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A NEW ANTIAROMATIC HETEROCYCLAZINE: [1,3]THIAZINO[4,3,2-cd]INDOLIZINE[1)]

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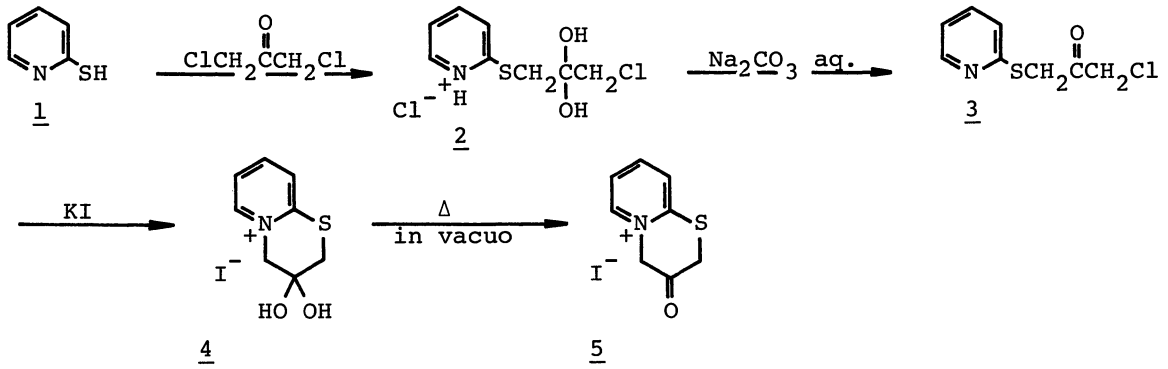
A peripheral azomethine ylid 1,3-dipole, anhydro 2,3-dihydro-3-oxo-4H-pyrido[2,1-b][1,3]thiazinium hydroxide, underwent a cycloaddition reaction to acrylic derivatives under dehydrogenating conditions giving 2,3-dihydro-3-oxo[1,3]thiazino[4,3,2-cd]indolizines. These cycloadducts were converted into the thiacyclazines with twelve electrons on the perimeter via reduction and subsequent dehydration. NMR spectra of the thiacyclazines showed appreciable shielding relative to simple indolizine and cycl[3.2.2]azine.

Only a few examples have been known so far for heterocyclazine with sp^3 heteroatom in its perimeter[2)]. Almost all the examples contain so many annular nitrogen atoms that they are not convenient examples to study physical and chemical properties of this family with. Some chemist have attempted in vain to synthesize theoretically interesting model of heterocyclazine containing an additional heteroatom[3)]. A new aromatic thiacycl[2.2.2]azine, thiazolo[2,3,4-cd]pyrrolizine, recently showed up in patents as the first heterocyclazine with only an additional sp^3 heteroatom[4)]. Slow advance of chemistry of this field might be because there has been few useful synthetic method available for the system. It is enthusiastically requested to find out the general synthetic method. An azomethine ylid 1,3-dipole with a central nitrogen atom at a point of fusion of fused heterocycle may open a way to the construction of heterocyclazine skeleton.

The author would like to communicate here a useful method to a new antiaromatic thiacycl[3.3.2]azine, [1,3]thiazino[4,3,2-cd]indolizine. The route involves a generation of a peripheral azomethine ylid, its cycloaddition reaction, and some chemical conversions into the final target.

2-Mercaptopyridine 1 was refluxed with equivalent 1,3-dichloro-2-propanone in methylene chloride for 2 hr to give colorless precipitate of 2 (mp 147-148°C) in 95% yield, whose structure was assigned as a hydrate of the 1:1 adduct on the basis of

the spectral data as well as the chemical conversion into 3 (mp 57.5-58°C) with aqueous sodium carbonate solution in 89% yield. No carbonyl stretching vibration appeared in the IR spectrum of 2 but OH absorption did at 3000 cm^{-1}. 1-Chloro-3-(2-pyridylthio)-2-propanone 3 has two methylene singlets at δ4.07 and 4.46 ppm, and a carbonyl stretching at 1730 cm^{-1} in its NMR and IR spectra, respectively. The compound 3 is so unstable that it changed, gradually at room temperature and very rapidly on heating above the melting point, into a brown solid which is hygroscopic and insoluble in almost all organic solvent.

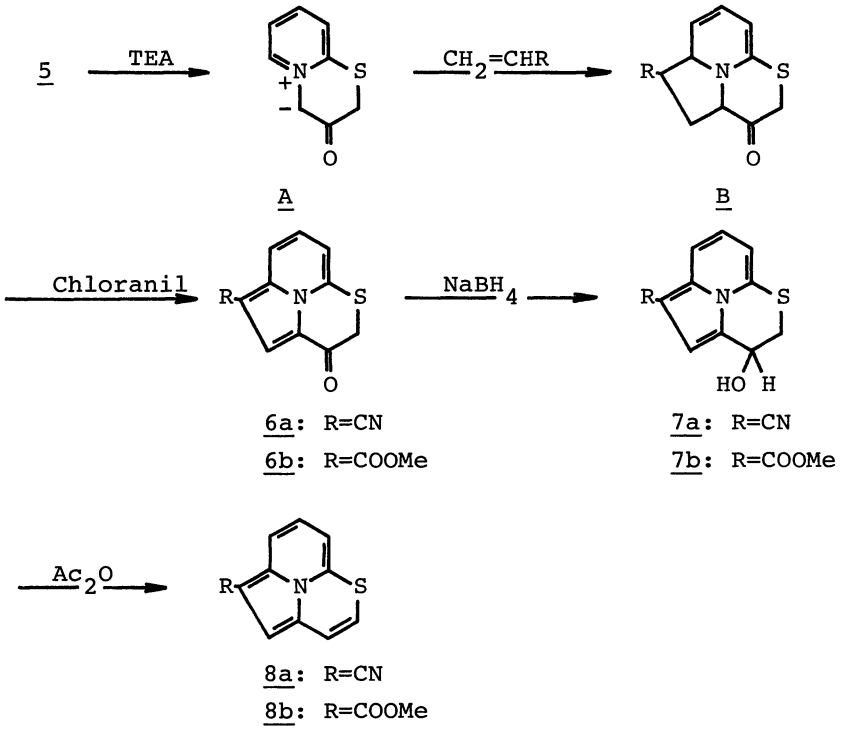


1 2 3 4 5

Cyclization took place when 3 was treated with excess potassium iodide in acetone at room temperature for 3 hr. The colorless product 4 (mp 156-157.5°C) separated in 72% yield has no carbonyl stretching again in the IR spectrum. The spectral data indicated that 4 could be also a hydrate of the expected product 5: the NMR spectrum in CF_3COOH, δ4.06 and 5.54 ppm as singlets for the two methylenes and the IR spectrum, 3190 cm^{-1}(OH). Actually, 4 was dehydrated into 2,3-dihydro-3-oxo-4H-pyrido[2,1-b][1,3]thiazin-5-ium iodide 5 (mp 153-154.5°C) in quantitative yield by heating it at 110-120°C under vacuum (5-7mmHg). The IR spectrum, this time, revealed a carbonyl stretching vibration at 1730 cm^{-1}. Purification of 5 was unsuccessful since it went back to the starting hydrate 4 on recrystallization from methanol.

Treatment of 5 with triethylamine led to a color change of the mixture into deep brown indicating a formation of the ylid A. Cycloaddition reaction, when started with 5, to acrylonitrile and subsequent chloranil oxidation provided a poor yield of the expected cycloadduct 6a. Better yield was obtained when the same cycloaddition reaction was carried out starting from 3. Thus, the solution of 3 in dry acetone was treated with an equivalent amount of potassium iodide at room temperature. The acetone was evaporated and the residue obtained was suspend-

ed in dry methylene chloride. This suspension was then treated with excess acrylonitrile, triethylamine, and after a few minutes with chloranil under reflux. This procedure gave the product 6a in 90% yield based on 3. The structure of 6a was determined mainly on the basis of the NMR spectrum shown in the Table.



The carbonyl group of 6a was easily reduced with sodium borohydride in methanol forming the alcohol 7a (mp 120-121°C) whose structure was determined from the result that the carbonyl absorption disappeared in the IR spectrum and that the methylene singlet in 6a changed into a doublet in 7a. The final goal, 5-cyano-[1,3]thiazino[4,3,2-cd]indolizine 8a, was reached via dehydration of 7a with acetic anhydride.

Similarly, methyl acrylate reacted with the ylid A giving the corresponding cycloadduct 6b, which was then converted into 8b via the alcohol 7b (mp 137.5-138°C) by the similar method.

These unusual compounds 8 have twelve electrons on the perimeter and should be antiaromatic heteroannulenes. All the hydrogens of 8 exhibited signals considerably in high field in the NMR spectra (4.99 to 6.47 ppm in the case of 8a) as shown in the Table. This shielding could be attributed to a paramagnetic contribution to the ring current in the peripheral 12π electron system. Indolizine and cycl[3.2.2]azine

Table. 5-Substituted 2,3-Dihydro-3-oxo[1,3]thiazino[4,3,2-cd]indolizines 6 and 5-Substituted [1,3]Thiazino[4,3,2-cd]indolizines 8.

Compounds	Mp(°C)	Yield(%)	Appearance	IR(cm^{-1})
6a	199-200	90[a]	Yellow Needles	2200(C≡N), 1650(C=O)
6b	192-194	59[a]	Yellow Needles	1705(C=O), 1630(C=O)
8a	155-156.5	76[b]	Red Prisms	2195(C≡N)
8b	117-117.5	60[b]	Red Needles	1695(C=O)

NMR Spectra in $CDCl_3$, δ (ppm)

	2-H	3-H	4-H[s]	6-H[dd]	7-H[t]	8-H[dd]	Others
6a	3.66[s](CH_2)	-	7.73	7.55	7.25	7.05	-
6b	3.74[s](CH_2)	-	8.15	8.27	7.37	7.15	3.99[s](COOMe)
8a	5.60[d]	4.99[d]	6.00	6.47	6.24	5.41	-
8b	5.70[d]	4.95[d]	6.30	7.08	6.30	5.46	3.76[s](COOMe)

a,b) Yields based on a) 3 and b) 6.

are appropriate counterparts which show typical deshielding in the NMR spectra[5].

These antiaromatic thiacyclazines are unexpectedly very stable. Investigation of the chemical property of this family is now in progress.

References

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