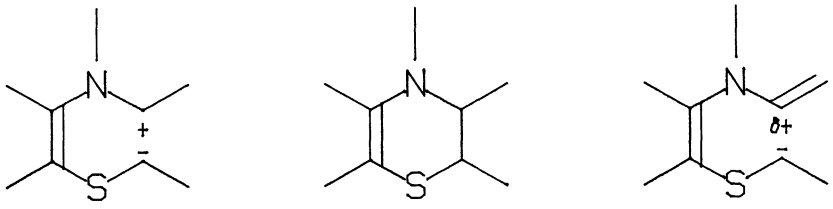
CHEMISTRY LETTERS, pp. 2229-2232, 1989. 

# First Syntheses of 1,4-Thiazino[3,4,5-*cd*]indolizine Derivatives[1)]

Akikazu KAKEHI,* Suketaka ITO, and Susumu HATANAKA
Department of Chemistry and Material Engineering, Faculty of Engineering, Shinshu University, Wakasato, Nagano 380

Title compounds were prepared in moderate yields by the reactions of 3-(mercaptomethylene)-1-phenyl-2(3*H*)-indolizinones with bromoacetonitrile or phenacyl bromide in the presence of base.

We have recently reported that 1-[2-(acylmethylthio)vinyl]pyridinium halides, readily obtainable from the *S*-alkylations of the corresponding pyridinium 1-(thiocarbonyl)methylides, undergo smooth dehydrohalogenation with base to afford 1,9a-dihydropyrido[2,1-*c*]-1,4-thiazine derivatives.[2)] Possible intermediates involved in these reactions are zwitterionic species such as (A) (see Figure) and their intramolecular cyclization to 1,4-thiazine derivatives such as (B) was not reported so far. The versatility of this reaction[2,3)] and the pharmaceutical interest for some fused 1,4-thiazine derivatives[4)] prompted us to investigate another possible reaction leading to 1,4-thiazine derivatives in which an ionic species such as (C) is involved as an intermediate. In this communication we wish to report first syntheses of some 2(5*H*)-5a,6-dihydro-1,4-thiazino[3,4,5-*cd*]-indolizinone derivatives from the reactions of 3-(mercaptomethylene)-2(3*H*)-indolizinones with bromoacetonitrile or phenacyl bromide in the presence of base.

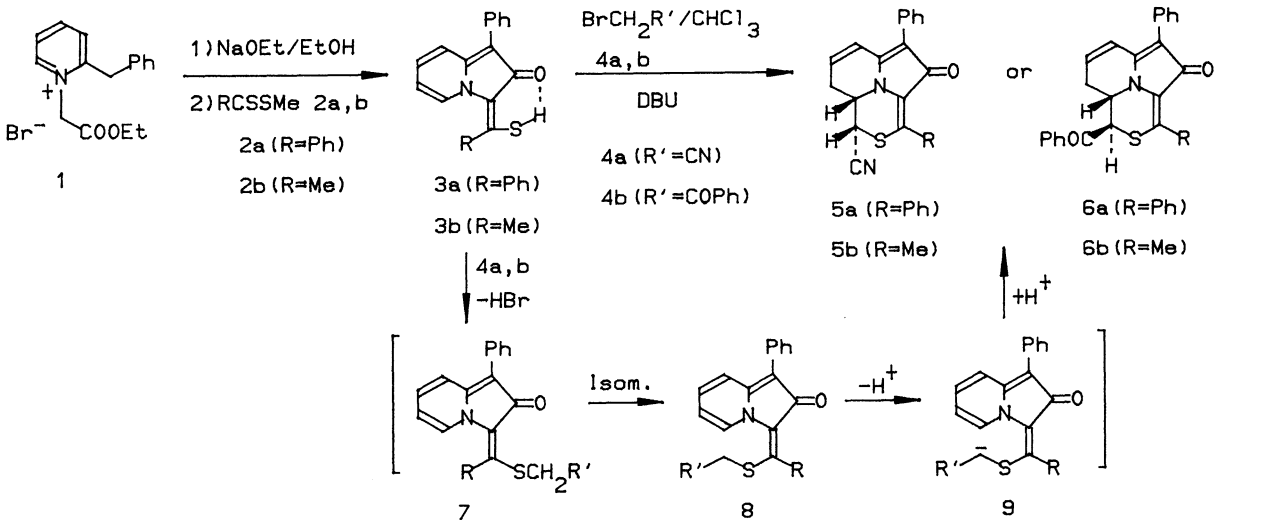



A B C

We selected first 3-(mercaptomethylene)-2(3*H*)-indolizinone derivative as a starting material for the model system (C) for the following reasons; 1) The high

electrophilicity of the carbon at the 5-position can be expected owing to the 2-methylene-1,2-dihydropyridine and the trienone structures. 2) The *S*-alkylation of this compound can lead to the precursor of the intermediate (C) with ease. When an ethanolic solution of 2-benzyl-1-(ethoxycarbonylmethyl)pyridinium bromide (1) and methyl dithiobenzoate (2a) was treated with ethanolic sodium ethoxide at room temperature, the corresponding 3-[(mercapto)phenylmethylene]-1-phenyl-2(3*H*)-indolizinone (3a),[5] 65%, red needles, mp 171–172 °C, ν(KBr) 1579 (CO) and 2520 $cm^{-1}$ (SH), δ($CDCl_3$) 6.36 (1H, m, 6-H), 7.0–7.8 (13H, m, 5-H, 7-H, 8-H, and 2×phenyl-H), and 13.34 (1H, br s, SH, exchangeable with $D_2O$), was obtained with the elimination of methanethiol. The similar treatment of pyridinium salt (1) with ethyl dithioacetate (2b) gave compound 3b, 55%, red needles, mp 172–173 °C, ν(KBr) 1589 (CO) and 2285 $cm^{-1}$ (SH), δ($CDCl_3$) 3.09 (3H, s, Me), 6.81 (1H, m, 6-H), 7.2–7.9 (7H, m, 7-H, 8-H, and phenyl-H), 8.64 (1H, br d, J=7.0 Hz, 5-H), and 14.03 (1H, br s, SH). The structural assignments of these compounds 3a,b were accomplished mainly by the comparisons of their physical and spectral properties with those of 3-[(alkylthio)mercaptomethylene]-2(3*H*)-indolizinone derivatives reported earlier by us.[6]

The reactions of 2(3*H*)-indolizinones 3a,b with bromoacetonitrile (4a) in chloroform at room temperature in the presence of 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) did not afford the initially expected 3-[(cyanomethylthio)methylene-2(3*H*)-indolizinones such as 7 (see Scheme), but, instead of them, gave each one product, 5-cyano-2(5*H*)-5a,6-dihydro-1,4-thiazino[3,4,5-*cd*]indolizinones, 5a, 33%, red needles, mp 199–200 °C, ν(KBr) 1587 (CO) and 2240 $cm^{-1}$ (CN), δ($CDCl_3$) 2.3-3.0 (2H, m, 6-H), 3.99 (1H, d, J=2.0 Hz, 5-H), 4.25 (1H, m, 5a-H), 6.33 (1H, m, 7-H), 6.77



(1H, dd, J=10.0 and 2.5 Hz, 8-H), and 7.1–7.8 (10H, m, 2×phenyl-H), 5b, 45%, brown prisms, mp 207–210 °C, ν(KBr) 1580 (CO) and 2238 $cm^{-1}$ (CN), δ($CDCl_3$), *inter alia*, 2.3–3.0 (2H, m, 6-H), 2.54 (3H, s, 3-Me), 3.95 (1H, d, J=2.0 Hz, 5-H), 4.18 (1H, m, 5a-H), 6.31 (1H, m, 7-H), and 6.74 (1H, dd, J=10.0 and 2.5 Hz, 8-H), respectively. On the other hand, similar reactions of compounds 3a,b with phenacyl bromide (4b) afforded only the 5-benzoyl derivatives, 6a, 62%, red prisms, mp 181–182 °C, ν(KBr) 1579 and 1666 $cm^{-1}$ (CO), δ($CDCl_3$) 2.0–3.2 (2H, m, 6-H), 4.60 (1H, m, 5a-H), 5.17 (1H, d, J=10.0 Hz, 5-H), 6.22 (1H, m, 7-H), 6.71 (1H, dd, J=10.0 and 2.5 Hz, 8-H) and 7.0–8.3 (10H, m, 2×phenyl-H), and 6b, 74%, orange needles, mp 210–212 °C, ν(KBr) 1600 and 1677 $cm^{-1}$ (CO), δ($CDCl_3$), *inter alia*, 2.0–3.0 (2H, m, 6-H), 2.50 (3H, s, 3-Me), 4.45 (1H, m, 5a-H), 5.16 (1H, d, J=10.0 Hz, 5-H), 6.16 (1H, m, 7-H), and 6.69 (1H, dd, J=10.0 and 2.5 Hz, 8-H), respectively. These results are shown in above Scheme. The structures of these compounds 5a,b and 6a,b were determined mainly by their $H^1$-NMR spectral analyses and by their mechanistic consideration. In particular, both values of the cis coupling (J=2.0 Hz) in 5a,b and the trans coupling constant (J=10.0 Hz) in 6a,b between the 5- and 5a-protons supported strongly our proposed structures, since these values are approximately parallel with those expected for the cis (its dihedral angle is about 62°) and the trans configurations (its dihedral angle is about 173°) in such molecules.[7] Interestingly, the skeletal carbonyl absorption bands in their IR spectra of thiazinoindolizinones 5a,b and 6a,b did not appear over 1600 $cm^{-1}$ at all, but exhibited at the same region (1570–1600 $cm^{-1}$) as observed in those of 3-methylene-2(3*H*)-indolizinone derivatives.[6] This fact may suggest the contribution of highly polarized structures in these molecules.

Mechanistically, these reactions can be considered to proceed via the *S*-alkylation of 3-(mercaptomethylene-2(3*H*)-indolizinones 3a,b with alkylating agents 4a,b, the cis-trans isomerization of the exomethylene group in the resulting *S*-alkylated compound (7), the abstraction of a proton from the active methylene group in (8) by base (DBU) employed here, followed by the intramolecular cyclization of the icnic intermediates (9) to thiazinoindolizinones 5a,b and 6a,b.

The scope and the limitation of this reaction will be given in near future.

References

1) Preparation of new nitrogen-bridged heterocycles. 20. For part 19 of this

series, see A. Kakehi, S. Ito, T. Fujii, Y. Morimoto, S. Matumoto, and M. Shiohara, Bull. Chem. Soc. Jpn., 62, 119 (1989).

2) A. Kakehi, S. Ito, S. Yonezu, K. Maruta, and K. Yuito, Heterocycles, 23, 33 (1985); A. Kakehi, S. Ito, S. Yonezu, K. Maruta, K. Yuito, M. Shiohara, and K. Adachi, Bull. Chem. Soc. Jpn., 60, 1867 (1987); A. Kakehi, S. Ito, Y. Ohno, S. Shiba, and S. Kamata, *ibid.*, 60, 3713 (1987).

3) A. Kakehi, S. Ito, S. Matsumoto, and Y. Morimoto, Chem. Lett., 1987, 2043; A. Kakehi, S. Ito, N. Kinoshita, and Y. Abaka, Bull. Chem. Soc. Jpn., 61, 2055 (1988); Ref. 1).

4) C. Bodea and I. Silberg,"Advanced Heterocyclic Chemistry,"John Wiley and Sons, Inc (1968), p. 321.

5) All new compounds 3a,b, 5a,b, and 6a,b were recrystallized from chloroform-hexane and gave satisfactory elemental analyses.

6) A. Kakehi, S. Ito, K. Nakanishi, K. Watanabe, and M. Kitagawa, Bull. Chem. Soc. Jpn., 53, 1115 (1980).

7) R. M. Silverstain and G. C. Bassler,"Spectrometric Identification of Organic Compounds,"John Wiley and Sons, Inc (1967), p. 131.

(Received October 4, 1989)