A Rearrangement of 3-Pyrazolines as a Missing Link[1])

by **Jürgen A. Finke**, **Rolf Huisgen***, and **Robert Temme**

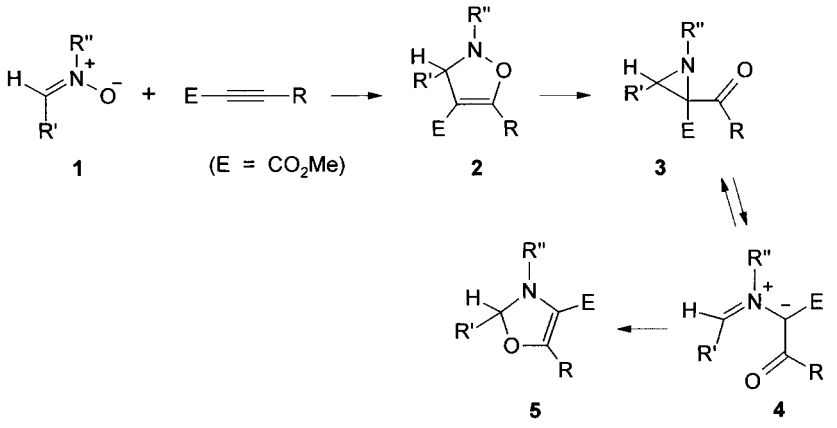
Department Chemie der Ludwig-Maximilians-Universität München, Butenandtstrasse 5–13 (Haus F), D-81377 München

Dedicated to *Paul von R. Schleyer* on the occasion of his 70th birthday

The thermal conversion of 4-isoxazolines to 4-oxazolines involves the transposition of two ring members. The ring-contraction and ring-expansion sequence in the reaction **2** → **5** has been previously clarified. The low N–N bond energy should favor an analogous conversion of 3-pyrazolines **6** to 4-imidazolines **7**; the first example of such a transformation is reported here. In the yellow **16**, the 3-pyrazoline is part of a pyrazolo-[5,1-*a*]isoquinoline system. Daylight induces a ring contraction, which affords the 2-isoquinolylaziridine derivative **21**. The latter is converted at 65° to the tricyclic 4-imidazoline **26** by a sequence of electrocyclic aziridine ring-opening and 1,5-electrocyclization of a C=N-conjugated azomethine ylide **25**.

1. Introduction. – 4-Isoxazolines (=2,3-dihydroisoxazoles) **2** are accessible by 1,3-dipolar cycloaddition of nitrones **1** with acetylenecarboxylates [2]. They easily undergo rearrangement by a sequence of steps, **2** → **5** [3–5] (*Scheme 1*). Depending on the substituents, the 2-acylaziridine **3** can be isolated and converted to 4-oxazoline **5** by heating. The electrocyclic ring opening of **3** at the C–C bond affords azomethine ylide **4**, which furnishes **5** by 1,5-electrocyclization. The overall isomerization **2** → **5** involves the transposition of two ring members, *i.e.*, the group R′CH–NR″.

Scheme 1

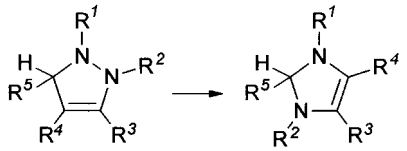


[1]) 1,3-Dipolar Cycloadditions, Part 119; Part 118: [1]

The acylated azomethine ylide **4** becomes isolable when its C=N bond is part of an aromatic ring [4][6] or a 3,4-dihydroisoquinoline system [3]. The ylides **4** are amenable to 1,3-dipolar cycloadditions with suitable dipolarophiles [7]. In 1983, *Freeman* reviewed a colorful variety of thermal rearrangements of 4-isoxazolines in which the ylides **4** were key intermediates [8].

Analogous transpositions of 3-pyrazolines **6** to yield 4-imidazolines **7** have not been reported previously (*Scheme 2*). The chemistry of 3-pyrazolines (=2,3-dihydro-1*H*-pyrazoles) appears to be somewhat underdeveloped [9], being limited to UV, NMR, and protonation (at C(4) rather than at N) studies [10].

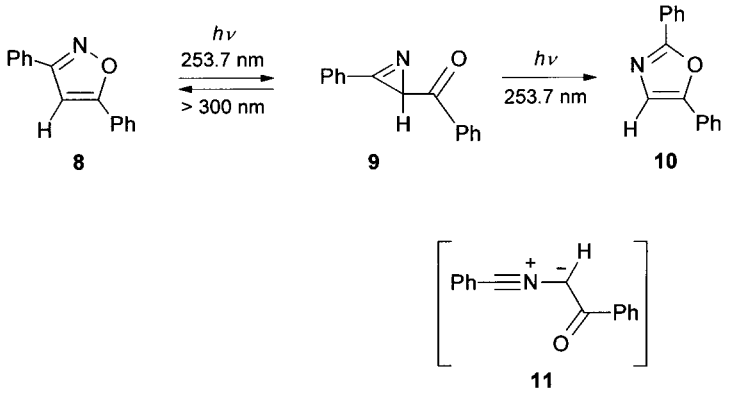
Scheme 2



6 **7**

In the 1960s, several groups discovered photoreorganizations of five-membered heteroaromatic systems. *Ullman* and *Singh* converted 3,5-diphenylisoxazole (**8**) by irradiation with the Hg resonance line to 2,5-diphenyloxazole (**10**), and 3-benzoyl-2-phenylazirine (**9**) was isolated as an intermediate [11] (*Scheme 3*). Interestingly, **9** afforded **10** on further irradiation with Hg (254 nm), but **8** was regenerated by light of >300 nm. *Schmid* and *Padwa* had later shown that the photolysis of 2*H*-azirines is the most versatile route to nitrile ylides (for a review, see [12]); **11** may be the logical intermediate on the pathway **9** → **10**.

Scheme 3

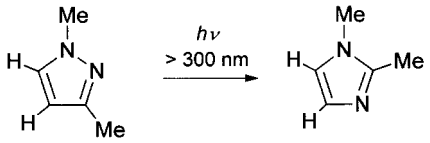


8 **9** **10**

11

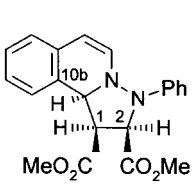
Schmid and co-workers observed a phototransposition of N(2)–C(3) in methylated pyrazoles furnishing imidazoles, *e.g.*, **12** → **13** (*Scheme 4*) and conjectured that a 3-imidoylazirine is an intermediate [13]. However, many photorearrangements of substituted indazoles [14], imidazoles [15], oxazoles [16], thiazoles [17], and thiophenes [18] are more complex and require additional steps.

Scheme 4

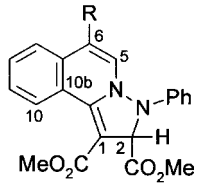


12 **13**

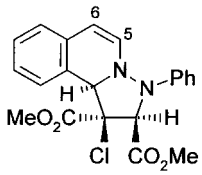
2. Results and Discussion. – 2.1. *Photoisomerization of 3-Pyrazoline Derivatives.* Cycloadduct **14** is formed by the reaction of isoquinolinium *N*-phenylimide with dimethyl maleate [19]. We reported recently on the conversion of two molecules of **14** by treatment with acid to give the triester **15** [1]. The structure of **15** was confirmed by X-ray analysis [20]; methyl isoquinoline-1-acetate and aniline were further products. The mechanism of the unique multi-step reaction was elucidated.



14



15 R = CH_2CO_2Me
16 R = H

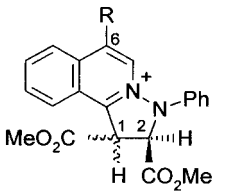


17

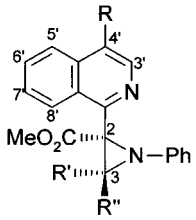
On treatment of **14** with chloranil (=2,3,5,6-tetrachlorocyclohexa-2,5-diene-1,4-dione), the pyrrolidine ring was dehydrogenated, and **16** was isolated in 65% yield. Another pathway to **16** is offered by the HCl elimination from **17**, the cycloadduct of isoquinolinium *N*-phenyl imide to dimethyl 2-chlorofumarate [19].

In both **15** and **16**, the chromophoric system is the same. Both compounds are bright-yellow, and the broad long-wave light absorption was found at 420 nm for **15** and 417 nm for **16** ($CHCl_3$). The N(4)-atom is part of two enamine systems; strong IR bands at 1677 (**15**) and 1688 cm^{-1} (**16**) are assigned to their C=C bonds. The chemical shifts of the enamine C(β)-atoms reflect the partial negative charge: the olefinic C(1)-atom resonates at 86.0 and 85.8 ppm in **15** and **16**, respectively, and C(6) appears at 109.9 in **15** and at 106.8 ppm in **16**.

The yellow color of **15** and **16** reversibly disappears in acidic medium. The ^{1}H-NMR spectra in CF_3COOH reveal pairs of stereoisomeric onium ions, 7:3 in the case of **16**-H^+ and 3:1 for **15**-H^+. An equilibrium protonation at C(1) is more probable than at C(6), since the isoquinolinium resonance in **18** and **19** provides an additional stabilization. Only protonation at C(1) of **16** generates a new stereogenic center, giving rise to two new *AB* spectra for H–C(1) and H–C(2) with $J_{trans}=3.2$ for the major isomer and $J_{cis}=10.0$ for the minor isomer of **19**. The H–C(6) loses its character as enamine-β-H in the conversion **16** → **19**; the *doublet* at 6.24 is shifted to 7.85 ppm. The ^{13}C-NMR parameters of **18** support the presence of the isoquinolinium system.



18 R = CH_2CO_2Me
19 R = H



	R	R'	R''
20	CH_2CO_2Me	H	CO_2Me
21	H	CO_2Me	H
22	H	H	CO_2Me

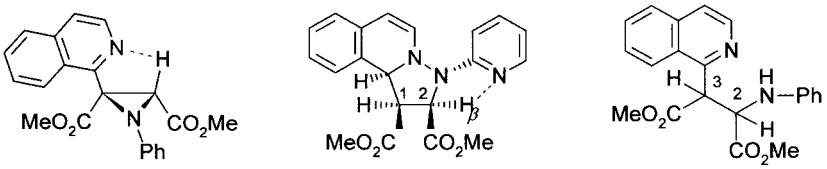
Bright-yellow solutions of **15** and **16** in benzene (*ca.* 0.02M) fade when exposed to diffuse daylight. The light sensitivity of **16** is so high that rapid recording was required to obtain the UV/VIS spectrum in $CHCl_3$. The pale-yellow benzene solutions provided colorless crystalline compounds, one from **15** and two from **16**, to which we assign the aziridine structures **20**–**22**. The contraction of the 3-pyrazoline rings in **15** and **16** to formal 2-imidoylaziridines in **20**–**22** can be regarded as an allylic shift with breaking of the weak N–N bond. Without a closer study of the photoconversion, we decline to postulate a mechanism. The energy gained by the isoquinoline aromaticity probably outweighs the strain of the aziridine ring in **20**–**22**. The photoreaction may be exothermic, although that is not mandatory for the conversion of a yellow to a colorless compound by visible light.

On irradiation, the dehydromaleate adduct **16** furnished 50% of the *cis*-aziridine-dicarboxylate **21** and 33% of the *trans*-dicarboxylate **22**. Only the 2,3-*trans*-diester **20** was isolated as photoproduct of **15**. The UV absorptions of **21** and **22** fit fairly well a superimposition of the spectra of isoquinoline and aniline. Double long-wave maxima (324 and 311 nm for **21**, 323 and 310 nm for **22**) resemble those of isoquinoline.

The ^{1}H- and ^{13}C-NMR parameters of **21** and **22** suggest diastereoisomers and establish 1-substituted aromatic isoquinolines when compared with the parameters of the isoquinoline parent. The resonances assigned to C(2) and C(3) of the aziridine rings appear at 57.2 and 45.0 ppm for **21** and at 55.0 and 47.6 for **22**.

The tentative *cis*,*trans*-assignment of aziridines **21** and **22** rests on the chemical shifts of the H–C(3): 4.84 for **21** *vs.* 4.31 ppm for **22**. Supposedly, the shift to higher frequency by 0.53 ppm is the result of an intramolecular H-bond to the isoquinoline N-atom, as shown for **21A**. We have observed a similar phenomenon when the *N*-Ph group of cycloadduct **14** was replaced by *N*-(pyridin-2-yl): the δ(H) of H_β–C(2) is shifted from 4.39 in **14** to 5.48 in **23** [19]. The X-ray analyses of related *N*-Ph and *N*-(pyridin-2-yl) compounds revealed distances that confirm the C–H···N bond in the *N*-(pyridin-2-yl) case [21]. The ester Me groups of **21** likewise resonate at higher field than those of **22**; mutual deshielding of the *cis*-ester groups in **21** could be one of the reasons.

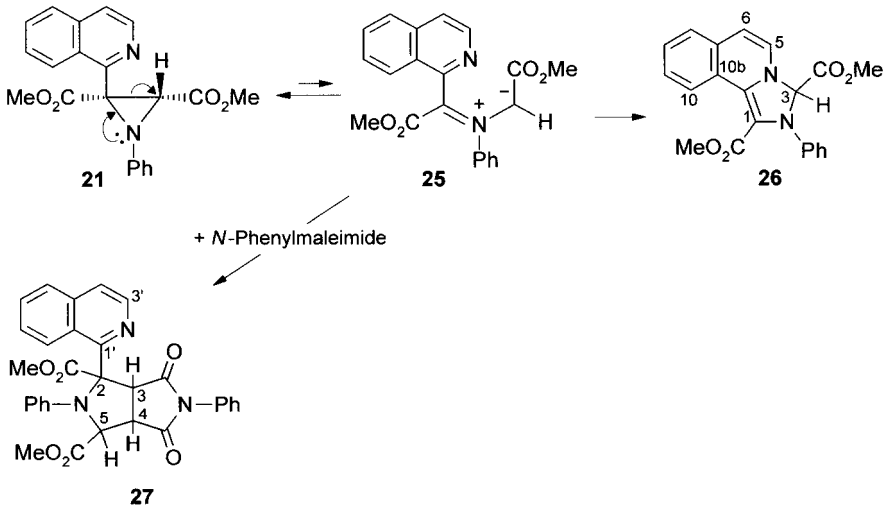
Aziridines are amenable to C–N hydrogenolysis, and preferably the higher substituted C-atom is involved [22]. More than 1 mol-equiv. of H_2 was consumed in the



hydrogenation of **21**, and 30% of **24** was isolated; the same compound **24** was also formed from **14** by treatment with an acidic buffer [1].

2.2. *Thermal Rearrangement to an Imidazo[5,1-*a*]isoquinoline Derivative.* When *cis*-diester **21** was heated under reflux in MeOH for 6 h, deep-orange crystals of the imidazo-isoquinoline **26** were isolated in 70% yield (*Scheme 5*). An experiment in methanolic H_2SO_4 furnished 54% of **26**; thus, protonation of the isoquinoline N-atom is unimportant for the rearrangement.

Scheme 5



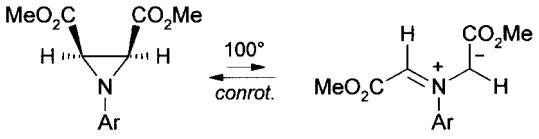
The structure of **26** was firmly established by two-dimensional NMR spectroscopy, as discussed in the *Exper. Part*. The close correlation of the NMR parameters with those of the isomeric 3-pyrazoline **16** is emphasized. The six-membered heterocycle shows a strongly diminished aromaticity in both compounds. A broad absorption band at 435 nm (sh at 535 nm) is responsible for the color of **26**.

Chemical evidence for the imidazolo ring was offered by the cleavage of the aminal group with 2,4-dinitrophenylhydrazine (2,4-DNPH) in methanolic H_2SO_4, which furnished methyl glyoxylate 2,4-dinitrophenylhydrazone.

A highly probable mechanism consists of electrocyclic opening of the aziridine ring to give the azomethine ylide **25**, which, in turn, furnishes **26** by 1,5-electrocyclization. Aziridines that bear electron-attracting substituents at the 2- and 3-positions are at elevated temperature in equilibrium with azomethine ylides, as we discovered in 1966

[23]. The thermal ring opening at the C–C bond proceeds by *conrotation*, and the preferred photochemical mode is *disrotation*, as demonstrated with the *cis*-diester **28** and the *trans*-isomer in 1967 [24] (*Scheme 6*); since aziridines are isoelectronic with cyclopropyl anions, this was the first verification of the *Woodward-Hoffmann* prediction for the steric course of the conversion of cyclopropyl anions to allyl anions [25].

Scheme 6



28 **29**

Ar = C_6H_4OMe

The intermediacy of the azomethine ylide **25** was established by interception. When *cis*-diester **21** and *N*-phenylmaleimide were refluxed in benzene, the crystalline cycloadduct **27** was obtained in 69% yield. The angular protons H–C(3) and H–C(4) appear in the ^{1}H-NMR spectrum as an *AB* pattern at 4.43 and 3.95 ppm with $J = 8.6$, and the 3.95 signal is further split by H–C(5) (5.62 ppm) with $J = 1.8$. Formula **25** would be the expected product of *conrotatory* ring-opening of **21**. In formula **27**, stereochemical assignments are omitted due to lack of evidence, the more so, as the *cis*,*trans*-assignments of **21** and **22** are only tentative.

No isomerization of the aziridine *trans*-diesters **20** and **22** to give 4-imidazolines was observed. The aziridines were recovered largely unchanged after heating under reflux in MeOH. However, an orange color of the hot methanolic solution of **20** was observed, which hints at an azomethine ylide intermediate. Treatment of **20** with *N*-phenylmaleimide in boiling benzene led to an ill-defined, nearly insoluble product. It is worth mentioning that the rate constants for **28** → **29** and that of the corresponding *trans*-aziridine dicarboxylate are hardly different [26].

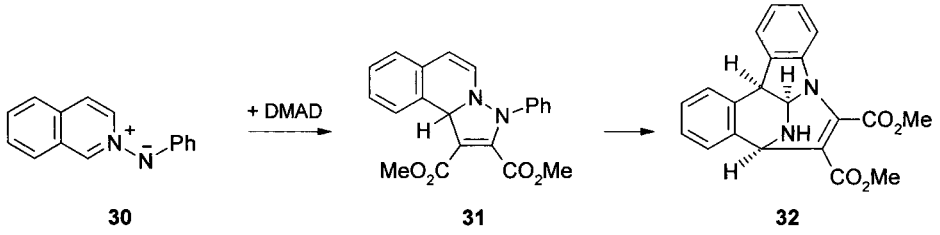
The conversion **25** → **26** belongs to the 1,5-electrocyclizations of conjugated 1,3-dipoles, which are of great importance in heterocyclic chemistry (for a review, see [27]). In **25**, the azomethine ylide is conjugated with the C=N bond of the isoquinoline system. It is not rare that such cyclizations overcome the loss of aromatic resonance. The *disrotatory* course, predicted by orbital control, is of no concern here since we do not have stereogenic centers at *both* termini.

The analogy of the ring closure **25** → **26** with the 1,5-electrocyclization of the acyl-conjugated azomethine ylide, **4** → **5**, is obvious. As in the conversion of 4-isoxazolines to 4-oxazolines, two contiguous centers of the five-membered ring are interchanged in the overall reaction **16** → **26**. Here, it is the fragment PhN–$CHCO_2$Me that undergoes the formal transposition in the framework of a multistep reaction. The alternation of photochemical and thermal steps provides a special note to this first example of the general scheme **6** → **7**.

We make a final, brief reference to **31**, an isomer of **16**, in which the C=C bond is located between C(1) and C(2). In the cycloaddition of isoquinolinium *N*-phenylimide (**30**) to dimethyl acetylenedicarboxylate, the 3-pyrazoline **31** cannot be isolated

because it rapidly enters into a hydrazo rearrangement (related to *Fischer*'s indole synthesis), which furnishes the tetracyclic aminal **32** [28] (*Scheme 7*). The thermodynamic driving force of both isomerizations, **16** → **26** and **31** → **32**, has the same origin, *i.e.* the low N–N bond energy.

Scheme 7



We thank the *Fonds der Chemischen Industrie*, Frankfurt, for the support of our work. Our thanks go to cand. chem. *Josef Geisenberger* for skillful assistance during some experiments and to Dr. *David S. Stephenson* for a two-dimensional NMR analysis. We are grateful to *Helmut Huber* for his help in NMR spectroscopy, to *Reinhard Seidl* for the MS, and to *Helmut Schulz* and *Magdalena Schwarz* for the elemental analyses.

Experimental Part

1. *General*. See [1].

2. *Dimethyl 2,3-Dihydro-3-phenylpyrazo[5,1-*a*]isoquinoline-1,2-dicarboxylate* (**16**). 2.1. *By Dehydrogenation of Dimethyl Maleate Adduct* **14**. When the hot soln. of **14** [19] (4.50 g, 12.3 mmol) in benzene (50 ml) was combined with 2,3,5,6-tetrachlorocyclohexa-2,5-diene-1,4-dione (3.20 g, 13.0 mmol) in benzene (50 ml), a dark-brown color was observed. After heating under reflux in the dark for 4 h, cooling, and filtering, the soln. was diluted with Et_2O (20 ml) and extracted with 2 × 50 ml of ice-cold 0.5N NaOH and 2 × 50 ml of H_2O. The org. phase was concentrated at the rotary evaporator, and the residue crystallized from acetone/pentane, giving **16** (2.93 g, 65%) as deep-yellow crystals, m.p. 158–160°; 160–162° after recrystallization.

2.2. *By Dehydrochlorination of Dimethyl 2-Chlorofumarate Adduct* **17**. Compound **17** [19] (1.00 g, 2.51 mmol) was dissolved in CH_2Cl_2 (10 ml) and MeOH (6 ml) and treated with 4 ml of methanolic 2.7N HCl for 2 h at r.t.; workup with CH_2Cl_2/2N NH_3 furnished **16** as coarse yellow crystals (538 mg, 59%), m.p. 160–162°.

2.3. *Data of* **16**. The light sensitivity of solns. of **16** exceeds that of **15** and requires rapid handling in diffuse daylight. UV ($CHCl_3$): λ_{max} (log ε), 417 (3.46), 375 (sh, 3.37), 324 (3.55), 311 (4.53), 275 (4.76); the extinctions at 417 and 375 nm are minimum values, because the soln. was decolorized after 15 min. IR: 698*w*, 762*m*, 773*m*, 784*m*, 1090*s*, 1188v*s* (br.), 1279*m*, 1338*s*, 1540v*s*, 1628*m*, 1688*s*, 1756*s*. ^{1}H-NMR: 3.60, 3.76 (2*s*, 2 MeO); 5.05 (*s*, H–C(2)); 6.24 (*d*, *J* = 7.4, H–C(6)); 6.86 (*d*, *J* = 7.4, H–C(5)); 6.95–7.62 (8 arom. H); 9.98 (*m*, H–C(10)). ^{13}C-NMR (20.2 MHz): 50.6, 52.5 (2*q*, 2 MeO); 75.5 (*d*, C(2)); 85.8 (*s*, C(1)); 106.8 (*d*, C(6)); 118.6 (*d*, C(2′/6′)); 125.2 (*d*, C(4′)); 129.5 (*d*, C(3′/5′)); 126.2, 126.7, 128.2, 131.1, 131.9 (5 arom. CH); 123.4, 135.1, 147.4, 151.3 (4 arom. quat. C); 164.3, 171.0 (2*s*, 2 C=O). MS (100°): 362 (75, M^+), 331 (3, $[M - MeO]^+$), 303 (100, $[M - CO_2Me]^+$), 271 (8), 243 (5), 151.5 (5), 128 (4), 77 (7). Anal. calc. for $C_{21}H_{18}N_2O_4$ (362.37): C 69.60, H 5.01, N 7.73; found: C 69.69, H 5.11, N 7.91.

2.5. *Protonation of* **16**. ^{1}H-NMR (80 MHz, CF_3CO_2H as solvent, major/minor of **19** 7:3): 3.93/3.88, 4.04/3.96 (4*s*, 2 × 2 MeO); 5.88, 5.40 (2*d*, *J* = 3.2, H–C(1), H–C(2) of major isomer); 5.60, 6.05 (2*d*, *J* = 10.0, H–C(1), H–C(2) of minor isomer); 7.1–8.5 (*m*, 11 arom. H). ^{13}C-NMR (20.2 MHz, $CDCl_3$, 10 equiv. of CF_3CO_2H, major/minor 89:11; in off-resonance spectrum only major isomer discernible): 52.8/51.9, C(1); 55.6/55.1, 55.8/55.8 (2 MeO); 72.0/72.1 (C(2)); 126.2/125.9 (C(10a)); 146.5/143.4, 146.8/144.0 (C(10b), C(1′)); 168.8/168.3 (C=O); 170.9/169.2 (C=O); clear signals only for major isomer: 124.1 (C(2′/6′)); 126.2 (C(4′)); 132.2 (C(3′/5′)); 128.2, 128.7, 129.6, 130.0, 131.3, 134.6 (6*d*, 6 arom. C).

2.6. *Protonation of* **15**. ^{1}H-NMR (80 MHz, CF_3CO_2H as solvent, major/minor of **18** 3:1): signals of major isomer: 3.86, 3.90, 4.00 (3*s*, 3 MeO); 4.36 (*s*, CH_2); 5.40, 5.76 (2*d*, *J* = 3.2, H–C(1), H–C(2)); 7.2–8.5

(*m*, 10 arom. H); signals of minor isomer: 3.81, 3.88, 3.96 (3*s*, 3 MeO); 4.30 (*s*, CH_2); 6.02, 5.57 (2*d*, $J = 9.8$, H–C(1), H–C(2)).

3. *Dimethyl 2-(Isoquinolin-1-yl)-1-phenylaziridine-2,3*-cis- *and* -trans-*dicarboxylate* (**21** and **22**, resp.). 3.1. *Photoisomerization of* **16**. *a*) Compound **16** (1.30 g, 3.59 mmol) was dissolved in benzene (150 ml) on stirring at r.t. for 20 min under Ar. On exposure to diffuse daylight, the deep-yellow soln. faded within 3 d and became light yellow. After removal of the solvent at r.t., colorless **21** (644 mg, 50%) crystallized from MeOH. M.p. 136–137° (dec.). The ^{1}H-NMR spectrum of the mother liquor showed the signals of **21** and **22** besides some unidentified absorptions. Compound **22** (427 mg, 33%) crystallized from Et_2O/pentane at −20°. M.p. 126–127°.

b) On exposure of **16** (300 mg, 0.83 mmol) in CH_2Cl_2 (20 ml) to sunlight, the soln. became pale yellow within 1 h. The CH_2Cl_2 was evaporated *i.v.*, and the residue was dissolved in ice-cold Et_2O. After addition of pentane, **21** (225 mg, 75%) crystallized in 12 h at 4°. M.p. 140–143° (dec., red). The colorless crystals became orange on storing for several weeks, and the soln. in CH_2Cl_2 at r.t. becomes orange after some h.

3.2. *Data of* **21**. UV (EtOH): 324 (3.71), 311 (3.65), 274 (3.79), 220 (4.70). IR: 695*m*, 753*m*, 767*m*, 1118*m*, 1242*s*, 1257*s*, 1440*m*, 1492*m*, 1587*w*, 1596*w*, 1760v*s* (br.). ^{1}H-NMR: 3.75, 3.84 (2*s*, 2 MeO); 4.84 (*s*, H–C(3)); 6.50–6.94, 7.18–7.74 (2*m*, 10 arom. H); 8.22 (*d*, $J = 5.8$, H–C(3′)). ^{13}C-NMR (20.2 MHz): 45.0 (*d*, C(3)); 52.3, 53.2 (2*q*, 2 MeO); 57.2 (*s*, C(2)); 121.2, 121.9, 123.9, 124.7, 127.5, 128.0, 128.1, 136.2 (8*d*, arom. CH); 141.4 (*d*, C(3′)); 128.7, 136.4, 145.1, 149.6 (4*s*, 4 arom. quat. C); 168.1, 168.8 (2*s*, 2 C=O). MS (130°): 362 (9, M^+), 331 (0.4, $[M - MeO]^+$), 318 (4, $[M - CO_2]^+$), 303 (100, $[M - CO_2Me]^+$), 271 (7, 303 − MeOH), 151.5 (5, M^{2+}), 140 (10), 128 (3), 77 (6); resembles the MS of **16**. Anal. calc. for $C_{21}H_{18}N_2O_4$ (362.37): C 69.60, H 5.01, N 7.73; found: C 69.63, H 5.01, N 7.61.

3.3. *Data of* **22**. UV (EtOH): 323 (3.76), 310 (3.70), 273 (3.90), 219 (4.78). ^{1}H-NMR (400 MHz, sample contained *ca.* 5% of **21**): 3.25, 3.47 (2*s*, 2 MeO); 4.31 (*s*, H–C(3)); 7.10 (*tt*, H–C(4) of Ph); 7.21 (*dt*, H–C(2/6) of Ph); 7.33 (*tt*, H–C(3/5) of Ph); 7.61 (*tm*, H–C(7′)); 7.68 (br. *d*, H–C(4′)); 7.70 (*td*, H–C(6′)); 7.88 (br. *d*, H–C(5′)); 8.20 (br. *s*, at 50° br. *d*, H–C(8′); coalescence probably due to hindered rotation at C(1′)–C(2) bond); 8.65 (br. *d*, H–C(3′)); assignments are based on parameters of isoquinoline and aniline [29]. ^{13}C-NMR (100 MHz, DEPT): 47.6 (C(3)); 52.2, 53.2 (2 MeO); 55.0 (C(2)); 119.4 (C(2/6) of Ph); 121.1 (C(4) of Ph); 123.9 (C(4′)); 129.2 (C(3/5) of Ph); 127.54, 127.74, 129.2, 130.1 (C(5′)–C(8′)); 142.3 (C(3′)); 127.0 (C(8a′)); 136.2 (C(4a′)); 147.2 (C(1) of Ph); 152.4 (C(1′)); 166.4, 167.2 (2 C=O). Anal. calc. for $C_{21}H_{18}N_2O_4$ (362.37): C 69.60, H 5.01, N 7.73; found: C 69.65, H 5.15, N 7.56.

3.4. *Hydrogenolysis of* **21**. A soln. of **21** (500 mg, 1.38 mmol) was shaken with H_2 and *Raney*-Ni (50 mg) in MeOH (50 ml) at r.t. and atm. pressure. After uptake of 3 equiv. of H_2, the reaction was interrupted, and workup furnished **24** (152 mg, 30%), m.p. 139–141°, identified by comparison of the ^{1}H-NMR spectrum with that of an authentic sample [1].

3.5. *2-(Isoquinolin-1-yl)-2,5-bis(methoxycarbonyl)-1,*N*-diphenylpyrrolidine-3,4-dicarboximide* (**27**). *cis*-Aziridine **21** (371 mg, 1.02 mmol) and *N*-phenylmaleimide (216 mg, 1.25 mmol) were heated under reflux in benzene (5 ml) for 5 h. The red-brown soln. was evaporated; **27** (378 mg, 69%) was obtained from MeOH as colorless powder. M.p. 238–239°. IR: 688*w*, 728*w*, 751*m*, 1180*s* (br.), 1224*s* (br.), 1383*s* (br.), 1503*s*, 1600*m*, 1714v*s*, 1738*s* (br.), 1781*w*. ^{1}H-NMR: 3.34, 3.63 (2*s*, 2 MeO); 3.95 (*dd*, $J = 8.6$, 1.8, H–C(4)); 4.43 (*d*, $J = 8.6$, H–C(3)); 5.62 (*d*, $J \approx 1.8$, H–C(5)); 6.61–7.89 (*m*, 15 arom. H); 8.21 (*d*, $J = 5.6$, H–C(3′)). ^{13}C-NMR (20.2 MHz): 47.3, 56.3 (2*d*, C(3), C(4)); 52.3, 53.0 (2*q*, 2 MeO); 63.0 (*d*, C(5)); 80.6 (*s*, C(2)); 117.6, 120.0, 122.2, 126.4, 127.2, 127.7, 128.2, 128.8, 129.1, 129.5 (10*d*, 15 arom. CH); 131.9 (*s*, C(8a′)); 137.4 (*s*, C(4a′)); 139.8 (*d*, C(3′)); 144.7 (*s*, 2 C(1) of 2 Ph); 155.0 (*s*, C(1′)); 170.0 (*s*, 2 C=O); 175.3, 175.8 (2*s*, 2 C=O). Anal. calc. for $C_{31}H_{25}N_3O_6$ (525.53): C 69.52, H 4.71, N 7.85; found: C 69.54, H 4.79, N 7.65.

3.6. *Attempted Isomerization of* trans-*Diester* **22**. Heating **22** (150 mg) in MeOH (5 ml) and conc. H_2SO_4 (0.1 ml) under reflux for 2 h and workup with 2N NH_3/CH_2Cl_2 gave back **22** (86 mg), m.p. 128–129°; the ^{1}H-NMR spectrum of the mother liquor showed essentially the signals of **22**.

4. *Dimethyl 2-{[(4-Methoxycarbonyl)methyl]isoquinolin-1-yl}-1-phenylaziridine-2,3*-trans-*dicarboxylate* (**20**). 4.1. *Photoisomerization of* **15**. The deep-yellow soln. of **15** [1] (1.10 g, 2.53 mmol) in abs. benzene (150 ml) obtained by stirring for 1 h under Ar was exposed to diffuse daylight for 3 d, and the solvent was evaporated at r.t. The residue of the pale-yellow soln. was recrystallized from MeOH and provided colorless **20** (488 mg, 44%). M.p. 137–138° (red color). The ^{1}H-NMR spectrum of the mother liquor showed more **20**, as well as some impurities. IR: 706*m*, 767*s* (br.), 1030*s* (br.), 1257*s* (br.), 1435*s*, 1497*s*, 1600*m*, 1739v*s* (br.), 1762 (sh). ^{1}H-NMR: 3.20, 3.44, 3.67 (3*s*, 3 MeO); 4.01 (*s*, CH_2–C(4′)); 4.26 (*s*, H–C(3)); 6.85–8.30 (*m*, 9 arom. H); 8.49 (*s*, H–C(3′)). Anal. calc. for $C_{24}H_{22}N_2O_6$ (434.43): C 66.35, H 5.10, N 6.45; found: 66.64, H 5.19, N 6.49.

4.2. *Attempted Isomerization of* **20**. The colorless **20** (300 mg) dissolved in hot MeOH (5 ml) with orange-red color. After heating under reflux for 8 h, 249 mg of **20**, m.p. 138–139°, crystallized from the partially

decolorized soln. in the cold. When **20** was refluxed in benzene for 6 h (orange color), 24% of the starting material was recovered; new ^{1}H-NMR signals of the mother liquor could not be assigned. In a third experiment, **20** was refluxed in toluene for 1 h. The red-brown soln. was evaporated; the ^{1}H-NMR spectrum of the dark-brown residue indicated a complex mixture.

4.3. *Reaction of* **20** *with* N-*Phenylmaleimide*. On heating for 2.5 h in benzene under reflux, the soln. became turbid; after 10 h, cooling afforded a pale-yellow microcrystalline substance. M.p. 312–318° (charring). The lack of solubility did not allow characterization.

5. *Dimethyl 2,3-Dihydro-2-phenylimidazo[5,1-*a*]isoquinoline-1,3-dicarboxylate* (**26**). 5.1. *Thermal Isomerization of* **21** *in Refluxing MeOH*. The nearly colorless soln. of **21** (354 mg, 0.98 mmol) in MeOH (7 ml) assumed a deep-red color on refluxing. After 6 h, orange-red **26** (247 mg, 70%), m.p. 181–184°, crystallized on cooling. M.p. 184–185° (recrystallized from MeOH). In an experiment in refluxing benzene, 46% of **26**, m.p. 185–186°, was isolated. In a third experiment, **21** (381 mg, 1.05 mmol) was refluxed in MeOH (10 ml) and 1.0 ml of conc. H_2SO_4. Workup with aq. Na_2CO_3/CH_2Cl_2 afforded **26** (207 mg, 54%). M.p. 184–185° (dec.).

5.2. *Data of* **26**. UV/VIS (CH_2Cl_2): 535 (sh, 2.60), 435 (br., 4.01), 310 (sh, 3.94), 284 (4.15). IR: 695*m*, 758*s*, 783*s*, 1103*s*, 1148*s*, 1225v*s* (br.), 1278*s*, 1343*s*, 1491*s*, 1511v*s*, 1596*m*, 1628*m*, 1659*s*, 1750*s*. MS (80 eV, 140°): 362 (9, M^+), 303 (100, $[M - CO_2Me]^+$), 271 (18, $[M - NPh]^+$), 243 (8, $[M - CO_2Me - HCO_2Me]^+$), 140 (13), 77 (8, $[Ph]^+$). Anal. calc. for $C_{21}H_{18}N_2O_4$ (362.37): C 69.60, H 5.01, N 7.73; found: C 69.64, H 5.08, N 7.73.

5.3. *Two-Dimensional NMR Analysis of* **26** (^{1}H-NMR (400 MHz), ^{13}C-NMR (100 MHz, DEPT); *Table 1*). The heteronuclear shift correlation of ^{13}C and ^{1}H signals was achieved by the HETCOR method [30]. The NOESY [31] experiment identified the MeOCO–C(3) by the proximity relationships between the Me protons to H–C(3) and H–C(5). Furthermore, NOESY points to the spatial relationship of both ester-MeO groups to H–C(2/6) of *N*-Ph. The enamine resonance feeds negative charge from N(4) of **26** to C(1) and its ester C=O. The latter resonates at δ(C) 163.8, whereas MeOCO–C(3) shows C=O at 168.9. As expected, the C=O resonances of **16** differ even more: 164.4, 171.0 ppm. C(1) of **16** is the enamine C(β)-atom and appears as low as 85.8 ppm. Due to substitution by N(2), C(1) of **26** absorbs at the higher δ(C) 104.2. C(1), and the other four quaternary C-atoms of **26** are unequivocally assigned on the basis of their ^3J(CH) couplings according to a COLOCS [32] experiment. As for H–C(5) to H–C(10), the large J_{vic} in the well-resolved spectrum generates *triplets* for H–C(8) and H–C(9), a *doublet* for the others. A DQF-COSY [33] experiment allowed the ordering

Table 1. *NMR Parameters of Dimethyl 2,3-Dihydro-2-phenylimidazo[5,1-*a*]isoquinoline-1,3-dicarboxylate* (**26**) *in $CDCl_3$ and Two-Dimensional Analysis*

Atom	δ(H) [ppm]	Multiplicity	DQF-COSY, H-Position	NOESY, H-Position	δ(C) [ppm]	COLOCS ^3J(C,H), (^2J(CH)) H-Position
*Me*OCO–C(1)	3.64	*s*		2′/6′, 10	51.0	
*Me*OCO–C(3)	3.88	*s*		3, 5, 2′/6′	53.4	
H–C(3)	5.76	*s*		5, 2′/6′, MeO(3)	83.4	5
H–C(6)	6.24	*d*	5	5, 7	108.1	7
H–C(5)	6.68	*d*	6	3, 6	126.8	(6)
H–C(4′)	7.03	*tm*	3′/5′ > 2′/6′	3′/5′	122.6	2′/6′
H–C(2′/6′)	7.14	*dm*	3′/5′ > 4′	3, 3′/5′ > MeO(1), MeO(3)	118.9	4′
H–C(3′/5′)	7.30	*tm*	2′/6′, 4′	2′/6′, 4′	129.0	(2′/6′) small
H–C(7)	7.32	*dd*	8	8, 6	126.1	9, 6, (8)
H–C(9)	7.44	*td*	8, 10	8, 10	127.0	7
H–C(8)	7.50	*td*	7, 9	7, 9	131.6	10
H–C(10)	9.82	*dm*	9	9, MeO(1)	130.7	8
C(1)					104.2	3
C(6a)					135.3	8, 5, 10
C(10a)					122.9	9, 7, 6
C(10b)					143.4	3, 5, 10
C(1′)					151.0	3, 3′/5′
O=C–C(1)					163.8	*Me*OCO–C(1)
O=C–C(3)					168.9	*Me*OCO–C(3)

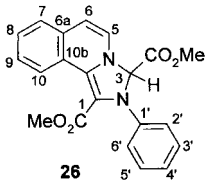


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Table 2. *Comparison of ^{1}H- and ^{13}C-NMR Data for Corresponding Aromatic Positions of* **26**, **16**, **14**, *and Isoquinoline* (δ in ppm)

Imidazoline **26**	H–C(5)	6.68	H–C(6)	6.24	C(5)	126.8	C(6)	108.1
Pyrazoline **16**	H–C(5)	6.86	H–C(6)	6.24	C(5)	126.2	C(6)	106.8
Cycloadduct **14**	H–C(5)	6.42	H–C(6)	5.30	C(5)	?	C(6)	100.3
Isoquinoline [29]	H–C(3)	8.45	H–C(4)	7.50	C(3)	142.7	C(4)	120.2

in two sequences, which were connected by the proximity relationship of H–C(6) and H–C(7) (NOESY). In addition, H–C(10) is close to the Me of MeOCO–C(1) (NOESY) and responsible for the high frequency of H–C(10) (9.82 ppm). The ^{1}H and ^{13}C parameters of H–C(5) and H–C(6) reveal the structural correspondence of **16** and **26**, as well as the strongly diminished isoquinoline aromaticity. The cross-conjugated π system of the six-membered heterocycle in **16** and **26** comes closer to that of the dihydroisoquinoline system in **14** (*Table 2*).

5.4. *Acid Hydrolysis.* Compound **26** (304 mg, 0.84 mmol) was heated under reflux with the soln. of 2,4-dinitrophenylhydrazine (2,4-DNPH; 354 mg, 1.79 mmol) in MeOH (10 ml), H_2O (3 ml), and conc. H_2SO_4 (2 ml) for 2 h. The yellow 2,4-dinitrophenylhydrazone of methyl glyoxylate (179 mg, 80%) crystallized on cooling. M.p. 162–164° (no depression of m.p. upon mixing with authentic sample [1]).

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