

## THE CHEMISTRY OF AN ISOLABLE AZOMETHINE YLIDE

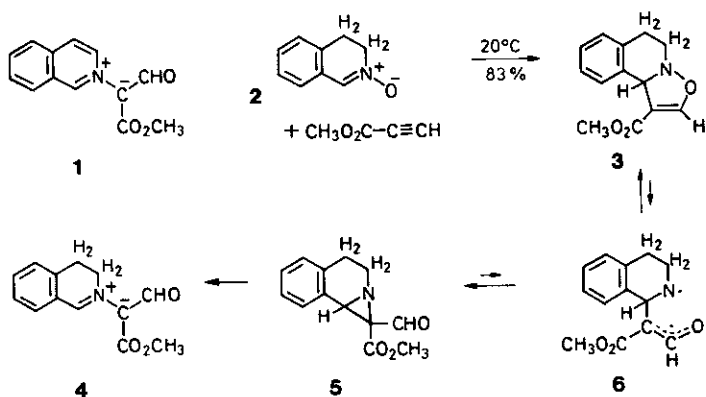
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*Abstract* - The 4-isoxazoline 3 undergoes ring contraction to the acylaziridine 5 which is converted to the azomethine ylide 4. The small influence of solvent polarity on the rate constant of the conversion 3 → 4 suggests a mechanism via a trimethylene type species for the rate-determining step. Whereas 4 is the first azomethine ylide which can be isolated without being stabilized by aromatic resonance, the ylides 20 - 22 dimerize to piperazine derivatives. 1,3-Dipolar cycloadditions of the azomethine ylides 4 and 20 - 22 are described.

In 1963 the orange crystals of a 1:1 product from isoquinoline *N*-oxide and methyl propiolate were obtained in the Munich Laboratory.<sup>1</sup> A tentatively suggested structure was later revised in favor of the azomethine ylide 1<sup>2</sup> after Takahashi and Kano<sup>3</sup> had clarified the products from benzimidazole *N*-oxides and acetylenic carboxylic esters to be enol-betaines. In the case of 3,4-dihydroisoquinoline *N*-oxide (2), the cycloaddition to methyl propiolate produced the colorless 4-isoxazoline 3 which was converted to the crystalline orange ylide 4 at 80°C<sup>4</sup>. That a 2-acylaziridine - here 5 - occurs on the pathway of the nitron addition to acetylenes was conjectured by the Japanese authors<sup>3</sup> and established by Baldwin et al.<sup>5</sup> In the meantime the chemistry of 4-isoxazolines has been fully developed, and the wealth of their rearrangements is the subject of an excellent review<sup>6</sup>.

Compound 4 is the first *isolable* azomethine ylide in which the 1,3-dipolar system is not part of an aromatic nucleus. In 1 - and many ylides of this type - the CN bond is incorporated in an aromatic system, and in the case of oxazolium-5-olates (münchnones)<sup>7</sup> the whole azomethine ylide structure is embedded into a mesoionic ring. Less stabilized azomethine ylides are formed by conrotatory electrocyclic

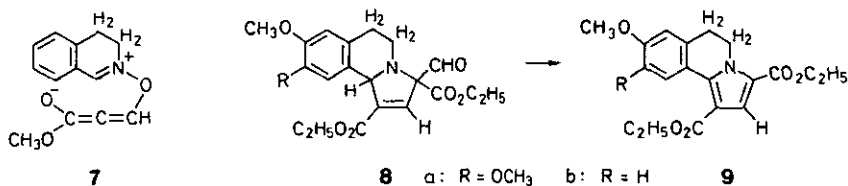


ring opening of suitably substituted aziridines; they occur only in small equilibrium concentrations.<sup>8</sup> To make them *visible* flash photolysis is required.<sup>9,10</sup> In the case of 5 the substituents strongly favor the ring opening to the azomethine ylide 4.

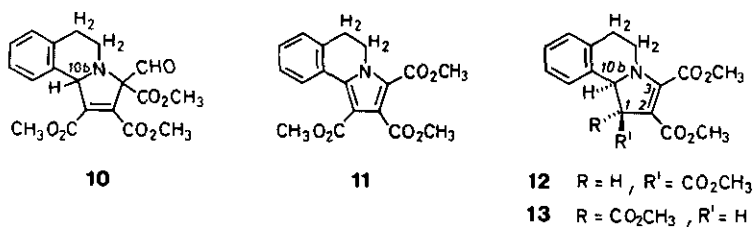
On carrying out the rearrangement 3 → 4 in the NMR tube, we detected no intermediate, i.e., the step 5 → 4 must be faster than 3 → 5. What is the mechanism of the ring contraction 3 → 5? We are probably confronted with an example of the vinylcyclopropane ⇌ cyclopentene conversion. Whereas the parent system favors the 5-membered ring and requires 300°C for the ring enlargement, substituted systems with heteroatoms are rearranged at 100°C or below. 2,3-Dihydrofuran equilibrates with cyclopropanecarboxaldehyde.<sup>11</sup> In the case of 4-isoxazolines like 3, the disappearance of the weak N-O bond - only 52 kcal mol<sup>-1</sup> of bond energy - shifts the equilibrium in favor of the formylaziridine 5. On the basis of additivity of bond energies, ΔH = -19 kcal mol<sup>-1</sup> is expected for 3 → 5.

The rearrangement of N-arylidene-2,2-diphenylcyclopropylamines to 1-pyrrolines is a hetero-analog of the vinylcyclopropane conversion. Investigation of its kinetics<sup>12</sup> strongly suggested a trimethylene species as an intermediate for which a biradical structure is a simplifying description. One of the "radical" centers is of allylic type as illustrated by 6. The light absorption of 4 in acetonitrile (λ<sub>max</sub> 440 nm, ε 7800) and in benzene (λ<sub>max</sub> 456 nm, ε 9500) allowed the spectrophotometric rate measurement of the conversion 3 → 4 by the ampoule technique at 60°C. The rearrangement follows the first order; the half-reaction times of 70 min in the polar acetonitrile and 52 min in the nonpolar benzene differ insignificantly. A greater response to solvent polarity would have been expected for the formation of 7 as an intermediate - an allylic rearrangement of 7 was one of the mechanisms considered by Takahashi

and Kano <sup>3</sup> - as well as for a rate-determining ring opening 5 → 4 within the scheme above. The data are consistent with the passing of the trimethylene type species 6; on the other hand, they do not exclude the possibility of a one-step sigmatropic process 3 → 5. However, the latter as a [ $\pi 2_s + \sigma 2_s$ ] process would be forbidden to be concerted by orbital symmetry.



Does 4 show 1,3-dipolar activity despite its stabilization? Kano, Yokomatsu, Yusa, and Shibuya <sup>13</sup> recently described the conversion of methoxy derivatives of 2 to 9a (45%) and 9b (30%) by 2 equiv. of ethyl propiolate in refluxing benzene; the methoxy-substituted azomethine ylides 4 and the 3-pyrrolines 8 are the supposed intermediates. We report here on experiments with the isolated 4.

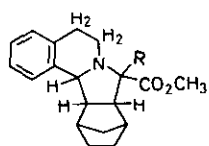


The addition of 4 to dimethyl acetylenedicarboxylate (DMAD) in CDCl<sub>3</sub> at 20°C (1 h) proceeded with quantitative formation of 10, as <sup>1</sup>H-NMR spectral comparison of the 10b-H signal with a weighed standard indicated. Two CHO signals at  $\delta$  9.78 and 9.52 pointed to a 82:18 mixture of two diastereomers which were not obtained in crystalline state. After addition of CH<sub>3</sub>OD the aldehyde signals of 10 disappeared and the CH singlet of methyl formate (77%) at  $\delta$  8.07 reveals the methanolysis of the vinylogous triacylmethane derivative 10; oxidation with methanolic bromine furnished 78% of the pyrrolo[2,1-a]isoquinoline derivative 11 (mp 128 - 129°C). <sup>14</sup> Thick-layer chromatography of 10 on moist silica gel afforded diastereomeric 2-pyrroline derivatives, 29% 12 and 30% 13, alongside with 17% 11. The enamine- $\beta$ -carboxylic ester system is

recognized by IR frequencies of 1670 (12) and 1685 (13) for C=O and of 1590 and 1600  $\text{cm}^{-1}$  for C=C. In the  $^1\text{H-NMR}$  spectrum the  $-\text{CO}_2\text{CH}_3$  singlet at as high a field as  $\delta$  3.20 indicates that it has to be in cis relation with  $\text{C}_6\text{H}_4$  in 12, whereas 13 shows a "normal" absorption at 3.82; furthermore,  $J_{1,10b} = 12.2$  Hz for 12 and 5.5 Hz for 13 support our structures.

The nucleophilic removal of the formyl group of 10 by methanol or water generates a well-stabilized allylic carbanion. Protonation at C-1 is favored by the formation of the enamine- $\beta$ -carboxylic ester in 12 and 13. Kobayashi et al.<sup>15</sup> likewise isolated the primary adducts of DMAD to aromatic isoquinolinium methylides.

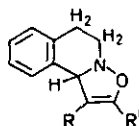
The disappearance of the orange color of ylide 4 in benzene (456 nm) was used to measure the rate of cycloaddition to DMAD (20 equiv.) under conditions of pseudo-first order;  $k_2 = 0.0256 \text{ M}^{-1}\text{s}^{-1}$  was found at 21°C. Measurements at four temperatures (21 - 42°C) provided the values  $\Delta H^\ddagger = 13.0 \pm 0.6 \text{ kcal mol}^{-1}$  and  $\Delta S^\ddagger = -22 \pm 2 \text{ e.u.}$ <sup>10</sup>



**14** R = CHO

**15** R = CH(OH)OCH<sub>3</sub>

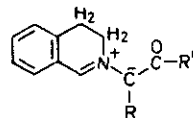
**16** R = CO-C<sub>6</sub>H<sub>5</sub>



**17** R = H, R' = C<sub>6</sub>H<sub>5</sub> **20**

**18** R = CO<sub>2</sub>CH<sub>3</sub>, R' = CH<sub>3</sub> **21**

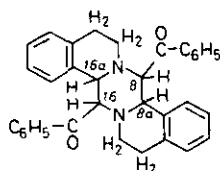
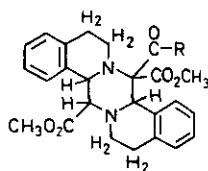
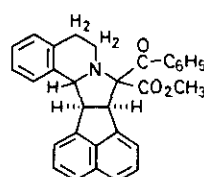
**19** R = CO<sub>2</sub>CH<sub>3</sub>, R' = C<sub>6</sub>H<sub>5</sub> **22**



Azomethine ylide 4 was decolorized in the presence of norbornene in  $\text{CH}_2\text{Cl}_2$  within 3 days and furnished two diastereomeric adducts 14 in a 1:1 ratio; the aldehydic protons occurred at  $\delta$  9.28 and 10.03. One of the hemiacetals 15 crystallized from methanol in 37% yield; mp 94 - 96°C,  $\text{CH}_3\text{O}$  singlets  $\delta$  3.39, 3.75.

The cycloadditions of nitrone 2 to phenylacetylene and methyl tetrolate yielding 17 (mp 99.5 - 101°C) and 18 (mp 43 - 45°C) required 10 days at 20°C. The isoxazoline 19 had been described before.<sup>4</sup> The thermal rearrangement of 17 - 19 did not stop at the stage of the azomethine ylides 20 - 22 as in the case 3  $\rightarrow$  4. Instead, 17 in DMF at 120°C produced via 20 the same crystalline dimer 23 in 56% yield which was earlier obtained by deprotonation of *N*-phenacyl-3,4-dihydroisoquinolinium bromide.<sup>16</sup> Likewise, heating of 18 and 19 afforded tetrasubstituted piperazine derivatives as viscous

oils. In methanolic solution one acyl group was removed, and the trisubstituted piperazines 24 (mp 160 - 161°C) and 25 (mp 171 - 172.5°C) crystallized in 35 and 54% yield; methyl benzoate was found in the mother liquor of 25.

**23****24** R = CH<sub>3</sub>**25** R = C<sub>6</sub>H<sub>5</sub>**26**

Dimer 23 occurs in two diastereomers. In the <sup>1</sup>H-NMR spectrum of 23a (mp 227 - 228°C), two identical AM spectra at δ 4.72 and 5.42 with  $J_{8,8a} = J_{16,16a} = 8.5$  Hz reveal high symmetry. In contrast, 23b (mp 191 - 194°C) shows two AM spectra, δ 4.30 and 5.08,  $J_{8,8a} = 4.0$  Hz, as well as 4.07 and 4.78,  $J_{16,16a} = 10.0$  Hz. The mass spectra indicate a cycloreversion: 249 ( $M/2^+$ , 83% and 85%), 248 ( $M/2^+ - 1$ , 100%). The MS of 24 and 25 likewise suggest the dissociation into radical cations corresponding to the azomethine ylides: the lower half furnishes the common fragment  $m/e = 203$  (60 and 64%), whereas 245 (62%) and 244 (100%), as well as 307 (94%) and 306 (100%), stem from the upper halves.

Why are the acetyl and benzoyl ylides 21 and 22 less stable than the formyl compound 4? The substituent constants  $\sigma^-$ , 1.04 for CHO and 0.85 for COCH<sub>3</sub>,<sup>17</sup> show the superior capability of the aldehyde group to stabilize the carbanionic charge.

However, the azomethine ylides 20 - 22 were trapped when the isoxazolines 17 - 19 were rearranged in the presence of dipolarophiles. Refluxing of 17 with dimethyl fumarate in acetonitrile procured 41% of a cycloadduct, mp 125 - 127°C. Interception of 21 and 22 was achieved by heating 18 and 19 with DMAD in ethyl acetate; the oily adducts afforded 38% of the pyrrole derivative 11 after chromatography on silica gel. The same product 11 was obtained from the piperazines 24 and 25 by heating with DMAD which suggests a thermal dissociation. Isoxazoline 19 and norbornene at 70°C furnished the 22-adduct 16 in two diastereomers (3:1) which were separated by fractional crystallization in 76% yield (mp 145 - 147°C and 118 - 120°C). The reaction of 19 via 22 with acenaphthylene in benzene at 70°C with subsequent thick-layer chromatography led to three crystalline 1:1 adducts 26: 34% of mp 166 - 168°C, 17% of mp

182 - 185°C, and 9% of mp 226 - 228°C. The  $^1\text{H-NMR}$  spectra ( $\text{CDCl}_3$ ) allow a tentative structural assignment of all three diastereomers. The high-field shift of the methyl-ester singlet ( $\delta$  3.01) in the main product, mp 166 - 168°C, indicates a cis relation with the naphthalene ring; according to  $\delta$  3.79 and 3.73, the ester groups are trans located in the two other isomers. Further confirmation of the structures is required.

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