substituents were present at the para position of the benzoyl moiety. These groups were supposed to enhance the electron density at carbon atom C-2 more than at C-8a and therefore reduce the rate of nucleophilic attack by methoxide ion at the former site. This surmise proved to be correct as can be seen from Table III which indicates the product distribution of the two isomers 11 and 12 as a function of the benzoyl para substituent. *p*-Alkoxy and *p*-dimethylamino groups preferentially oriented the oxadiazolium ring opening toward carbon atom C-8a, whereas cyano and chloro groups led to opposite results.

Ultraviolet irradiation of the pyridinium ylides 11 (λ_{max} at 280–290 and 310–320 nm) in a toluene–acetonitrile solution through Pyrex glass led regiospecifically and in good yields to the expected 3-methoxy-1,2-diazepines 15, which are yellow-to-orange crystalline compounds (Scheme IV). Structure analyses of these products were straightforward by means of proton NMR (Table IV) and ^{13}C NMR spectroscopy. The alternative 7-methoxy regioisomeric 1,2-diazepines could not be isolated. Another photochemical reaction was also observed: some of the ylides 11 underwent, although in low yield, photofragmentation leading to 2-methoxypyridine and to the respective isocyanates; in the presence of trace amounts of water the isocyanates hydrolyzed in part to the corresponding anilines which added to the remaining isocyanates, forming

(16) H. Pauls and F. Kröhnke, *Chem. Ber.*, 110, 1294 (1977).
(17) T. Mukaiyama, Y. Aikawa, and S. Kobayashi, *Chem. Lett.*, 57, (1976).

Scheme VI



N,N'-diarylureas (Scheme VI).

From mechanistic considerations, which had been explored earlier,[18] it is assumed that the ring-expansion process proceeds from an excited singlet state. Photolytic cleavage stems from an excited triplet state and leads, by way of a Curtius rearrangement, to the isocyanides.[19]

The final step involved C–O bond cleavage of the imino ether moiety and was achieved in good yield by using trimethylchlorosilane and sodium iodide in anhydrous acetonitrile.[20] The resulting 1-benzoyl-1,2-dihydro-1,2-diazepin-3-ones proved to be stable, colorless, and crystalline substances whose spectral data fully agreed with the proposed structure 16 (Table V).

In conclusion, the five-step reaction scheme proved to operate throughout, leading in particular to the expected oxadiazolium salts 10 and, by means of a regiospecific photoinduced ring enlargement of the 2-methoxypyridinium ylides 11, to the corresponding 3-methoxy-1,2-diazepines 15. It is hoped that these model reactions, which were performed with 1-chloropyridine as the starting material, will be applicable to benzo-annelated 2-chloropyridines also, whereby benzodiazepinones should be obtained after the final reaction step.

Experimental Section

General Methods. The proton nuclear magnetic resonance (^1H NMR) spectra were recorded in chloroform-*d* solution, unless otherwise stated, on a Varian T-60 spectrophotometer; chemical shifts are reported in parts per million (δ) from internal tetramethylsilane (Me_4Si). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Carbon-13 NMR experiments were performed by using a Brucker WP-80 DS spectrophotometer. Typically, a 4- to 6-μs pulse width was used with a pulse repetition rate of 1–4 s. The number of data points employed in the time domain was 8K. Carbon-13 chemical shifts are referenced in parts per million from internal Me_4Si. The following notations are used for reporting the ^{13}C spectra: splitting patterns are designated by capital letters for ^1J coupling constants and by small letters for ^2J and ^3J coupling constants. Infrared (IR) spectra were obtained on a Perkin-Elmer 157 G grating spectrophotometer and ultraviolet spectra on a Beckman DB spectrophotometer. Melting points were determined on a Tottoli apparatus (Büchi) and are uncorrected.

The photochemical experiments were carried out under a nitrogen atmosphere in a Pyrex glass vessel by using a water-cooled Hanovia immersion well equipped with a Philips HPK 125 mercury high-pressure lamp. In one large-scale photochemical experiment a 2000-W "falling-film" type photoreactor was used.[5] The column and thin-layer chromatographic separations were

(18) J. Streith, J. P. Luttringer, and M. Nastasi, *J. Org. Chem.*, 36, 2962 (1971).
(19) C. Wentrup, "Reaktive Zwischenstufen, Taschenlehrbuch der Organischen Chemie", Georg Thieme Verlag, Stuttgart, 1979, p 146.
(20) T. Morita, Y. Okamoto, and H. Sakurai, *J. Chem. Soc., Chem. Commun.*, 874 (1978).
(21) Several pharmacological, bacteriological, and parasitological tests have been performed with the diazepinones 16a–c by the Centre Nicolas Grillet of the Rhone-Poulenc Co. in Vitry. None of the compounds tested proved to be active. However, they proved to be nontoxic products.

Table III. Product Distribution of the Pairs of Isomers 11 and 12 after Ring Opening of the Corresponding Oxadiazolium Perchlorate Salts 10a by Methoxide Ion

	yield, %					
p-R-C_6H_4	a, R = NMe_2	b, R = OMe	c, R = OEt	d, R = H	e, R = Cl	f, R = CN
11	65	63	60	35	26	13
12	11	34	33	65	69	85

carried out on silica gel (Merck, Darmstadt), and the high-performance analytical liquid chromatographic analyses with a 3500 Spectra-Physics chromatograph using Spherisorb ODS and Lichrosorb columns. Microanalyses were performed by Service Central de Microanalyses of CNRS, division of Lyon. All new compounds gave satisfactory microanalyses for C, H, and N within ±0.3%.

N-Amination of 2-Chloropyridine. Isolation of 1-Amino-2-chloropyridinium Mesitylenesulfonate 8. To a stirred mixture of 8.0 g (700 mmol) of 2-chloropyridine and 200 mL of CH_2Cl_2, which was kept at 0 °C, was added dropwise a mixture of 20 g (93 mmol) of MSH and 100 mL of CH_2Cl_2. After 1 h, 300 mL of diethyl ether was added to this reaction mixture, and colorless crystals precipitated. Recrystallization from methanol/ethyl acetate gave 16 g (49 mmol, 70%) of 8, mp 114–115 °C.

Synthesis of 2-Arylpyrido[2,1-*b*]-1,3,4-oxadiazolium Perchlorate Salts 10.[22] General Procedure Described for the Synthesis of 2-Phenylpyrido[2,1-*b*]-1,3,4-Oxadiazolium Perchlorate (10d). A stirred mixture of 15 g (44 mmol) of the sulfonate salt of 8 and 17 mL (150 mmol) of benzoyl chloride was heated at 80 °C under nitrogen for 16 h. Methanol (30 mL) was then added at 0 °C, followed by 52.5 mL of 70% perchloric acid. A colorless product precipitated, which was recrystallized from $Me_2SO/CHCl_3$ to yield 8.7 g (30 mmol) of the perchlorate salt **10d** (67.5%): decomposes above 300 °C before melting; IR (KBr) 1635, 1610, 1590 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.7 (d, 1, H-6, $J_{5,6}$ = 6 Hz), 8.8 (m, 2, H-3 and H-4), 8.3 (m, 3, *o*-H, H-5), 7.9 (m, 3, *m*-*p*-H); ^{13}C NMR (Me_2SO-d_6) δ 164.84 (St, C-2), 153.04 (Sdd, C-8a), 144.84 (Dd, C-7), 135.55 (Dt, *p*-C), 133.50 (Ddd, C-4), 130.31 (Ddd, *m*-C), 128.54 (Dt, *o*-C), 123.12 (Ddd, C-6), 120.25 (St, Cs), 111.55 (Ddd, C-8).

2-(4′-Methoxyphenyl)pyrido[2,1-*b*]-1,3,4-oxadiazolium Perchlorate (10b). This compound was prepared according to the general procedure (79%): decomposes above 300 °C before melting; IR (KBr) 1635, 1610 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.7 (d, 1, H-6, $J_{5,6}$ = 7 Hz), 8.6 (m, 2, H-3, H-4), 8.2 (m, 3, *o*-H, H-5), 7.3 (d, 2, *m*-H, *J* = 9 Hz), 4.0 (s, 3, OCH_3); ^{13}C NMR (Me_2SO-d_6) δ 165.02 (Sm, *p*-C), 164.84 (St, C-2), 152.91 (Sdd, C-8a), 144.25 (Ddd, C-7), 133.28 (Dt, C-5), 130.82 (Dd, *o*-C), 122.98 (D, C-6), 115.92 (Dd, *m*-C), 112.00 (St, C-5), 111.37 (Dd, C-8), 56.07 (Qs, OMe).

[2-(4′-Ethoxyphenyl)pyrido[2,1-*b*]-1,3,4-oxadiazolium Perchlorate (10c). This was prepared according to the general procedure (92%): decomposes above 300 °C before melting; IR (KBr) 1635, 1610 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.6 (d, 1, H-6, $J_{5,6}$ = 8 Hz), 8.7 (m, 2, H-3, H-4), 8.3 (m, 3, *o*-H, H-5), 7.3 (m, 2, *m*-H), 4.3 (q, 2, OCH_2CH_3, *J* = 7 Hz), 1.5 (t, 3, OCH_2CH_3, *J* = 7 Hz); ^{13}C NMR (Me_2SO-d_6) δ 164.84 (St, C-2), 164.29 (Stt, *p*-C), 152.86 (Sdd, C-8a), 144.21 (Dd, C-7), 133.28 (Dt, C-5), 130.82 (Dd, *o*-C), 122.98 (D, C-6), 116.24 (Dd, *m*-C), 111.78 (St, Cs), 111.37 (Dd, C-8), 64.27 (Tq, CH_2), 14.39 (Qt, CH_3).

2-[4′-(Dimethylamino)phenyl]pyrido[2,1-*b*]-1,3,4-oxadiazolium Perchlorate (10a). This was prepared according to the general procedure (70%): decomposes above 300 °C before melting; IR (KBr) 1610, 1590 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.8 (d, 1, H-6, $J_{5,6}$ = 7 Hz), 8.6 (m, 2, H-3, H-4), 8.1 (m, 3, *o*-H, H-5), 7.0 (d, 2, *m*-H, *J* = 9 Hz), 3.2 (s, 6, $N(CH_3)_2$).

2-(4′-Chlorophenyl)pyrido[2,1-*b*]-1,3,4-oxadiazolium Perchlorate (10e). This was prepared according to the general procedure (80%): decomposes above 300 °C before melting; IR (KBr) 1635, 1610 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.8 (d, 1, H-6, $J_{5,6}$ = 7 Hz), 8.8 (m, 2, H-3, H-4), 8.4 (m, 3, *o*-H, H-5), 7.3 (m, 2, *m*-H); ^{13}C NMR (Me_2SO-d_6) δ 164.11 (St, C-2), 152.99 (Sdd, C-8a), 145.03 (Dd, C-7), 140.56 (Stt, *p*-C), 133.55 (Dt, C-5), 130.59 (Dd, *m*-C), 130.27 (Dd, *o*-C), 123.25 (D, C-6), 119.11 (St, Cs), 111.55 (Dd, C-8).

2-(4′-Cyanophenyl)pyrido[2,1-*b*]-1,3,4-oxadiazolium Perchlorate (10f). This was prepared according to the general procedure (84%): decomposes above 300 °C before melting; IR (KBr) 2240, 1635, 1620 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.7 (d, 1, H-6, $J_{5,6}$ = 6 Hz), 8.8 (m, 2, H-3, H-4), 8.5 (d, 2, *m*-H, *J* = 7 Hz), 8.2 (m, 3, H-5, *o*-H); ^{13}C NMR (Me_2SO-d_6) δ 163.70 (St, C-2), 153.13 (Sdd, C-8a), 145.62 (Dd, C-7), 134.10 (Dd, *m*-C), 133.82 (Dt, C-5), 129.31 (Dd, *o*-C), 124.35 (St, C-6), 123.57 (D, C-6), 117.79 (St, CN), 117.38 (St, *p*-C), 111.78 (Dd, C-8).

N-(Benzoylimino)-2-methoxypyridinium Ylide 11d and N-[(α-Methoxybenzylidene)amino]pyridone (12d). General Procedure (Tables I and II). To a stirred mixture of 2 g (6.8 mmol) of dry perchlorate salt **10a** and 100 mL of anhydrous acetonitrile was added dropwise a solution prepared from 164 mg (1.05 equiv) of sodium and 15 mL of dry methanol. After 1 h the reaction mixture was poured into 300 mL of water, extracted with chloroform, and dried (Na_2SO_4), the chloroform solution was evaporated in vacuo, and the residue was chromatographed over silica gel. Elution with ethanol led to the isolation of **11d** and **12d.**

Compound **11d** was recrystallized from ethyl acetate/cyclohexane, and 550 mg (35%) was obtained: ^{13}C NMR ($CDCl_3$) δ 170.24 (St, C=O), 158.62 (Sm, C-2), 143.41 (Dd, C-6), 140.59 (Dd, C-4), 136.76 (St, Cs), 129.43 (Dt, *p*-C), 127.56 (Dt, *o*-C), 127.26 (Dt, *m*-C), 116.95 (Dt, C-5), 109, 11 (Dd, C-3), 57.51 (Qs, OCH_3).

Compound **12d** was distilled at 160 °C (1 torr), and 1.0 g (65%) of product was obtained: ^{13}C NMR ($CDCl_3$) δ 171.73 (Ss, C-7), 158.02 (Sm, C-2), 137.34 (Dd, C-4), 135.84 (Dt, C-6), 130.14 (Dt, *p*-C), 129.32 (St, Cs), 127.59 (Dd, *m*-C), 126.77 (Ddd, *o*-C), 120.17 (Ddd, C-3), 104.68 (Dm, C-5), 55.17 (Qs, OCH_3).

***N*-[(4′-Methoxybenzoyl)imino]-2-methoxypyridinium ylide 11b and *N*-[(α-methoxy-4′-methoxybenzilidene)-amino]-2-pyridone (12b)** were prepared according to the general procedure and thence separated by column chromatography. Compound **11b** was recrystallized from chloroform/hexane (63% yield). Compound **12b** was distilled at 150 °C (1 torr) (34% yield).

***N*-[(4′-Ethoxybenzoyl)imino]-2-methoxypyridinium ylide 11c and *N*-[(α-methoxy-4′-ethoxybenzylidene)amino]-2-pyridone (12c)** were prepared according to the general procedure and thence separated by column chromatography.

Compound **11c** was recrystallized from chloroform/hexane (60%): ^{13}C NMR ($CDCl_3$) δ 170.41 (St, CO), 160.37 (Stt, *p*-C), 159.29 (Sddq, C-2), 144.40 (Dd, C-6), 140.44 (Ddd, C-4), 129.73 (St, Cs), 129.55 (Dd, *o*-C), 117.21 (Ddd, C-5), 113.47 (Dd, *m*-C), 109.33 (Dd, C-3), 63.28 (Tq, CH_2), 57.90 (Qs, OCH_3), 14.59 (Qt, CH_3).

Compound **12c** was distilled at 150 °C (1 torr) (33% yield). When the same general procedure is employed, under *non-anhydrous* conditions, in addition to **11c** and **12c** the *N*-(*p*-ethoxybenzoyl)-α-pyridone **13** is isolated and recrystallized from acetone/hexane: mp 212–213 °C; IR (KBr) 3160, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.9 (d, *o*-H, *J* = 9.0 Hz), 7.5 (m, H-4, H-6), 6.8 (d, *m*-H, *J* = 9.0 Hz), 6.7 (dd, H-3, *J* = 9.0, 2.0 Hz), 6.3 (ddd, H-5, *J* = 7.0, 7.0, 2.0 Hz), 2.0 (br s, NH).

***N*-[[4′-(Dimethylamino)benzoyl]imino]-2-methoxypyridinium ylide 11a and *N*-[[α-methoxy-4′-(dimethylamino)benzilidene]amino]-2-pyridone (12a)** were prepared according to the general procedure and thence separated by column chromatography. Compound **11a** was recrystallized from ethyl acetate (65% yield). Compound **12a** was distilled at 150 °C (1 torr) (11% yield).

***N*-[(4′-Chlorobenzoyl)imino]-2-methoxypyridinium ylide 11e and *N*-[(α-methoxy-4′-chlorobenzylidene)amino]-2-pyridone (12e)** were prepared according to the general procedure and thence separated by column chromatography. Compound **11e** was recrystallized from chloroform/hexane (26% yield). Compound **12e** was distilled at 180 °C (1 torr) (68% yield).

***N*-[(4′-Cyanobenzoyl)imino]-2-methoxypyridinium ylide 11f and *N*-[(α-methoxy-4′-cyanobenzylidene)amino]-2-pyridone (12f)** were prepared according to the general procedure and thence separated by column chromatography. Compound **11f** was recrystallized from chloroform/hexane (13% yield).

(22) For indolizine numbering, see J. Rigaudy and S. P. Klesney, "IUPAC Nomenclature of Organic Chemistry", Pergamon Press, Oxford, 1979.

Table IV. Yields and Physical Data of 3-Methoxy-1,2-diazepines 15

	yield, %	mp, °C	UV (EtOH) λ_{max} (ϵ)	^{1}H NMR ($CDCl_3$), δ (J, Hz) H-4	H-5	H-6	H-7
15a	46	92-93	225 (13 500), 315 (18 000)	6.3 (d, $J_{4,5}$ = 11)	6.7 (m)	5.8 (br t)	6.7 (m)
15b	73	65-66	220 (10 200), 265 (11 500), 324 (1000)	6.3 (dd, $J_{4,5}$ = 11, $J_{4,6}$ = 1)	6.6 (dd, $J_{4,5}$ = 11, $J_{5,6}$ = 5)	5.8 (ddd, $J_{6,7}$ = 7, $J_{5,6}$ = 5, $J_{4,6}$ = 1)	6.9 (m)
15c	77	80-82	220 (9000), 265 (10 500), 324 (800)	6.4 (dd, $J_{4,5}$ = 12, $J_{4,6}$ = 1)	6.7 (dd, $J_{4,5}$ = 12, $J_{5,6}$ = 6)	5.9 (ddd, $J_{6,7}$ = 8, $J_{5,6}$ = 6, $J_{4,6}$ = 1)	6.8 (m)
15d	72	60-61	250 (8200), 315 (1400)	6.25 (dd, $J_{4,5}$ = 11.5, $J_{4,6}$ = 1.5)	6.6 (dd, $J_{4,5}$ = 11.5, $J_{5,6}$ = 5)	5.8 (ddd, $J_{6,7}$ = 7.5, $J_{5,6}$ = 5, $J_{4,6}$ = 1.5)	6.8 (d, $J_{6,7}$ = 7.5)
15e	50	94-95	230 (12 500), 250 (8100), 326 (750)	6.3 (d, $J_{4,5}$ = 12)	6.6 (dd, $J_{4,5}$ = 12, $J_{5,6}$ = 5)	5.9 (dd, $J_{6,7}$ = 8, $J_{5,6}$ = 5)	6.8 (d, $J_{6,7}$ = 8)

Table V. Yields and Physical Data of 1,2-Dihydro-1,2-diazepin-3-ones 16

	yield, %	mp, °C	UV (EtOH), λ_{max} (ϵ)	^{1}H NMR ($CDCl_3$), δ (J, Hz) H-4	H-5	H-6	H-7
16a	73	165-166	315[a] (11 000)	6.3 (dd, $J_{4,5}$ = 12, $J_{4,6}$ = 1)	6.7 (m)	5.8 (ddd, $J_{6,7}$ = 8, $J_{5,6}$ = 8, $J_{4,6}$ = 1)	6.7 (m)
16b	66	151-153	255[a] (5900)	6.3 (dd, $J_{4,5}$ = 12, $J_{4,6}$ = 1)	6.7 (dd, $J_{4,5}$ = 12, $J_{5,6}$ = 7)	5.9 (ddd, $J_{6,7}$ = 7, $J_{5,6}$ = 7, $J_{4,6}$ = 1)	6.8 (m)
16c	65	139-140	260[a] (5500)	6.3 (dd, $J_{4,5}$ = 12, $J_{4,6}$ = 1)	6.7 (dd, $J_{4,5}$ = 12, $J_{5,6}$ = 6)	5.9 (ddd, $J_{6,7}$ = 8, $J_{5,6}$ = 6, $J_{4,6}$ = 1)	6.9 (m)
16d	70	167-168	240 (7500), 270[a] (5300)	6.4 (dd, $J_{4,5}$ = 11, $J_{4,6}$ = 1)	6.7 (dd, $J_{4,5}$ = 11, $J_{5,6}$ = 6)	6.0 (ddd, $J_{6,7}$ = 7, $J_{5,6}$ = 6, $J_{4,6}$ = 1)	6.8 (d, $J_{6,7}$ = 7)
16e	63	187-188	230[a] (11 500)	6.35 (dd, $J_{4,5}$ = 11, $J_{4,6}$ = 1)	6.7 (m)	6.0 (ddd, $J_{6,7}$ = 8, $J_{5,6}$ = 7, $J_{4,6}$ = 1)	6.7 (m)

[a] All these absorption bands are tailing out above 400 nm.

Compound **12f** was recrystallized from acetone/hexane (85% yield).

Photochemical Synthesis of 1-Benzoyl-3-methoxy-1,2-diazepine (15d). General Procedure. A stirred mixture of 760 mg (3.3 mmol) of pyridinium ylide **11d**, 750 mL of toluene, and 15 mL of acetonitrile was irradiated in a 1-L vessel equipped with a Hanovia immersion well under nitrogen atmosphere at room temperature by means of a Philips HPK 125 mercury high-pressure lamp through Pyrex glass. The reaction was monitored by TLC and by UV spectroscopy and the irradiation stopped after complete disappearance of the starting material. After evaporation of the solvents in vacuo, the residue was chromatographed over silica gel with cyclohexane/ethyl acetate. Sublimation at 45 °C under 10^{-2} torr yielded 550 mg (72%) of **15d** as yellow crystals: IR (KBr) 1635, 1610, 1280 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 169.91 (St, C=O), 168.91 (Sdq, C-3), 138.75 (Ddd, C-5), 136.06 (Dm, C-7), 134.56 (St, Cs), 130.60 (Dt, *p*-C), 129.23 (Ddd, *o*-C), 127.68 (Ddd, *m*-C), 125.68 (Dd, C-4), 119.68 (Ddd, C-6), 55.85 (Qs, OMe).

Iron Tricarbonyl Complex of 1-Benzoyl-3-methoxy-1,2-diazepine (15d). To a stirred solution of 310 mg (1.35 mmol) of diazepine **15d** in 60 mL of benzene was added portionwise 1.0 g of $Fe_2(CO)_9$ at room temperature. After 8 h excess reagent was filtered off and the remaining solution evaporated to dryness. The residue was recrystallized in ether whereby 150 mg of the iron tricarbonyl complex of **15d** was obtained: mp 138–140 °C; IR (KBr) 2050, 2000, 1980, 1655 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.7–7.25 (m, 5, Ph), 6.6 (dd, 1, H-7, $J_{6,7}$ = 7 Hz, $J_{5,7}$ = 2 Hz), 5.3 (ddd, 1, H-5, $J_{5,6}$ = 5 Hz, $J_{5,4}$ = 6 Hz, $J_{5,7}$ = 2 Hz), 4.8 (ddd, 1, H-6, $J_{6,7}$ = 6 Hz, $J_{5,6}$ = 5 Hz, $J_{4,6}$ = 2 Hz), 3.3 (s, 3, OCH_3), 3.2 (dd, 1, H-4, $J_{4,5}$ = 6 Hz, $J_{4,6}$ = 2 Hz).

Photochemical Synthesis of 1-(4′-Methoxybenzoyl)-3-methoxy-1,2-diazepine (15b). A stirred mixture of 4.4 g (17.4 mmol) of pyridinium ylide **11b**, 900 mL of toluene, and 50 mL of acetonitrile was irradiated according to the general procedure. After evaporation of the solvent in vacuo, ether was added to the residue. A colorless product precipitated, which was recrystallized from acetone/ether to yield 200 mg (0.24 mmol) of *N,N′*-bis-(4′-methoxybenzoyl)urea, mp 225–227 °C.[23] The filtrate was evaporated in vacuo and the residue chromatographed over silica gel with cyclohexane/ethyl acetate. A homogenous solid compound was isolated; recrystallization from ether led to 3.27 g (127 mmol) of **15b** (73%) as yellow crystals: IR (KBr) 1645, 1600 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 169.27 (St, C=O), 168.77 (Sdq, C-3), 161.71 (Sm, *p*-C), 138.84 (Ddd, C-5), 136.47 (Ddt, C-7), 131.51 (Dd, *o*-C), 126.59 (St, Cs), 125.63 (Ddt, C-4), 119.26 (Dt, C-6), 112.97 (Dd, *m*-C), 55.85 (Qs, OMe), 55.22 (Qs, OMe).

Large-Scale Synthesis of Diazepine 15b. A mixture of 20 g of the ylide **11b**, 10 L of toluene, and 500 mL of acetonitrile was irradiated in a 2000-W falling-film photoreactor.[5] The starting material was consumed after 15 h. The workup was identical with that reported in the smaller scale experiment, and 12.3 g of diazepine **15b** (61.5%) was obtained.

Photochemical Synthesis of 1-(4′-Ethoxybenzoyl)-3-methoxy-1,2-diazepine (15c). A stirred mixture of 1 g (3.7 mmol) of pyridinium ylide **11c**, 900 mL of toluene, and 50 mL of methanol was irradiated according to the general procedure. After evaporation of the solvent in vacuo, ether was added to the residue, and a colorless product precipitated, which was recrystallized from acetone to yield 50 mL (0.26 mmol) of *N*-(carbomethoxy)-4-ethoxyaniline. The filtrate was evaporated in vacuo and the residue chromatographed over silica gel with cyclohexane/ethyl acetate. Recrystallization from ether gave 770 mg (2.83 mmol, 70%) of **15c**: mp 80–82 °C (yellow crystals); IR (KBr) 1635, 1600 cm^{-1}.

Photochemical Synthesis of 1-[4′-(Dimethylamino)-benzoyl]-3-methoxy-1,2-diazepine (15a). A stirred mixture of 220 mg (0.8 mmol) of ylide **11a**, 200 mL of toluene, and 6 mL of acetonitrile was irradiated according to the general procedure. After evaporation of the solvent in vacuo, the residue was purified by thick-layer chromatography (silicic acid) and recrystallized from diethyl ether to yield **15a**: 46% yield; yellow crystals; IR (KBr) 1620, 1600 cm^{-1}.

Photochemical Synthesis of 1-(4′-Chlorobenzoyl)-3-methoxy-1,2-diazepine (15e). A stirred mixture of 600 mg (2.3 mmol) of ylide **11e**, 700 mL of toluene, and 50 mL of acetonitrile was irradiated according to the general procedure. After evaporation of the solvent in vacuo, the residue was purified by thick-layer chromatography (silicic acid) and recrystallized from diethyl ether to yield **15e**: 50% yield; yellow crystals; IR (KBr) 1635, 1610 cm^{-1}.

Preparation of 1-Benzoyl-1,2-dihydro-1,2-diazepin-3-ones 16. General Procedure for the Preparation of Diazepinone 16d. To a stirred mixture of 228 mg of diazepine **15d** (1 mmol), 225 mg of sodium iodide (1.5 mmol), and 30 mL of anhydrous acetonitrile at 0 °C was added dropwise a mixture of 162 mg (1.5

(23) Y. Iurakura, T. Nishiguchi, and A. Nabeya, *J. Org. Chem.*, 31, 1651 (1966).

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

Akikazu Kakehi,* Suketaka Ito, Kozo Watanabe, Masahiko Kitagawa, Sadafumi Takeuchi, and Toshio Hashimoto

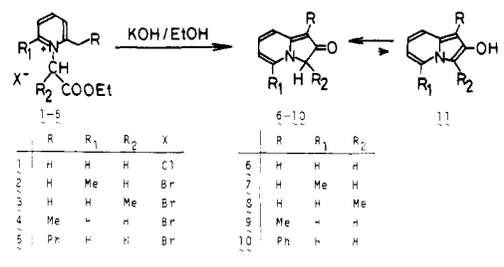
Department of Industrial Chemistry, Faculty of Engineering, Shinshu University, Wakasato, Nagano 380, Japan

Received May 22, 1980

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