# Preparation of New Nitrogen-bridged Heterocycles. 8.[1] Syntheses of Some Fused Indolizine Derivatives *via* the Acid-catalyzed Cyclizations of Functionalized 1- and 3-Vinylindolizines

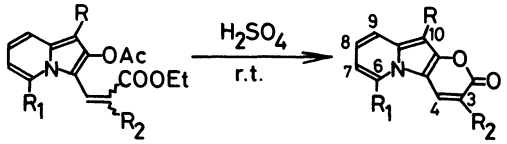
Akikazu KAKEHI,* Suketaka ITO, Shinji MURAKAMI, and Hiroaki SANO
*Department of Industrial Chemistry, Faculty of Engineering, Shinshu University, Wakasato, Nagano 380*
(Received October 1, 1983)

Pyrano[3,2-*a*] and pyrano[2,3-*b*]indolizin-2-one derivatives were prepared in 12—86% yields by the acid-catalyzed deacetylation-cyclization of 2-acetoxy-1- and 3-[2-(ethoxycarbonyl)vinyl]indolizines with concentrated sulfuric acid at room temperature. On the other hand, similar reactions of 2-acetoxy-3-[1,2-bis(methoxycarbonyl)vinyl]indolizines did not give the initially expected pyrano[2,3-*b*]indolizinones at all, but, instead of them, afforded 3-(methoxycarbonylmethylene)furo[2,3-*b*]indolizin-2-one derivatives in fair yields. Formation mechanisms and some physical properties are also discussed.

In our pevious paper, we reported the direct formation of ethyl 2-oxo-2*H*-pyrano[2,3-*b*]indolizine-3-carboxylates by the reactions of 1-(ethoxycarbonylmethyl)-2-methylpyridinium bromides with diethyl (ethoxymethylene)malonate, in which we proposed the presence of 3-[2,2-bis(ethoxycarbonyl)vinyl]-2-indolizinols as the key intermeiates.[2] More recently, it was found that these 2-indolizinol intermediates could be trapped smoothly with various acylating and alkylating agents to give the corresponding esters and ethers,[3] and that an acetate, 2-acetoxy-[2,2-bis(ethoxycarbonyl)vinyl]-5-methylindolizine, in these compounds was converted slowly to the corresponding pyranoindolizinone in various solvents. These findings focused our attention to the syntheses of fused indolizines starting from readily available 2-acetoxy-3-vinylindolizine derivatives. In this paper, we wish to report the preparations of some 2*H*-pyrano[3,2-*a*] and [2,3-*b*]indolizin-2-one and 3-methylene-2*H*-furo[2,3-*b*]indolizin-2-one derivatives from the reactions of functionalized 2-acetoxy-1- or 3-vinylindolizines with concentrated sulfuric acid.

## Results and Discussion

*Preparations of 2H-Pyrano[2,3-b]indolizin-2-one Derivatives.* Since the spontaneous deacetylation-cyclization of these 2-acetoxy-3-vinylindolizine derivatives could not be actually observed in various solvents except only one example described above, we examined the possibility of this process under various acidic and basic conditions[4] and found a method in which concentrated sulfuric acid was employed as a catalyst. Treatment of 2-acetoxy-3-[2,2-bis(ethoxycarbonyl)vinyl]indolizines (**1**—**4**) with a small amount of concentrated sulfuric acid (1 ml per 1 mmol indolizine) at room temperature gave the expected ethyl 2-oxo-2*H*-pyrano[2,3-*b*]indolizine-3-carboxylates (**5**—**8**) in 41—86% yields as strongly fluorescent orange crystals. Similar treatment of 3-[2-acetyl-2-(ethoxycarbonyl)vinyl]indolizines (**9**—**12**) (cis-trans mixtures) afforded the corresponding 3-acetyl derivatives (**13**—**16**), but the yields were lower (12—54%) than those of **5**—**8**. On the other hand, the reactions of 3-[2-cyano-2-(ethoxycarbonyl)vinyl]indolizines (**17** and **19**) with sulfuric acid at room temperature afforded only undeterminable insoluble substances but those of **17**—**20** at 80—95 °C gave 3-unsubstituted 2*H*-pyranoindolizinones (**21**—**24**) in variable yields (0—50%) (Scheme 2). Several attempts to prepare **23** from indolizine (**19**) and ethyl 2-oxo-2*H*-pyranoindolizine-3-carboxylate (**7**) under various conditions were unsuccessful.



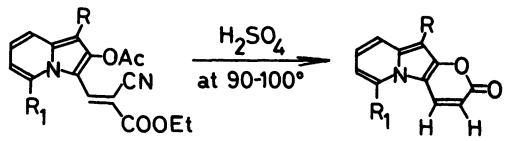

1-4,9-12

| | R | $R_1$ | $R_2$ |
|---|---|---|---|
| 1 | Me | H | COOEt |
| 2 | Et | H | COOEt |
| 3 | Ph | H | COOEt |
| 4 | H | Me | COOEt |
| 9 | Me | H | Ac |
| 10 | Et | H | Ac |
| 11 | Ph | H | Ac |
| 12 | H | Me | Ac |

5-8,13-16

| | R | $R_1$ | $R_2$ |
|---|---|---|---|
| 5 | Me | H | COOEt |
| 6 | Et | H | COOEt |
| 7 | Ph | H | COOEt |
| 8 | H | Me | COOEt |
| 13 | Me | H | Ac |
| 14 | Et | H | Ac |
| 15 | Ph | H | Ac |
| 16 | H | Me | Ac |

Scheme 1.




17-20

| | R | $R_1$ |
|---|---|---|
| 17 | Me | H |
| 18 | Et | H |
| 19 | Ph | H |
| 20 | H | Me |

21-24

| | R | $R_1$ |
|---|---|---|
| 21 | Me | H |
| 22 | Et | H |
| (23) | Ph | H |
| 24 | H | Me |

Scheme 2.

The structures of pyranoindolizinones (**5**—**8**, **13**—**16**, **21**, **22**, and **24**) were determined by their NMR spectral inspection and partly by the comparisons of **5**, **7**, and **8** with authentic samples prepared previously by us.[2] In particular, the structures of 3-unsubstituted pyranoindolizinones (**21**, **22**, and **24**) were determined by the presence of a AB type proton signals at near $\delta$ 5.9 and 8.0 with the coupling constant of 9.5 Hz together with other signals due to the indolizine moiety in their NMR spectra (see Table 1).

TABLE 1. SOME DATA OF FUNCTIONALIZED 1- AND 3-VINYLINDOLIZINES

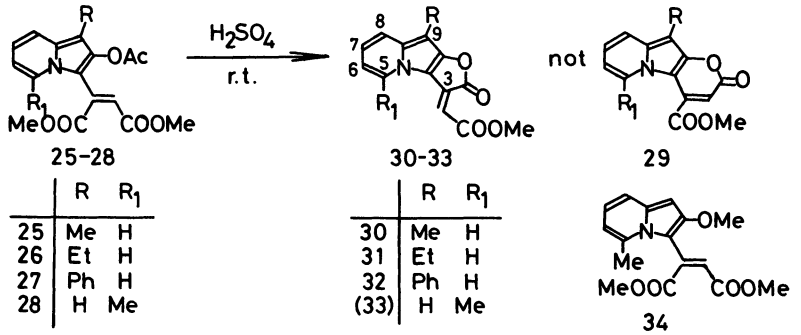
| Compd No. | Yield % | Mp $\theta_m$/°C | $\nu_{C=O}^{KBr}$/cm$^{-1}$ | δ (vinyl proton) | Formula | Calcd(%) C | H | N | Found(%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **2** | 59 | 99—100 | 1771 1718 1700 | 7.93 | $C_{20}H_{23}NO_6$ | 64.33 | 6.21 | 3.75 | 64.29 | 5.98 | 3.80 |
| **4** | 67 | 113—115 | 1755 1705 1695 | 8.41 | $C_{19}H_{21}NO_6$ | 63.50 | 5.89 | 3.90 | 63.62 | 5.78 | 3.89 |
| **9**[a] | 68 | 105—106 | 1769 1716 | 7.93 and 7.98[b] | $C_{18}H_{19}NO_5$ | 65.64 | 5.82 | 4.25 | 65.69 | 5.61 | 4.39 |
| **10**[a] | 69 | 65—67 | 1770 1701 | 7.92 and 7.95[b] | $C_{19}H_{21}NO_5$ | 66.46 | 6.16 | 4.08 | 66.19 | 6.02 | 3.87 |
| **11**[a] | 58 | 123—125 | 1770 1700 | 7.98 and 8.03[b] | $C_{23}H_{21}NO_5$ | 70.58 | 5.41 | 3.58 | 70.67 | 5.61 | 3.29 |
| **12**[a] | 30 | 112—115 | 1760 1683 | 8.43[c] | $C_{18}H_{19}NO_5$ | 65.64 | 5.82 | 4.25 | 65.53 | 5.80 | 4.38 |
| **26** | 60 | 100—102 | 1769 1721 1702 | 4.13 | $C_{18}H_{19}NO_6$ | 62.60 | 5.55 | 4.06 | 62.45 | 5.49 | 3.98 |
| **28** | 53 | 84—85 | 1760 1712 | 4.52 | $C_{17}H_{17}NO_6$ | 61.63 | 5.17 | 4.23 | 61.88 | 5.19 | 4.39 |
| **34** | 49 | 86—87 | 1724 1714 | 6.18 | $C_{16}H_{17}NO_5$ | 63.36 | 5.65 | 4.62 | 63.18 | 5.64 | 4.63 |
| **35** | 61 | 105—106 | 1751 1709 1673 | 8.06 | $C_{18}H_{19}NO_5$ | 65.64 | 5.82 | 4.25 | 65.56 | 5.82 | 4.28 |
| **36** | 45 | 110—111 | 1755 1693 1681 | 8.10 | $C_{19}H_{21}NO_5$ | 66.46 | 6.16 | 4.08 | 66.49 | 6.15 | 4.07 |

a) This compound is a cis-trans mixture, but its ratio could not be calculated because of the absence of definitely separated signals in the NMR spectrim. b) The peak of major isomer. c) Both vinyl proton signals of cis and trans isomers were overlapped.

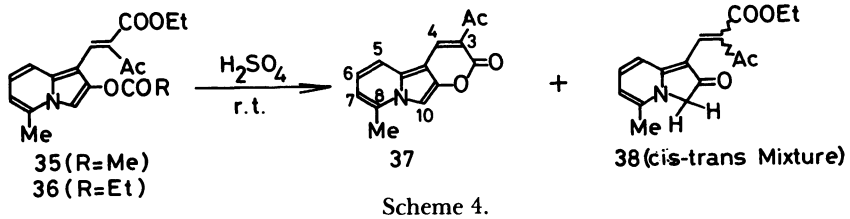
*Preparations of 3-Methylene-2H-furo[2,3-b]indolizines.* When the acidic treatment of 2-acetoxy-3-[1,2-bis(methoxycarbonyl)vinyl]indolizines (**25—27**) at room temperature were carried out, the initially expected 2-oxo-2*H*-pyranoindolizine-4-carboxylates such as **29** could not be obtained at all, but, instead of them, reddish crystalline substances **30—32** were obtained in 51—68% yields (Scheme 3). Although various reaction conditions such as the quantity and the concentration of sulfuric acid, the reaction time, and the reaction temperature, were tested in the case of 5-methylindolizine (**28**), no furoindolizine (**33**) could be isolated and only a small amount of 2-methoxy-3-vinylindolizine (**34**) could be always obtained.

The structural assignment of 3-methylenefuroindolizinones (**30—32**) was accomplished mainly by their physical and spectral means. The facts that these compounds have not any strong fluorescence characteristics of pyranoindolizinone as seen in **5—8**, **13—16**, **21**, **22**, and **24** and that their NMR spectra were very similar to those of the starting materials **25—27** except the loss of an acetoxyl and a methoxyl proton signals supported clearly these structures fused with a nonaromatic furan ring. The cis configuration of the exo-methylene group in **30—32** was decided by the similarity of the chemical shifts (δ 6.2—6.4) due to the olefinic proton with those (δ 6.1—6.3) of **25—27**. On the other hand, an abnormal product **34** from the reaction of 5-methyl-3-vinylindolizine (**28**) was concluded to be 3-[1,2-bis(methoxycarbonyl)vinyl]-2-methoxy-5-methylindolizine by its NMR inspecion and an unequivocal synthesis (see Experimental section).

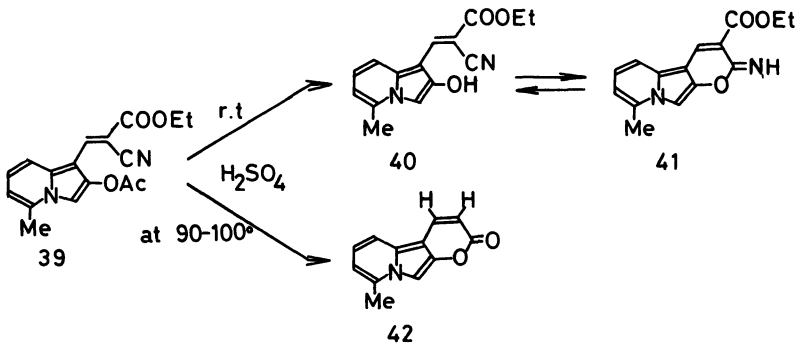
*Preparations of 2H-Pyrano[3,2-a]indolizines.* Similar reaction of 2-acetoxy-1-[2-acetyl-2-(ethoxycarbonyl)vinyl]-5-methylindolizine (**35**) at room temperature gave the corresponding 3-acetyl-8-methyl-2*H*-pyrano[3,2-*a*]indolizin-2-one (**37**) and an unexpected 1-vinyl-2(3*H*)-indolizinone (**38**) in 12 and 87% yields. The major product **38** was obtained also from the reaction using 2-propionyloxyindolizine deriva-




Scheme 3.




Scheme 4.

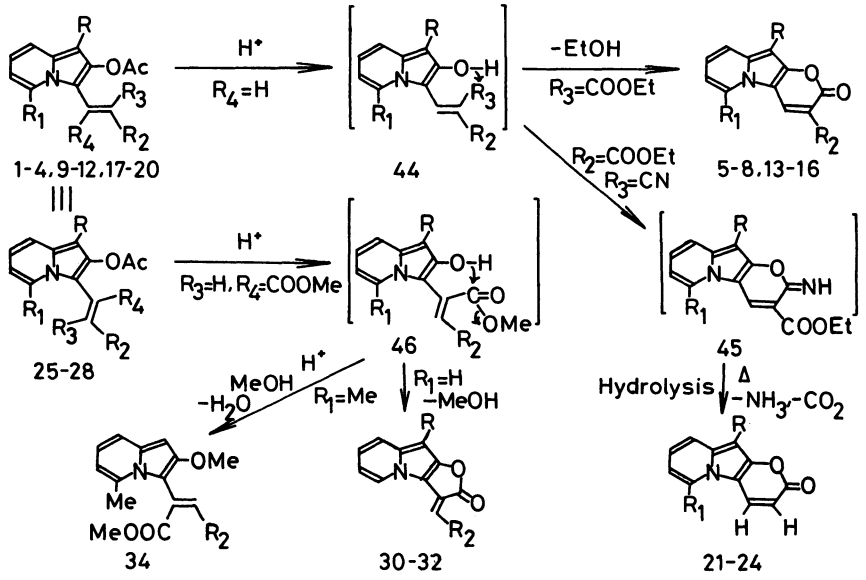



Scheme 5.

tive (**36**) in 89% yield (Scheme 4). Similar reaction of 1-[2-cyano-2-(ethoxycarbonyl)vinyl] derivative (**39**) gave 1-vinyl-2-indolizinol (**40**) and/or pyranoindolizin-2-imine (**41**) in 95% yield. On the other hand, the reaction of **39** under heating conditions afforded the corresponding 3-unsubstituted 8-methyl-2*H*-pyrano[3,2-*a*]indolizin-2-one (**42**) in 41% yield (Scheme 5).

The structures of pyrano[3,2-*a*]indolizinones (**37** and **42**) were determined by the comparisons of their physical and spectral data with those of pyrano[2,3-*b*]indolizinone derivatives. On the other hand, the structure of 1-vinyl-2(3*H*)-indolizinone (**38**) was decided by its NMR inspection and its chemical conversion to acetate 43. Since this compound **38** was a cis-trans mixture (cis:trans=3:4),[5] the NMR spectrum showed multiple complex signals due to the two sets of protons, but a two proton singlet attributable to the 3-methylene group was appeared clearly at $\delta$ 4.30. Furthermore, the fact that this group is an active methylene was also indicated by the disappearance of the proton signal with deuterium oxide as seen in known 2(3*H*)-indolizinones.[2] The acetate **43** obtained from **38** was same with compound **35** in the IR spectra, but an another set of proton signals were also appeared in the NMR spectrum of **43** and the melting point (102—104°C) was lower than that (mp 105—106°C) of **35**. Thus, we concluded compound **43** to be a cis-trans mixture[6] of 2-acetoxy-1-[2-acetyl-2-(ethoxycarbonyl) vinyl]-5-methylindolizin (**35**). The structure of product from the reaction of **39** at room temperature was tentatively assigned to be an equilibrium mixture of 1-vinyl-2-indolizinol (**40**) and pyranoindolizin-2-imine (**41**), because this compound has a very strong fluoresence similar to that of tricyclic pyranoindolizinones and extremely low solubility in contract with bicyclic vinylindolizines and vinylindolizinone, and its IR spectrum exhibited a weak cyano absorption band at 2198 $cm^{-1}$.[7] On the other hand, an alternative possibility of the presence of its 3-cyanopyranoindolizinone derivative was neglected clearly by its elementary analysis, by which the composition of the product was completely in accord with the structure possessing an ethoxycarbonyl group.[8]

*Reaction Mechanisms.* The formation reaction of 2*H*-pyrano[2,3-*b*]indolizin-2-ones (**5**—**8** and **13**—**16**) and 3-methylenefuro[2,3-*b*]indolizin-2-ones (**30**—**32**) can be explain reasonably by considering the intermediacy of 3-vinyl-2-indolizinol intermediate **44** or **46** from the acetates (**1**—**4**, **9**—**12**, and **25**—**28**) and subsequent intramolecular nucleophilic reactions between the hydroxyl and the ester carbonyl group in the




Scheme 6.

six- or five-membered transition states. Similarly, 3-unsubstituted pyrano[2,3-*b*]indolizin-2-ones (**21**—**24**) must be formed *via* the nucleophilic attack of the hydroxyl group onto the cyano group in **44** followed by the acid hydrolysis and then decarboxylation of the resulting 2*H*-pyrano[2,3-*b*]indolizin-2-imine (**45**). Furthermore, the acid-catalyzed dehydration from indolizinol (**46**) and a methanol generated by the hydro lysis of the methoxycarbonyl group may afford 2-methoxyindolizine (**34**). These mechanisms are summarized in Scheme 6. The fact that no 2-oxopyranoindolizine-4-carboxylate such as **29** could be obtained in the reactions of indolizines (**25**—**28**) may suggest the cis character of the two ester groups in **25**—**28** and the difficulty of the cis-trans isomerization of the vinyl group under reaction conditions employed here. We described previously the cis configuration of this group in **25** and **27**[3] and, here, observed the cis character of the exocyclic 3-methylene group in **30**—**32** and the more diminished yields of 3-acetylpyranoindolizinones (**13**—**16**) compared with those of 2-oxopyranoindolizine-3-carboxylate (**5**—**8**). In the reaction of 5-methylindolizine (**28**), the fact that no tricyclic product such as **29** and **32** was obtained seems to indicate the loss of requisite of planarity for the transition states in such cyclizations owing to the steric repulsion between the 5-methyl and the 3-[1-(methoxycarbonyl)] group, and, thus, to lead to the formation of an ethereal product (**34**) from 2-indolizinol (**46**).

The formation mechanisms of 2*H*-pyrano[3,2-*a*]-indolizinone derivatives (**37**, **41** (or **40**), and **42**) can be also considered by similar manners described above in the cases of 2-acetoxy-3-vinylindolizines, while 1-vinyl-2(3*H*)-indolizinone (**38**) is simply a keto-isomer of 1-vinyl-2-indolizinol intermediate.

## Experimental

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 in $\delta$ values. The IR spectra were taken with a Hitachi 260-10 Infrared Spectrophotometer.

*Preparations of 1- and 3-Vinylindolizine Derivatives.* These functionalized 2-acetoxy-3-vinylindolizines (**1**—**4**), (**9**—**12**), (**17**—**20**), and (**25**—**28**) and 2-methoxy-5-methyl-3-vinylindolizine (**34**) were obtained as red prisms by the 2(3*H*)-indolizinone route[3] and 2-acetoxy-1-vinylindolizine derivatives (**35**, **36**, and **39**) were given as orange needles by the 2-allylidene-1,2-dihydropyridine route appeared in our previous papers.[9,10] These results and some physical data of new 1- and 3-vinylindolizine derivatives (**2**, **4**, **9**—**12**, **26**, **28**, and **34**—**36**) are summarized in Table 1.

*Reactions of 1- and 3-Vinylindolizines with Sulfuric Acid.* *Method A*: To 1 mmol of 2-acetoxy-1- or 3-vinylindolizine derivative 1 ml of concentrated sulfuric acid was added and the resulting mixture was kept overnight at room temperature. The reaction solution was poured slowly into a 20 ml of ice-water, neutralized carefully with aqueous potassium carbonate under stirring, and extracted twice with 50 ml portions of chloroform. After the combined extract was filtered through a phase-separating filter paper, the filtrate was concentrated at reduced pressure and the residue was separated by column chromatography (alumina) using ether and then chloroform as eluents. Recrystallization of the crude products from chloroform or ethanol gave the corresponding pyranoindolizinones (**5**—**8** and **13**—**16**) as yellow to orange needles and methylenefuroindolizinones (**30**—**32**) as red prisms.

*Method B*: The similar mixture of vinylindolizine and concentrated sulfuric acid was heated in a sealed tube at 90—100°C for 1—2 h. The usual work-ups of the resulting solutions gave the corresponding 3-unsubstituted pyranoindolizinones (**21**, **22**, **24**, and **42**) as yellow needles.

Table 2. NMR spectral data of pyrano-[2,3-*b*]indolizin-2-ones

| Compd[a] | C-3 | | C-4 | C-6 | C-7 | C-8 | C-9 | R | |
|---|---|---|---|---|---|---|---|---|---|
| **5** | 1.41 t | 4.42 q | 8.78 s | 8.38 br d | 6.93 dt | 7.30 br t | 7.59 br d | 2.31 s | |
| **6** | 1.38 t | 4.37 q | 8.74 s | 8.26 br d | 6.83 dt | 7.18 br t | 7.48 br d | 1.27 t | 2.79 q |
| **7** | 1.41 t | 4.45 q | 8.97 s | 8.45 br d | 7.02 dt | b) | b) | 7.2—8.1 m | |
| **8** | 1.40 t | 4.38 q | 8.91 s | 2.88 s | 6.76 br d | 7.26 q | 7.45 dd | 6.37 s | |
| **13** | 2.71 s | | 8.83 s | 8.35 br d | 6.88 dt | 7.28 br t | 7.49 br d | 2.32 s | |
| **14** | 2.72 s | | 8.88 s | 8.38 br d | 6.90 dt | 7.28 br t | 7.54 br d | 1.30 t | 2.83 q |
| **15** | 2.77 s | | 8.94 s | c) | c) | c) | c) | 6.9—8.1 m | |
| **16** | 2.70 s | | 8.97 s | 2.91 s | 6.78 br d | 7.28 q | 7.50 dd | 6.42 s | |
| **21** | 5.97 d | | 7.88 d | 8.10 br d | 6.73 dt | 7.00 br t | 7.46 br d | 2.34 s | |
| **22** | 5.96 d | | 7.90 d | 8.11 br d | 6.72 dt | 7.02 br t | 7.48 br d | 1.30 t | 2.87 q |
| **24** | 5.91 d | | 8.17 d | 2.82 s | 6.59 br d | 7.04 q | 7.45 dd | 6.44 s | |

a) These coupling constants are as follows: $J_{6,7}=J_{7,8}=7.0$, $J_{3,4}=J_{8,9}=9.0$, $J_{7,9}=1.5$, $J_{Et}=7.0$ Hz. b) Overlapped with the phenyl signals. c) These proton signals could not be determined by its low solubility in deuteriochloroform.

Table 3. NMR spectral data of methylenefuro-[2,3-*b*]indolizin-2-ones and pyrano-[3,2-*a*]indolizin-2-ones

| Compd[a] | C-5 | C-6 | C-7 | C-8 | R | | 3(1)-H | COOMe |
|---|---|---|---|---|---|---|---|---|
| **30** | 8.79 br d | 6.62 dt | 7.00 br t | 7.38 br d | 2.30 s | | 6.25 s | 4.00 s |
| **31** | 8.78 br d | 6.63 dt | 7.00 br t | 7.43 br d | 1.27 t | 2.43 q | 6.27 s | 4.03 s |
| **32** | 8.87 br d | 6.74 dt | 7.09 br t | b) | 7.2—8.0 m | | 6.37 s | 4.05 s |

| Compd[c] | C-3 | C-4 | C-5 | C-6 | C-7 | C-8 | C-10 |
|---|---|---|---|---|---|---|---|
| **37** | 2.72 s | 8.95 s | 7.75 dd | 7.28 q | 6.87 br d | 2.63 s | 7.14 s |
| **42** | 6.98 d | 7.94 d | 7.54 dd | 7.09 q | 6.71 br d | 2.58 s | 7.13 s |

a) $J_{5,6}=J_{6,7}=7.0$, $J_{7,8}=9.0$, $J_{6,8}=1.5$, $J_{Et}=7.0$ Hz. b) Overlapped with the phenyl signals. c) $J_{5,6}=9.0$, $J_{6,7}=7.0$, $J_{5,7}=1.5$ Hz.

TABLE 4. SOME DATA OF FUSED INDOLIZINE DERIVATIVES

| React. No. | Prod. No. | Method | Yield % | Mp $\theta_m$/°C | $\nu_{C=O}^{KBr}$/cm$^{-1}$ | | Formula | Calcd(%) C | H | N | Found(%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | **5** | A | 75 | 239—241 | a) | | | | | | | | |
| **2** | **6** | A | 80 | 202—203 | 1735 | 1685 | $C_{16}H_{15}NO_4$ | 67.35 | 5.29 | 4.90 | 67.31 | 5.31 | 4.94 |
| **3** | **7** | A | 86 | 212—213 | a) | | | | | | | | |
| **4** | **8** | A | 41 | 190—192 | a) | | | | | | | | |
| **9** | **13** | A | 24 | 292—293 | 1715 | | $C_{14}H_{11}NO_3$ | 69.70 | 4.60 | 5.81 | 69.71 | 4.66 | 5.74 |
| **10** | **14** | A | 54 | 255—256 | 1708 | | $C_{15}H_{13}NO_3$ | 70.58 | 5.13 | 5.49 | 70.80 | 5.07 | 5.23 |
| **11** | **15** | A | 49 | >300 | 1715 | | $C_{19}H_{13}NO_3$ | 75.24 | 4.32 | 4.62 | 74.95 | 4.30 | 4.92 |
| **12** | **16** | A | 12 | 247—250 | 1700 | | $C_{14}H_{11}NO_3$ | 69.70 | 4.60 | 5.81 | 69.91 | 4.62 | 5.57 |
| **17** | **21** | B | 8 | 191—193 | 1705 | | $C_{12}H_9NO_2$ | 72.35 | 4.55 | 7.03 | 72.05 | 4.75 | 7.12 |
| **18** | **22** | B | 50 | 185—186 | 1690 | | $C_{13}H_{11}NO_2$ | 73.23 | 5.20 | 6.57 | 73.27 | 5.24 | 6.36 |
| **19** | **23** | B | 0 | | | | | | | | | | |
| **20** | **24** | B | Trace | b) | | | | | | | | | |
| **25** | **30** | A | 51 | 196—197 | 1715 | 1700 | $C_{14}H_{11}NO_4$ | 65.37 | 4.31 | 5.45 | 65.49 | 4.31 | 5.46 |
| **26** | **31** | A | 68 | 149—151 | 1722 | 1708 | $C_{15}H_{13}NO_4$ | 66.41 | 4.83 | 5.16 | 66.48 | 4.88 | 5.05 |
| **27** | **32** | A | 67 | 201—203 | 1717 | 1700 | $C_{19}H_{13}NO_4$ | 71.47 | 4.10 | 4.39 | 71.43 | 4.17 | 4.36 |
| **28** | **34(33)** | A | 7(0) | 86—87 | 1724 | 1714 | $C_{16}H_{17}NO_5$ | 63.36 | 5.65 | 4.62 | 63.18 | 5.64 | 4.63 |
| **35** | **37** | A | 12 | 264—266 | 1700 | 1656 | $C_{14}H_{11}NO_3$ | 69.70 | 4.60 | 5.81 | 69.53 | 4.61 | 5.97 |
| | **38** | | 87 | 161—162 | 1705 | 1663 | $C_{16}H_{17}NO_4$ | 66.89 | 5.96 | 4.88 | 67.07 | 5.89 | 4.76 |
| **36** | **38** | A | 89 | | | | | | | | | | |
| **39** | **40/41** | A | 95 | 237—244 | 1700 | 2198[c] | $C_{15}H_{14}N_2O_3$ | 66.65 | 5.22 | 10.37 | 66.51 | 5.26 | 10.16 |
| **39** | **42** | B | 41 | 174—176 | 1700 | | $C_{12}H_9NO_2$ | 72.35 | 4.55 | 7.03 | 72.62 | 4.65 | 7.21 |

a) Known compound, see Ref. 2. b) The preparation of the analytical sample was unsuccessful because of its low yield. c) Cyano band.

The reactions of vinylindolizine (**19**) and ethyl 2-oxo-2*H*-pyranoindolizine-3-carboxylate (**7**) with sulfuric acid were examined in detail under various conditions, but the synthesis of the corresponding 10-phenylpyranoindolizinone (**23**) was not unsuccessful. In the similar reaction (Method A) of **28**, the initially expected pyranoindolizinone such as **29** and methylenefuroindolizinone (**33**) were not obtained at all, but 2-methoxy-3-vinylindolizine (**34**) was isolated in only 7% yield. This compound (**34**) was completely in accord with authentic sample prepared above in all respects. These results and some properties of products are listed in Tables 2—4.

*Acetylation of 1-Vinyl-2(3H)-indolizinone (38).* A mixture of indolizinone **38** (144 mg, 0.5 mmol), acetic anhydride (1 ml), and pyridine (3 ml) was heated at 70—80 °C in a water bath for 2 h. The unreacted anhydride and pyridine was then removed at reduced pressure and the residual oil was separated by column chromatography (alumina) using hexane and then ether as eluents. The ether layer was collected and concentrated at reduced pressure. Recrystallization from ethanol gave pure 2-acetoxy-1-vinylindolizine (**43**), 118 mg, 72%, orange needles, mp 102—104 °C, $\nu$ (KBr) 1751, 1709, and 1673 cm$^{-1}$ (CO), $\delta$ ($CDCl_3$)[11] 1.19 (3H, t, $J$=7.0 Hz, $CH_2\underline{CH_3}$), 2.33, 2.42 (each 3H, s, 2Ac), 2.53 (3H, s, 5-Me), 4.25 (2H, q, $J$=7.0 Hz, $O\underline{CH_2}CH_3$), 6.61 (1H, br d, $J$=7.0 Hz, 6-H), 7.03 (1H, q, $J$=9.0 and 7.0 Hz, 7-H), 7.49 (1H, br d, $J$=9.0 Hz, 8-H), 7.53 (1H, s, 3-H), and 8.05 (1H, s, vinyl-H). Found: C, 65.89; H, 5.83; N, 4.26%. Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.82; N, 4.25%.

The NMR signals due to the main isomer in **43** were completely in accord with those of **35**.

## References


1) For part 7 of this series, see A. Kakehi, S. Ito, and B. Wada, this Bulletin, in press.

2) A. Kakehi, S. Ito, K. Watanabe, M. Kitagawa, S. Takeuchi, and T. Hashimoto, *J. Org. Chem.*, **45**, 5100 (1980).

3) A. Kakehi, S. Ito, B. Wada, K. Watanabe, K. Nishimura, and A. Kumagai, *Bull. Chem. Soc. Jpn.*, **55**, 3590 (1982).

4) The reaction conditions in which acidic and basic media such as hydrochloric acid, sulfuric acid, sodium ethoxide, potassium t-butoxide, sodium hydroxide, and po tassium carbonate were employed in various solvents were examined.

5) Or cis:trans=4:3. The NMR spectrum of **38** is as follows: Major isomer, $\delta$ ($CDCl_3$) 1.37 (3H, t, $J$=7.0 Hz, $OCH_2\underline{CH_3}$) 2.36 (3H, s, Ac), 2.48 (3H, s, 5-Me), 4.30 (2H, s, methylene, disappeared with deuterium oxide), 4.43 (2H, q, $J$=7.0 Hz, $O\underline{CH_2}CH_3$), 6.60 (1H, br d, $J$=7.0 Hz, 6-H), 7.42 (1H, s, vinyl-H), and 6.9—7.9 (2H, m, 7- and 8-H). Minor isomer, $\delta$ ($CDCl_3$) 1.34 (3H, t, $J$=7.0 Hz, $OCH_2\underline{CH_3}$), and 7.37 (1H, s, vinyl-H). The other proton signals due to the minor product were overlapped with those of major isomer.

6) The cis-trans ratio could not be calculated because of the absence of definitely separated signals in its NMR spectrum, but isomer **35** was major.

7) The presence of a strong interaction between these groups in a similar system was reported. See K. Kurita, H. Awaya, Y. Tominaga, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, **101**, 980 (1981).

8) Because of its extremely low solubility, our attempts to obtain further structural information were unsuccessful.

9) A. Kakehi, S. Ito, T. Maeda, R. Takeda, M. Nishimura, M. Tamashima, and T. Yamaguchi, *J. Org. chem.*, **43**, 4837 (1978).

10) The trans configuration of the 1-vinyl group in **35** and **36** was assigned tentatively from the reasons that the vinyl proton of the trans isomer may appear in lower magnetic field than that of the cis one and that the corresponding pyrano[3,2-*a*]indolizinone (**37**) was formed only in very low yield.

11) This is major compound (**35**). The NMR data of minor compound are as follows: $\delta$ ($CDCl_3$) 1.32 (3H, t, $J$=7.0 Hz, $OCH_2\underline{CH_3}$), 2.33 and 2.38 (each 3H, s, 2Ac), 2.53 (3H, s, 5-Me), and 8.03 (1H, s, vinyl-H). The other signals were overlapped with those of major isomer (**35**).