THE CHEMISTRY OF AN ISOLABLE AZOMETHINE YLIDE

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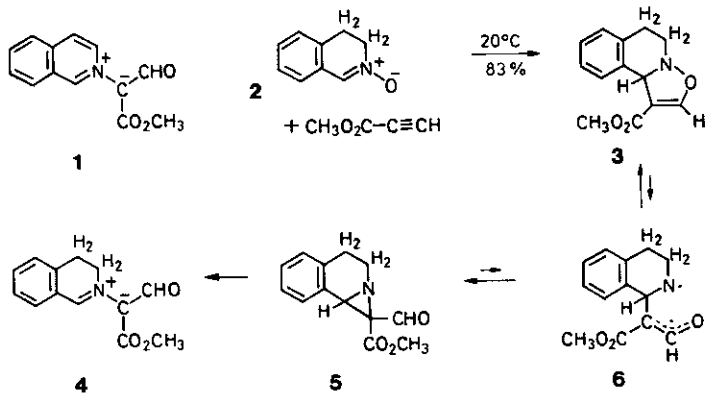
Abstract - The 4-isoxazoline 3 undergoes ring contraction to the acylaziridine 5 which is converted to the azomethine ylide 4. The small influence of solvent polarity on the rate constant of the conversion 3 → 4 suggests a mechanism via a trimethylene type species for the rate-determining step. Whereas 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.[1] A tentatively suggested structure was later revised in favor of the azomethine ylide 1 [2] after Takahashi and Kano [3] 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 [4]. That a 2-acylaziridine - here 5 - occurs on the pathway of the nitrone addition to acetylenes was conjectured by the Japanese authors [3] and established by Baldwin et al.[5] 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 [6].

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) [7] the whole azomethine ylide structure is embedded into a mesoionic ring. Less stabilized azomethine ylides are formed by conrotatory electrocyclic

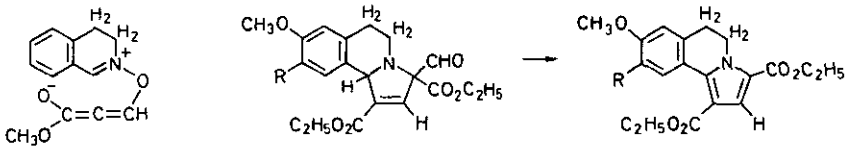


ring opening of suitably substituted aziridines; they occur only in small equilibrium concentrations.[8] To make them *visible* flash photolysis is required.[9,10] In the case of 5 the substituents strongly favor the ring opening to the azomethine ylide 4.

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.[11] In the case of 4-isoxazolines like 3, the disappearance of the weak N-O bond - only 52 kcal mol^{-1} of bond energy - shifts the equilibrium in favor of the formylaziridine 5. On the basis of additivity of bond energies, ΔH = -19 kcal mol^{-1} is expected for 3 → 5.

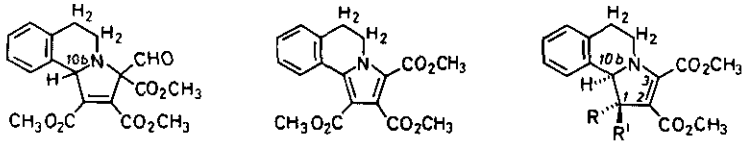
The rearrangement of N-arylidene-2,2-diphenylcyclopropylamines to 1-pyrrolines is a hetero-analog of the vinylcyclopropane conversion. Investigation of its kinetics [12] strongly suggested a trimethylene species as an intermediate for which a biradical structure is a simplifying description. One of the "radical" centers is of allylic type as illustrated by 6. The light absorption of 4 in acetonitrile (λ_{max} 440 nm, ε 7800) and in benzene (λ_{max} 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 [3] - 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.



7 8 a: R = OCH_3 b: R = H 9

Does 4 show 1,3-dipolar activity despite its stabilization ? Kano, Yokomatsu, Yuasa, and Shibuya [13] 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.



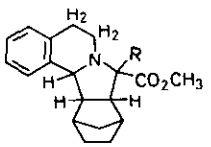
10 11 12 R = H, R' = CO_2CH_3 13 R = CO_2CH_3, R' = H

The addition of 4 to dimethyl acetylenedicarboxylate (DMAD) in $CDCl_3$ at 20°C (1 h) proceeded with quantitative formation of 10, as ^{1}H-NMR spectral comparison of the 10b-H signal with a weighed standard indicated. Two CHO signals at δ 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_3OD the aldehyde signals of 10 disappeared and the CH singlet of methyl formate (77%) at δ 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). [14] 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-β-carboxylic ester system is

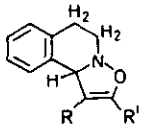
recognized by IR frequencies of 1670 (12) and 1685 (13) for C=O and of 1590 and 1600 cm^{-1} for C=C. In the ^{1}H-NMR spectrum the 1-CO_2CH_3 singlet at as high a field as δ 3.20 indicates that it has to be in cis relation with C_6H_4 in 12, whereas 13 shows a "normal" absorption at 3.82; furthermore, $J_{1,10b}$ = 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-β-carboxylic ester in 12 and 13. Kobayashi et al.[15] likewise isolated the primary adducts of DMAD to aromatic isoquinolinium methylides.

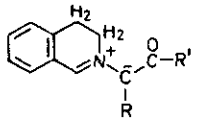
The disappearance of the orange color of ylide 4 in benzene (456 nm) was used to measure the rate of cycloaddition to DMAD (20 equiv.) under conditions of pseudo-first order; k_2 = 0.0256 $M^{-1}s^{-1}$ was found at 21°C. Measurements at four temperatures (21 - 42°C) provided the values $\Delta H^{\neq}$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



14 R = CHO
15 R = CH(OH)OCH_3
16 R = CO-C_6H_5



17 R = H, R' = C_6H_5
18 R = CO_2CH_3, R' = CH_3
19 R = CO_2CH_3, R' = C_6H_5



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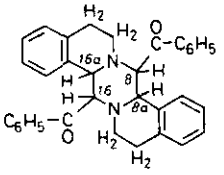
21
22

Azomethine ylide 4 was decolorized in the presence of norbornene in CH_2Cl_2 within 3 days and furnished two diastereomeric adducts 14 in a 1:1 ratio; the aldehydic protons occurred at δ 9.28 and 10.03. One of the hemiacetals 15 crystallized from methanol in 37% yield; mp 94 - 96°C, CH_3O singlets δ 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.[4] The thermal rearrangement of 17 - 19 did not stop at the stage of the azomethine ylides 20 - 22 as in the case 3 → 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.[16] 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.



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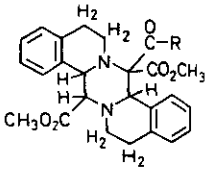
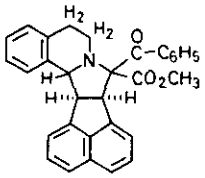


24 R = CH_3
25 R = C_6H_5



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Dimer 23 occurs in two diastereomers. In the ^{1}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 σ^-, 1.04 for CHO and 0.85 for $COCH_3$,[17] 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}H-NMR spectra ($CDCl_3$) allow a tentative structural assignment of all three diastereomers. The high-field shift of the methyl-ester singlet (δ 3.01) in the main product, mp 166 - 168°C, indicates a cis relation with the naphthalene ring; according to δ 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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