completely by gassing with O_2+CO_2 (95:5) and, in opposition, accelerated by gassing with nitrogen. The reaction seems to be an enzymatic one since the reaction is inhibited completely by boiling the intestinal loop. An interesting point in Table II is that the reaction was inhibited in the homogenate medium even when the homogenate was incubated with nitrogen as the gas phase and with co-factors. Feldman and Gibaldi[8] also reported that the extent of recovery of phenol red from the homogenate of rat intestinal tissue differed from the one obtained from the intact intestinal sacs. They attributed this difference to a different binding manner of phenol red in each preparation. One of the reasons why extent of methyl orange reduction was different in the homogenate and in the intact tissue may be that in the former, specific binding manner related to methyl orange reduction was destroyed, and other pathways became predominant. Further investigation will be necessary to clarify these mechanisms.

Two possible mechanisms of methyl orange transport from the large intestinal lumen are proposed; one, passive transport, and the other, active-like process having enzymatic reduction of methyl orange on the mucosal side of the membrane. Polysorbate 80 inhibited only the former at its concentration close to the critical micellar one. Since the concentration of the surfactant is so low, influence of its interaction with methyl orange[9] seems to be negligible and inhibition by Polysorbate 80 may better be related to a direct or indirect action of the surface-active agent molecules to the site of methyl orange reduction. It has been reported that Polysorbate 80 molecules were adsorbed on the surface of the intestinal membrane of the rat non-specifically.[10] Specific binding site of methyl orange related to methyl orange reduction are covered by Polysorbate molecules, or are destroyed by change of the protein structure followed by the adsorption of Polysorbate 80 molecules. It is also worthy to note that the manner of inhibition *in situ* by the surface-active agent was different from the one observed *in vitro*.

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Formation of Indolizines *via* Pyridinium 3-Carbomethoxyallylides

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In connection with our studies on the intramolecular 1,5-cyclization of ylides [1→2; X=CH, R=C_6H_5 and X=N, R=-$(CH_2)_3$-],[2,3] the cyclization reaction of pyridinium 3-carbomethoxyallyl bromide (**1a**) in the presence of base has been investigated. The product obtained, however, was not expected 1-carbomethoxyindolizine but methyl 3-(1′-carbomethoxy-3′-indolizinyl)acrylate (**5a**). In this report the structural assignment of the rather unusaual reaction product is described.

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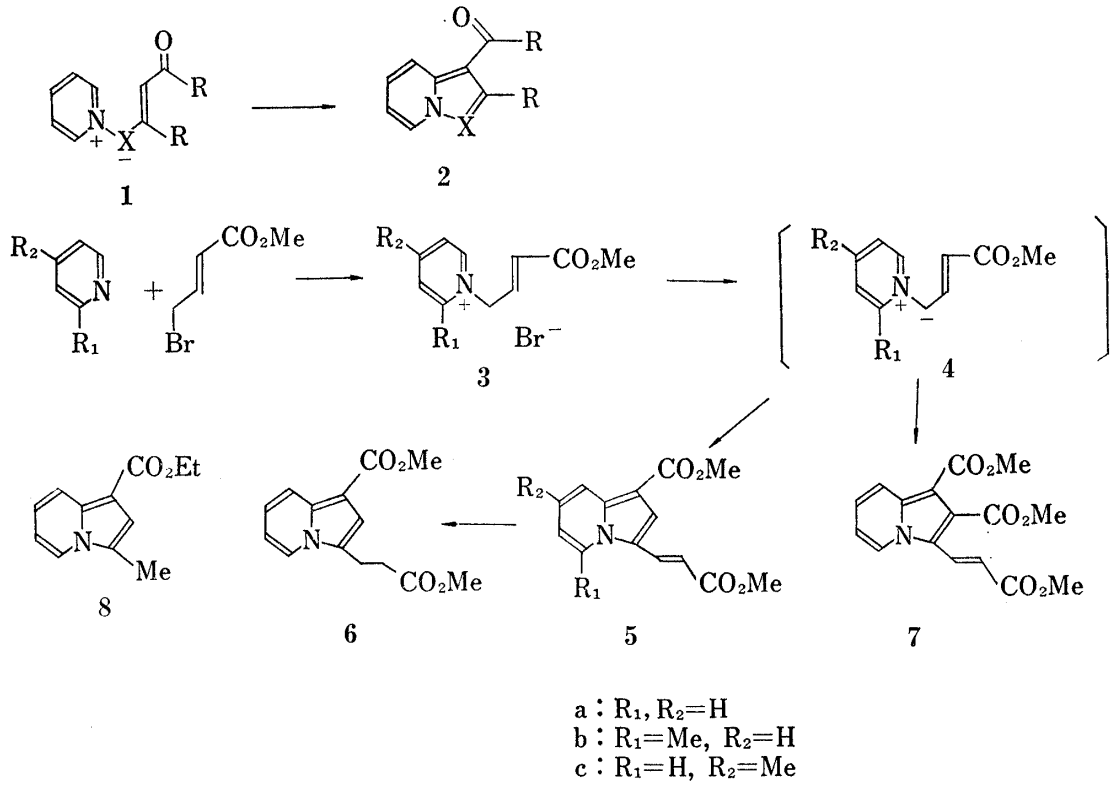

a : R_1, R_2=H
b : R_1=Me, R_2=H
c : R_1=H, R_2=Me

An ethylene chloride solution of the pyridinium salt **1a**, readily prepared from pyridine and methyl 4-bromocrotonate, was heated under reflux in the presence of triethylamine to afford yellow crystals, mp 147.5—148.5°, in 12% yield. Its microanalysis and mass spectroscopy (M^+; *m/e* 259) confirmed the molecular formula $C_{14}H_{13}O_4N$. The ultraviolet (UV) spectrum indicates the introduction of a potent chromophore as compared with that of 1-carbethoxy-3-methylindolizine (**8**),[4] while the infrared (IR) spectrum shows a single carbonyl band at 1690 cm^{-1}. The nuclear magnetic resonance (NMR) spectrum revealed the presence of two carbomethoxyl groups at τ 6.08 and 6.18, and two *trans*-olefinic protons at τ 2.10 and 3.67 (AB quartet, J=15 Hz). The rest of the NMR spectrum contains a singlet at τ 2.35 (H_2), a multiplet from τ 2.6—3.3 (H_6 and H_7) and a multiplet from τ 1.5—1.9 (H_5 and H_8).

Catalytic hydrogenation of **5a** over 5% Pd on charcoal in methanol gave the dihydro derivative **6**, mp 75—76°. The UV spectrum was identical to that of **8**, indicating the presence of 1-carbomethoxyindolizine skeleton. In the NMR spectrum of **6**, signals due to two *trans*-olefinic protons in that of compound **5a** disappeared and instead a multiplet corresponding to the four methylene protons appeared between τ 6.6 and 7.5. Furthermore, signals due to H_5 and H_2 were shifted to the higher field (τ 2.11 and 2.97, respectively) and the singlet due to H_2 was broadened, as compared with those of **5a**, suggesting the presence of the carbomethoxyethyl group at 3-position of the indolizine ring.

Finally the reaction of **3a** with dimethyl acetylenedicarboxylate in the presence of potassium carbonate in dimethylformamide afforded a 1,3-dipolar cycloaddition product **7**, $C_{16}H_{15}O_6N$. The NMR spectrum is very similar to that of **5a** except for an additional signal ascribed to the carbomethoxyl group at C-2. All of these data are consistent only with structure **5a**.

The pyridinium salts (**3b** and **3c**) also gave rise to the corresponding indolizine derivatives (**5b** and **5c**) under the same reaction conditions. The structures of the products were established by the comparison of the spectra with those of **5a**.

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Although the exact reaction mechanism for the formation of **5** is not yet clear, it appears likely that the first step of this transformation (**4**→**5**) is the formation of pyridinium 3-carbomethoxyallylides (**4**) which undergo a 1,3-dipolar cycloaddition with another molecule of **3** or **4**, followed by loss of two hydrogen atoms, pyridine and one carbon unit.

Experimental[5]

γ-Picolinium 3-Carbomethoxyallyl Bromide (3c)——The general procedure used is illustrated by this example. Methyl 4-bromocrotonate (960 mg) was added to γ-picoline (500 mg) with ice-cooling and the mixture was allowed to stand at room temperature for 2 days. The resulting dark-red solid was thoroughly washed with dry ether and recrystallized from acetone to give white needles of **3c** (890 mg, 61%), mp 136.5—137.5°. IR ν_{max}^{KBr} cm^{-1}: 1725 (sh) and 1710. NMR (in $CDCl_3$) τ: 0.50 (2H, d, J=7 Hz, α-protons), 2.06 (2H, d, J=7 Hz, β-protons), 2.91 (1H, td, J=7 and 15 Hz, -CH_2-C<u>H</u>=CH-), 3.73 (1H, d, J=15 Hz, -CH_2-CH=C<u>H</u>-), 3.95 (2H, d, J=7 Hz, -CH_2-), 6.31 (3H, s, OMe) and 7.30 (3H, s, Me). *Anal.* Calcd. for $C_{10}H_{13}O_2NBr$: C, 48.55; H, 5.18; N, 5.15. Found: C, 48.09; H, 5.22; N, 5.06.

The salts, **3a** and **3b**, were obtained as a dark-red viscous oil in 70 and 75% yields respectively, which were used for further reaction after washing with dry ether.

Methyl 3-(1′-Carbomethoxy-7′-methyl-3′-indolizinyl)acrylate (5c)——(Method A) To a suspension of **3c** (1 g) in ethylene chloride (10 ml) was added triethylamine (1 ml) and the suspension was heated under reflux for 4 hr. The reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was chromatographed over alumina. Elution with C_6H_6 was continued until the yellow fraction was removed from the column. Recrystallization from EtOH gave **5c** (102 mg, 20%), mp 152—153°; IR ν_{max}^{KBr} cm^{-1}: 1700 and 1680. UV λ_{max}^{EtOH} nm (log ε): 218 (4.29), 226 (4.26), 233 sh (4.21), 246 (4.09), 275 (4.08), 302 sh (4.13), 309 (4.15) and 383 (4.45). NMR (in $CDCl_3$) τ: 1.83 (1H, d, J=7 Hz, H_5), 1.94 (1H, d, J=2 Hz, H_8), 2.12 (1H, d, J=16 Hz, -C<u>H</u>=CHCO$_2$Me), 2.4 (1H, s, H_2), 3.25 (1H, dd, J=2 and 7 Hz, H_6), 3.69 (1H, d, J=16 Hz, -CH=C<u>H</u>CO$_2$Me), 6.09 and 6.18 (2×3H, 2×s, 2×OMe) and 7.57 (3H, s, Me). Mass Spectrum *m/e*: 273 (M^+). *Anal.* Calcd. for $C_{15}H_{15}O_4N$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.55; H, 5.79; N, 5.14. (Method B) A solution of **3c** (50 mg) in EtOH was passed through a column of Amberlite IRA-410 ion-exchange resin and the ethanolic eluate was concentrated under reduced pressure. The residue was dissolved in toluene and the solution was heated under reflux for 8 hr. Work-up as described above gave **5c** (3 mg, 12%).

The following indolizines (**5a** and **5b**) were prepared according to the method A.

Methyl 3-(1′-Carbomethoxy-3′-indolizinyl)acrylate (5a)——mp 147.5—148.5°, was obtained in 12% yield. IR ν_{max}^{KBr} cm^{-1}: 1690. UV λ_{max}^{EtOH} nm (log ε): 214 (4.30), 223 (4.26), 231 sh (4.22), 245 (4.08), 252 (4.08), 278 (4.16), 299 (4.19), 306 sh (4.18) and 377 (4.39). NMR (in $CDCl_3$) τ: 1.5—1.9 (2H, m, H_5 and H_8), 2.10 (1H, d, J=15 Hz, -C<u>H</u>=CHCO$_2$Me), 2.35 (1H, s, H_2), 2.6—3.3 (2H, m, H_6 and H_7), 3.66 (1H, d, J=15 Hz, -CH=C<u>H</u>CO$_2$Me), 6.08 and 6.18 (2×3H, 2×s, 2×OMe). Mass Spectrum *m/e* 259 (M^+). *Anal.* Calcd. for $C_{14}H_{13}O_4N$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.86; H, 4.97; N, 5.20.

Methyl 3-(1′-Carbomethoxy-5′-methyl-3′-indolizinyl)acrylate (5b)——mp 141—142°, was obtained in 14% yield. IR ν_{max}^{KBr} cm^{-1}: 1710 and 1690. UV λ_{max}^{EtOH} nm (log ε): 221 (4.22), 249 sh (4.06), 258 (4.07), 295 sh (4.02), 305 (4.04) and 366 (4.24). NMR (in $CDCl_3$) τ: 1.64 (1H, d, J=15 Hz, -C<u>H</u>=CHCO$_2$Me), 1.74 (1H, bd, J=9 Hz, H_8), 2.31 (1H, s, H_2), 2.93 (1H, dd, J=9 and 8 Hz, H_7), 3.38 (1H, bd, J=8 Hz, H_6), 3.76 (1H, d, J=15 Hz, -CH=C<u>H</u>CO$_2$Me), 6.10 and 6.20 (2×3H, 2×s, 2×OMe) and 7.11 (3H, s, Me). Mass Spectrum *m/e*: 273 (M^+). *Anal.* Calcd. for $C_{15}H_{15}O_4N$: C, 65.92; H, 5.53; N, 5.13. Found: C, 66.42; H, 5.64; N, 5.18.

Methyl 3-(1′-Carbomethoxy-3′-indolizinyl)propionate (6)——Compound **5a** (293 mg) was hydrogenated in MeOH (35 ml) over 5% Pd-C (150 mg) at atmospheric pressure and room temperature. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure to give a yellow solid (247 mg, 73%) which was recrystallized from MeOH, mp 75—76°. IR ν_{max}^{KBr} cm^{-1}: 1735 and 1685. UV λ_{max}^{EtOH} nm (log ε): 230 (4.51), 257 (3.90), 266 (3.87), 299 sh (3.95), 3.11 (4.06), 340 (3.95), 353 (3.96), 372 sh (3.75). NMR (in $CDCl_3$) τ: 1.79 (1H, bd, J=9 Hz, H_8), 2.11 (1H, bd, J=7 Hz, H_5), 2.97 (1H, bs, H_2), 2.8—3.4 (2H, m, H_6 and H_7), 6.11 and 6.28 (2×3H, 2×s, 2×OMe) and 6.6—7.5 (4H, m, -CH_2CH_2-). Mass Spectrum *m/e*: 261 (M^+). *Anal.* Calcd. for $C_{14}H_{15}O_4N$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.13; H, 5.77; N, 5.17.

Methyl 3-(1′,2′-dicarbomethoxy-3′-indolizinyl)acrylate (7)——A mixture of **3a** (1 g) and K_2CO_3 (540 mg) in MeOH–DMF (1:2, 20 ml) was stirred at room temperature for 30 min. To the mixture was added dimethyl acetylenedicarboxylate (710 mg) and stirring was continued for 2 days. The reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was chromatographed over

5) All melting points are uncorrected. The NMR spectra were determined with a Varian A-60 and Hitachi R-20 B (60 Mc) spectrometer with tetramethylsilane as internal reference, IR spectra with a Hitachi-EPI G2 spectrophotometer, UV spectra with a Hitachi EPS-3T spectrophotometer and Mass spectra with a Hitachi RMU-6E mass spectrometer.

alumina. Elution with C_6H_6 gave yellow crystals which was recrystallized from EtOH to give **7** (417 mg, 34%), mp 153—154°. IR ν_{max}^{KBr} cm^{-1}: 1735, 1720 and 1695. UV λ_{max}^{EtOH} nm (log ε): 251 (4.26), 289 sh (4.10), 299 (4.17), 363 (4.23). NMR (in $CDCl_3$) τ: 1.6—1.8 (2H, m, H_5 and H_8), 2.11 (1H, d, J=16 Hz, -C<u>H</u>=CHCO$_2$Me), 2.5—3.2 (2H, m, H_6 and H_7), 3.66 (1H, d, J=16 Hz, -CH=C<u>H</u>CO$_2$Me), 5.97, 6.08 and 6.17 (3×3H, 3×s, 3×OMe). Mass Spectrum *m/e*: 317 (M^+). *Anal.* Calcd. for $C_{16}H_{15}O_6N$: C, 60.56; H, 4.77; N, 4.41. Found: C, 60.78; H, 4.85; N, 4.27.

Ethyl 3-Methylindolizine-1-carboxylate (8)——According to a previously described procedure,[4] a solution of α-bromopropionaldehyde (1.4 g) and ethyl 2-pyridineacetate (3.3 g) in acetone (10 ml) was heated under reflux for 14 hr. Work-up yielded a yellow oil, which was purified by preparative thin-layer chromatography on alumina to give **6** (900 mg, 47%). IR ν_{max}^{KBr} cm^{-1}: 1670. UV λ_{max}^{EtOH} nm (log ε): 229 (4.57), 232 (4.57), 250 sh (3.79), 257 (3.91), 265 (3.87), 304 sh (3.97), 312 (4.09), 343 (3.95) and 353 (3.95). NMR (in $CDCl_3$) τ: 1.82 (1H, d, J=9 Hz, H_8), 2.28 (1H, d, J=7 Hz, H_5), 3.00 (1H, s, H_2), 2.8—3.5 (2H, m, H_6 and H_7), 5.65 (2H, q, J=7 Hz, -C<u>H</u>$_2$CH$_3$), 7.50 (3H, s, Me) and 8.61 (3H, t, J=7 Hz, -CH$_2$C<u>H</u>$_3$).

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On the Scavenging of Azido Radicals by Nitroso Compounds

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No electron spin resonance (ESR) evidence has ever been put forward on the azido radical (N_3·) in both solid and solution phases, although an unstable ultraviolet (UV) absorption band observable around 277 mμ, when a flash photolysis or pulse radiolysis was applied to an aqueous solution of sodium azide, has been assumed to be due to transient azido radicals.[2,3]

Since azido radicals have been presumed to be very short-lived, we applied a radical scavenging technique by use of olefinic and nitroso compounds; our reaction system consisted of A) a solution of sodium azide, olefinic compound and nitroso compound while B) a solution of cerium (IV) salt. On mixing the two solutions we expected the formation of some stable radical intermediate containing an azido group. In the present note is reported the result of such investigations.

Experimental

The method of radical detection by ESR has already been described elsewhere.[4–6] Preliminary experiments indicated that when Ce^{4+} was mixed with only NaN_3, the evolution of N_2 was recognized by a mass filter (Shimazu, MSPEQ) probably according to the reactions:

$$Ce^{4+} + N_3^- \longrightarrow Ce^{3+} + N_3\cdot \quad (1)$$

$$2N_3\cdot \longrightarrow 3N_2 \quad (2)$$

On the other hand, if olefinic compounds were present in the NaN_3 solution, the generation of N_2 was more or less suppressed. The phenomena may indicate that the azido radicals formed by (1) react with olefinic

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