# Molecular Design by Cycloaddition Reactions. Part IX.[1] Further Investigation of the Cycloaddition Reactions of Pyridinium Allylides [1-(1-Pyridinio)prop-2-enides] to give Indolizines

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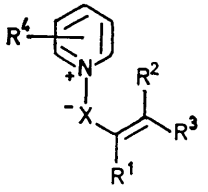
Pyridinium allylides, readily obtainable from 1-(2,3-bismethoxycarbonylallyl)pyridinium salts [(3)—(5) and (7)] in the presence of alkali, cyclised intramolecularly to give 3-unsubstituted indolizine derivatives [(10)—(14)]. However, similar treatment of the 4-methylpyridinium allylide (6) gave only tetramethyl benzene-1,2,4,5-tetracarboxylate (15). In contrast, reactions of the 1-(3,3-bisethoxycarbonylallyl)pyridinium salts (8) and (9) with ethyl propiolate in the presence of alkali gave the 3-vinylindolizine derivatives (16) and (17), respectively. The mechanisms for formation of the indolizine derivatives are discussed.

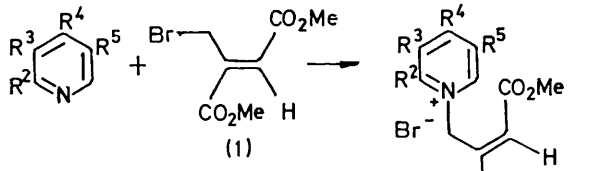
PYRIDINIUM ALLYLIDES [1-(1-pyridinio)prop-2-enides] (Ia) are readily available by dehydrohalogenation of the corresponding pyridinium salts. Since they have two powerful activating groups, an azomethine ylide and a double bond conjugated with a carbonyl group, they are not only expected to react intermolecularly at the two functional groups, but also to react as 1,5-dipoles.

We have previously reported that the 1,3- and 1,5-dipolar cyclisations of pyridinium allylides (Ia) or pyridinium *N*-vinylamides (Ib) are influenced by the



(I) a; CH
b; N

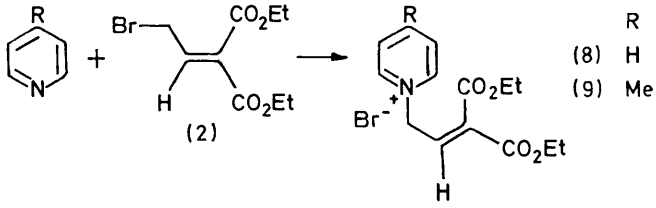
substituents on the double bond conjugated with the carbonyl group.[2-4] Related to this substituent effect, we now report the preparation and chemical behaviour of pyridinium allylides with 2,3- or 3,3-substituents on the allyl system.



(1)

| | $R^2$ | $R^3$ | $R^4$ | $R^5$ |
|---|---|---|---|---|
| (3) | H | H | H | H |
| (4) | Me | H | H | H |
| (5) | H | Me | H | H |
| (6) | H | H | Me | H |
| (7) | Me | H | H | Me |

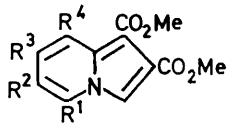
When excess of a pyridine derivative and dimethyl 2-bromomethylfumarate (1) were mixed in benzene at room temperature the corresponding pyridinium salts (3)—(7) were obtained in quantitative yields. Similar treatment of pyridine derivatives with diethyl 2-bromoethylidenemalonate (2) gave the hygroscopic salts (8) and (9) in almost quantitative yields. The salts were used in subsequent reactions without further purification.



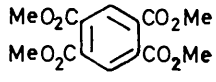
(2)

| | R |
|---|---|
| (8) | H |
| (9) | Me |

The pyridinium salts (3), (4), and (7) were treated with an excess of potassium carbonate in benzene at room temperature to afford the corresponding 1,2-bismethoxycarbonylindolizine derivatives (10), (11), and (14). A similar reaction with the unsymmetrically substituted pyridinium salt (5) gave two isomeric compounds, (12) and (13), together with tetramethyl benzene-1,2,4,5-tetracarboxylate (15); the former compound was



| | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|
| (10) | H | H | H | H |
| (11) | Me | H | H | H |
| (12) | H | H | H | Me |
| (13) | H | Me | H | H |
| (14) | Me | H | H | Me |



(15)

the major product (n.m.r. analysis). However, from similar treatment of the salt (6), only the tetramethyl ester (15) was isolated; no indolizine was detected, presumably because of the instability of the ylide.†

Treatment of the salts (8) and (9) with excess of potassium carbonate in benzene or chloroform afforded only intractable materials; no indolizines were detected by n.m.r. However, treatment of (8) and (9) with ethyl propiolate in the presence of potassium carbonate

† *Added in proof.*—Similar attempted cyclisation of the pyridinium salts (3) and (6) was recently reported [Y. Tamura, Y. Sumida, S. Tamada, and M. Ikeda, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 1139]; only black tars were formed and no indolizine derivatives were detected.

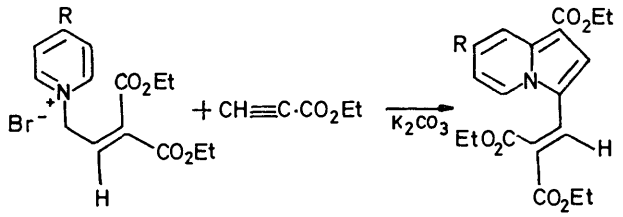
[1] Part VIII, T. Sasaki, K. Kanematsu, and Y. Yukimoto, *J. Org. Chem.*, in the press.

[2] T. Sasaki, K. Kanematsu, and A. Kakehi, *J. Org. Chem.*, 1972, **37**, 3106.

[3] T. Sasaki, K. Kanematsu, A. Kakehi, and G. Ito, *Tetrahedron*, 1972, **28**, 4947.

[4] T. Sasaki, K. Kanematsu, and A. Kakehi, *Tetrahedron Letters*, 1972, 5245.

afforded the 3-(2,2-bisethoxycarbonylvinyl)indolizine derivatives (16) and (17), respectively.



R
(16) H
(17) Me

The structures of the indolizine derivatives [(10)—(14), (16), and (17)] were established by elemental and

TABLE 1

N.m.r. data of indolizine derivatives (10)—(14) in $CCl_4$

| | δ Values | | | | | | |
|---|---|---|---|---|---|---|---|
| Compd. | 3-H | 4-H | 5-H | 6-H | 7-H | OMe | J/Hz |
| (10) | 7·45 (s) | 7·85 (d) | 6·54br (dd) | 6·85br (dd) | 7·96 (d) | 3·79 (s) | $J_{4,5}$ 7·0 $J_{5,6}$ 6·0 $J_{6,7}$ 10·5 |
| (11) | 7·33 (s) | [2·51 (s,Me)] | 6·43br (d) | 6·85 (dd) | 7·95br (d) | 3·81 (s) | $J_{5,6}$ 6·3 $J_{6,7}$ 9·0 |
| (12)* | 7·45 (s) | 7·53 (m) | 6·34br (t) | 6·37 (m) | [2·32 (s,Me)] | 3·77 (s) | |
| (14) | 7·36 (s) | [2·45 (s,Me)] | 6·21 (d) | 7·42 (d) | [2·34 (s,Me)] | 3·76 (s) | $J_{5,6}$ 7·0 |

* The isomer (13) shows δ 2·18 (s, 5-Me).

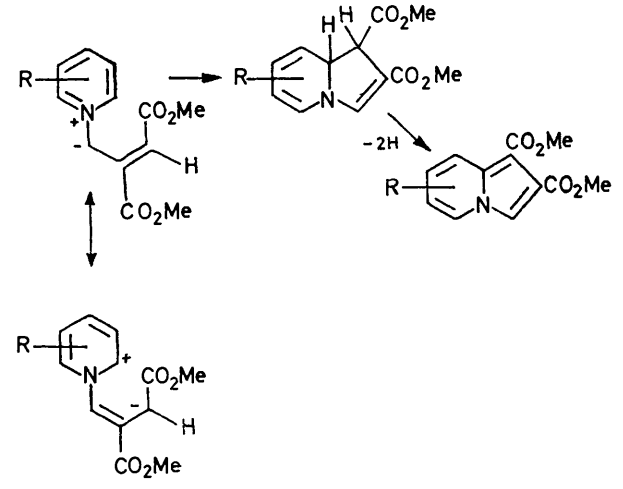
TABLE 2

N.m.r. data of indolizine derivatives (16) and (17) in $CCl_4$

| | δ Values | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Compd. | 2-H | 4-H | 5-H | 6-H | 7-H | =CH | $CH_2Me$ | $CH_3$-$CH_2$ |
| (16) | 7·47 (s) | 8·17br (d) | 6·80br (t) | 7·12br (t) | 8·25br (d) | 7·75 (s) | 4·30 (m) | 1·38 (m) |
| (17)* | 7·48 (s) | 8·08br (d) | 6·67br (d) | [2·41 (s,Me)] | 8·25br (s) | 7·76 (s) | 4·28 (m) | 1·37 (m) |

* $J_{4,5}$ 7·5 Hz.

spectral analyses. The n.m.r. spectral data are listed in Tables 1 and 2. The 3-unsubstituted indolizines

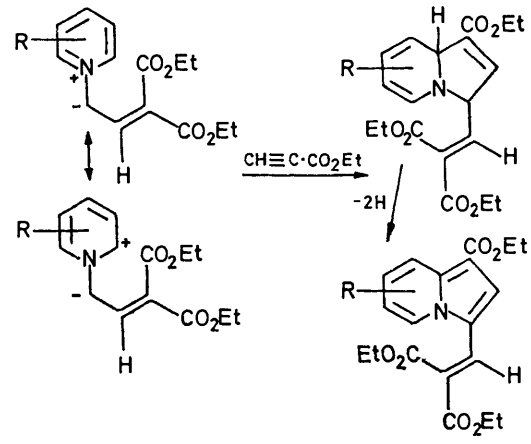


(10)—(14) showed a singlet in the region δ 7·5—7·3 attributable to the C-3 proton. The 3-vinylindolizines (16) and (17) showed two singlets, at δ 7·8 and 7·5, attributable to the olefinic proton and the C-2 proton, respectively.

The formation of the 3-unsubstituted indolizines (10)—(14) seems to proceed *via* intramolecular 1,5-dipolar cyclisation followed by dehydrogenation. Such a mechanism has been proposed by us for the intramolecular cyclisation of pyridinium *N*-vinylimides.[2] On the other hand, the formation of the tetramethyl ester (15) apparently proceeds *via* dimerisation of a vinylcarbene intermediate (A) or an allyl radical intermediate (B), produced by elimination of a pyridine molecule from the pyridinium allylide, followed by dehydrogenation.

(A) (B)

The formation of the 3-vinylindolizines (16) and (17) could be an example of the well known 1,3-dipolar cycloaddition reactions of pyridinium allylides, in which they behave as 1,3-dipoles and ethyl propiolate behaves as a 1,3-dipolarophile. This result implies that intramolecular 1,5-dipolar cyclisation of these pyridinium allylides is hindered by the geminal substituents; consequently these compounds act only as 1,3-dipoles.



## EXPERIMENTAL

M.p.s were measured with a Yanagimoto micro apparatus. Microanalyses were performed on a Perkin-Elmer 240 Elemental Analyser. N.m.r. spectra were determined with a Japan Optics Co., C-60-XL spectrometer with $Me_4Si$ as internal standard. I.r. spectra were taken with a JASCO IR-S spectrophotometer and u.v. spectra with a JASCO ORD/UV-5 recorder.

*Pyridinium Salts* (3)—(9).—*General method.* A mixture of dimethyl 2-bromomethylfumarate (1) or diethyl 2-bromoethylidenemalonate (2) and a small excess of pyridine derivative was stirred in benzene (50 ml) at room temperature for 1—2 days, then concentrated under reduced pressure. Unchanged pyridine derivatives were extracted with ether, and the corresponding pyridinium salts were obtained as hygroscopic oily materials in quantitative yield.

The crude pyridinium salts were used without further purification.

*Reactions of Pyridinium Salts* (3)—(7) *in the Presence of Potassium Carbonate.—General method.* A solution of pyridinium salt (1·0 g) and potassium carbonate (3·0 g) in benzene (50 ml) was stirred at room temperature for 1 day and then insoluble material was removed. The filtrate was concentrated *in vacuo* and the residue was separated by column chromatography (alumina; benzene as eluant). Recrystallisation from ether–n-hexane gave the indolizine derivative [(10)—(14)] and tetramethyl benzene-1,2,4,5-tetracarboxylate (15) (Table 3).

TABLE 3

| Product | Yield (%) | M.p. (°C) | Formula | Required (%) C | H | N | Found (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| (10) | 45 | 73—75 | $C_{12}H_{11}NO_4$ | 61·8 | 4·75 | 6·0 | 61·55 | 4·9 | 5·75 |
| (11) | 40 | 82—83 | $C_{13}H_{13}NO_4$ | 63·15 | 5·3 | 5·65 | 63·25 | 5·3 | 5·35 |
| (12) | 20* | | $C_{13}H_{13}NO_4$ | 63·15 | 5·3 | 5·65 | 63·2 | 5·5 | 5·5 |
| (13) | 1* | | | | | | | | |
| (14) | 34 | 136—137 | $C_{14}H_{15}NO_4$ | 64·35 | 5·8 | 5·35 | 64·15 | 5·8 | 5·2 |
| (15) | 20 | 138—140 | $C_{14}H_{14}O_8$ | 54·2 | 4·55 | | 53·95 | 4·55 | 5·2 |

* The ratio of (12) to (13) was determined by n.m.r.

*Reactions of Pyridinium Allylides with Ethyl Propiolate.*—A solution of the pyridinium salt (8) (1·03 g) or (9) (1·07 g) and ethyl propiolate (0·29 g) in benzene (50 ml) was stirred with potassium carbonate (3·0 g) at room temperature for 1 day. Work-up as in the previous experiments afforded the 3-vinylindolizine derivative (16) or (17) (Table 4).

TABLE 4

| Product | Yield (%) | M.p. (°C) | Formula | Required (%) C | H | N | Found (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| (16) | 30 | 74—76 | $C_{19}H_{21}NO_6$ | 63·5 | 5·9 | 3·9 | 63·75 | 5·85 | 4·0 |
| (17) | 29 | 64—65 | $C_{20}H_{23}NO_6$ | 64·35 | 6·2 | 3·75 | 64·4 | 6·15 | 3·7 |

[3/715 *Received, 5th April,* 1973]