Studies on Indolizine Derivatives[1] New Synthetic Methods of Azacycl[3.2.2]azine Derivatives XI[2]

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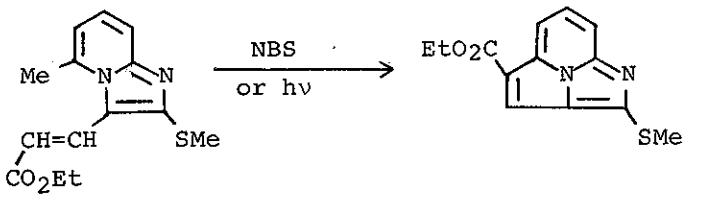
N-Bridged 10π electron ring systems, azacycl[3.2.2]-azine derivatives (II, III) were obtained by the photochemical reaction of azaindolizine derivative (I), or by the reaction of I with N-bromosuccinimide (NBS).

The chemistry of cycl[3.2.2]azine classes is one of the most interesting applied section of indolizine derivatives. So, variety of synthetic methods of N-bridged 10π electron ring systems, cycl[3.2.2]azine[3], 2-azacycl[3.2.2]azine[4], 1,4-diazacycl[3.2.2]azine[5] from indolizine derivatives as starting materials have been reported. We had also reported the synthesis of cycl[3.2.2]azine derivative by the reaction of indolizine derivative and dimethyl acetylenedicarboxylate[6].

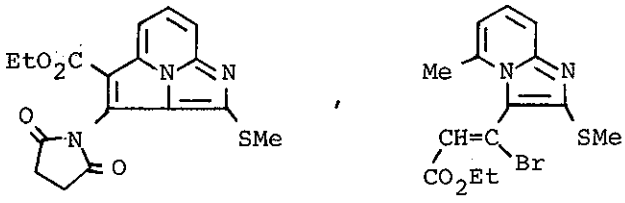
Now we wish to report new synthetic methods of azacycl-[3.2.2]azine derivatives (II, III) by the photochemical reaction of azaindolizine derivative (I), or by the reaction of I[1] with NBS.

Thus a solution of I in EtOH was irradiated with 400 watt of mercury lamp for 10 hr during the reaction had a color varying from pale yellow to colorless. Then the solvent was evaporated off and the residue was chromatographed on alumina. From benzene elution, the compound II was obtained. II was recrystallized from EtOH to give ethyl 2-methylthio-1-azacycl[3.2.2]azine-4-carboxylate, mp 144-145°, colorless needles, in 40% yield. Anal. Calcd. for $C_{13}H_{12}O_2N_2S$: C,59.99; H, 4.65; N, 10.77. Found : C, 59.86; H, 4.49; N, 10.91. Mass spectrum m/e : 260 (M^+). IR (KBr) cm^{-1} : 1700 (C=O). UV λ_{max}^{EtOH} nm (log ε) : 234(4.33), 244(4.24), 253(4.12, shoulder), 288(4.24), 350(4.30), 363(4.22, shoulder). NMR ($CDCl_3$) ppm : 1.42 (3H, triplet, -O-CH_2-$\underline{CH_3}$), 2.92 (3H, singlet, SCH_3), 4.42 (2H, qualtet, -O-$\underline{CH_2}$-CH_3), 6.80 (1H, doublet, J=8Hz, C_5-H or C_7-H), 7.40 (1H, triplet, J=8Hz, C_6-H), 7.66 (1H, doublet, J=8Hz, C_5-H or C_7-H), 8.18 (1H, singlet, C_3-H).

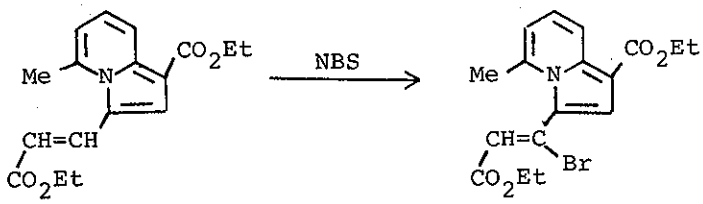
While, a solution of I and NBS in the presence of benzoyl peroxide in $CHCl_3$ was refluxed. After 3 hr, the solution was washed with 10% aqueous NaOH, and evaporated under reduce pressuer. The residue was chromatographed on alumina. From benzene elution, three crystalline solids II, III and IV were collected by turns. The first compound II was



I II



III IV



V VI

obtained in 30% yield. The second compound III was recrystallized from EtOH to give ethyl 2-methylthio-3-(2,5-dioxo-1-pyrrolidinyl)-1-azacycl[3.2.2]azine-4-carboxylate, mp 230-231°, yellow prisms, in 15% yield. Anal. Calcd. for $C_{17}H_{15}O_4N_3S$: C, 57.14; H, 4.23; N, 11.76. Found : C, 56.96; H, 4.16; N, 11.70. Mass spectrum m/e : 357 (M^+). IR (KBr) cm^{-1} : 1680, 1710, 1735 (C=O). UV λ_{max}^{EtOH} nm (log ε) : 234(4.47), 244(4.39), 253(4.26, shoulder), 288(4.40), 350(4.45), 363(4.37, shoulder), NMR ($CDCl_3$) ppm : 1.38 (3H, triplet, -O-CH_2-$\underline{CH_3}$), 2.69 (3H, singlet, SCH_3), 3.00 (4H, doublet, J=4Hz, pyrrolidinyl proton), 4.30 (2H, qualtet, -O-$\underline{CH_2}$-CH_3), 6.72 (1H, doublet, J=8Hz, C_5-H or C_7-H), 7.38 (1H, triplet, J=8Hz, C_6-H), 7.66 (1H, doublet, J=8Hz, C_5-H or C_7-H).

The third compound IV was recrystallized from EtOH to give ethyl 3-bromo-3-(2-methylthio-5-methyl-1-azaindolizyl-3)-acrylate, mp 140-141°, yellow needles, in 2-3% yield. Anal. Calcd. for $C_{14}H_{15}O_2N_2SBr$: C, 47.19; H, 4.21; N, 7.87. Found : C, 47.23; H, 4.23; N, 7.86. Mass spectrum m/e : 354 and 356 (M^+). IR (KBr) cm^{-1} : 1675 (C=O). UV λ_{max}^{EtOH} nm (log ε) : 229(4.24), 252(4.20), 282(4.03), 365(3.89). NMR ($CDCl_3$) ppm : 1.40 (3H, triplet, -O-CH_2-$\underline{CH_3}$), 2.68 (3H, singlet, CH_3), 2.72 (3H, singlet, SCH_3), 4.38 (2H, qualtet, -O-$\underline{CH_2}$-CH_3), 6.63 (1H, doublet, J=8Hz, C_6-H or C_8-H), 7.21 (1H, triplet, J=8Hz, C_7-H), 7.50 (1H, doublet, J=8Hz, C_6-H or C_8-H), 8.60 (1H, singlet, vinyl proton).

In the same manner, indolizine derivative (V) reacted with NBS to afford no cycl[3.2.2]azine derivative, but only brominated compound (VI). VI was recrystallized from EtOH to give ethyl 3-bromo-3-(1-carbethoxy-5-methylindolizyl-3)-acrylate, mp 87-89°, yellow needles, in 80% yield. Anal. Calcd. for $C_{17}H_{18}O_4NBr$: C, 53.70; H, 4.77; N, 3.68. Found : C, 53.79; H, 4.59; N, 3.53. Mass spectrum m/e : 379 and 381 (M^+). IR (KBr) cm^{-1} : 1680 (C=O). UV λ_{max}^{EtOH} nm (log ε) : 224 (4.29), 256(4.05), 305(4.06), 360(4.13). NMR (CCl_4) ppm : 1.40 (6H, triplet, $(-O-CH_2-\underline{CH}_3)_2$), 2.92 (3H, singlet, CH_3), 4.30 (4H, qualtet, $(-O-\underline{CH}_2-CH_3)_2$), 6.64 (1H, doublet, J=8Hz, C_8-H), 8.30 (1H, singlet, C_2-H or vinyl proton), 8.88 (1H, singlet, C_2-H or vinyl proton).

Further works on an evolution of these reaction mechanisms are in progress.

Refereneces

1. Part II ; K. Kurata, H. Awaya, Y. Tominaga, Y. Matsuda, and G. Kobayashi, Yakugaku Zasshi, submitted.
2. Part X ; K. Kurata, M. Matsuo, H. Awaya, Y. Tominaga, Y. Matsuda, and G. Kobayashi, Yakugaku Zasshi, submitted.
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