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Isoquinolinium *N*-Arylimides and Acetylenic Dipolarophiles; Cycloadducts and Their Rearrangements [1]

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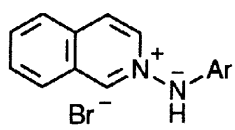
Abstract. Dimethyl acetylenedicarboxylate, methyl propiolate, and ethyl phenylpropiolate surpass the corresponding ethylenic carboxylic esters in dipolarophilic activity *vs.* isoquinolinium *N*-arylimides, a class of azomethine imines. The cycloadducts contain a N^{β}-vinylphenylhydrazine system and enter into a Fischer indole synthesis which stops one step short of the indole. The [3.3]-sigmatropic rearrangement involved is likewise faster for the cycloadducts of acetylenic dipolarophiles than for ethylenic ones and does not require acid catalysis; in some cases the initial adduct escapes ^{1}H NMR observation. The products **11-17**, obtained with ethyl phenylpropiolate, provide beautiful NMR models for steric interaction of benzo ring E and the 12-phenyl group. On treatment with strong acid, the pentacyclic rearrangement products suffer fragmentation; *e.g.*, **11** furnishes 4-(o-aminophenyl)-isoquinoline and methyl benzoylacetate in methanolic HCl.

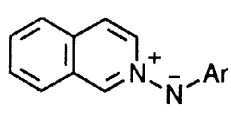
Introduction

The deep-red isoquinolinium *N*-arylimides **2** are accessible by deprotonation of the *N*-arylamino-isoquinolinium salts **1** [2] which, in turn, are prepared by the Zincke reaction.[3] The *N*-phenylimide **2a** and the *N*-(4-chlorophenyl)imide **2b** are only moderately stable in solution and cannot be isolated. Due to the increased stabilization of the anionic charge, the *N*-(2-pyridyl)imide **2c** and the *N*-(4-nitrophenyl)imide **2d** were obtained crystalline, but have a limited lifetime. The carbon disulfide adduct **3** is a convenient and neutral precursor of **2a**; the dissociation equilibrium of **3** with the reactants is mobile at room temperature .[2]



1

	Ar
a	C_6H_5
b	C_6H_4Cl-(4)
c	C_5H_4N-(2)
d	$C_6H_4NO_2$-(4)



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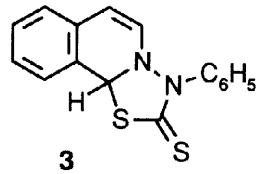

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The *N*-arylimides **2**, a class of azomethine imines, undergo (3+2) cycloadditions to electrophilic ethylenes; *e.g.*, **2a** combines with dimethyl fumarate affording **4** as the major of two diastereoisomers.[4] Ethylene itself is not sufficiently reactive, but the formal ethylene adduct is available via an indirect route. The structures of the cycloadducts have been clarified by X-ray analyses and NMR spectra.[4,5]

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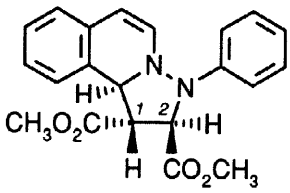

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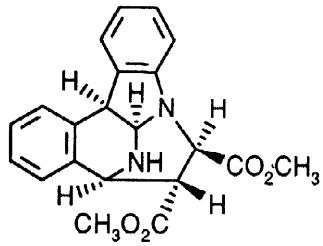

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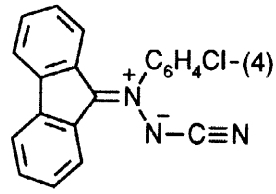

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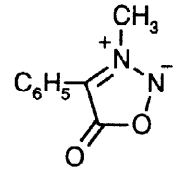


7

The bond system of cycloadducts of type **4** reveals a N^{β}-vinylphenylhydrazine which is amenable to hydrazo rearrangement; the Fischer indole synthesis stops short of the indole - the reason is given later. The pentacyclic aminal **5** is the product of the acid-catalyzed rearrangement of **4** which proceeds with retention of configuration at the stereocenters.[6]

Acetylenecarboxylic esters were more active as dipolarophiles towards azomethine imines than ethylenecarboxylic esters. The rate constants for cycloadditions to dimethyl acetylenedicarboxylate (DMAD) exceed those of dimethyl fumarate 240-fold for **6** [7] and 65-fold for the sydnone **7**.[8] Indeed, acetylenic dipolarophiles interacted rapidly with isoquinolinium *N*-arylimides **2**; also the subsequent hydrazo rearrangement of the primary cycloadducts was fast.

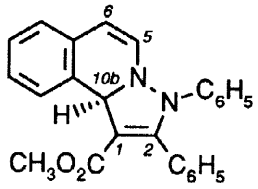
Phenylpropiolic Ester

When the pale-yellow carbon disulfide adduct **3** was dissolved in $CDCl_3$, the deep-red color of **2a** appeared in the equilibrium. After addition of 2 equiv. of methyl phenylpropiolate, the typical AB spectrum for 5-H and 6-H of the cycloadducts of 1,2-dihydroisoquinoline type was observed in the ^1H NMR spectrum; **8** showed δ 6.38 and 5.67 with $J_{5,6}$ = 7.5 Hz. The singlet of 10b-H (δ 5.88) is located in an allylic position and, therefore, shifted to higher frequency, compared with δ(10b-H) 4.64 and 4.47 for the methyl acrylate adducts **9** and **10**.[4] The ester methyl of **9** (δ 3.14) reveals the shielding by the benzo ring, in contrast to $\delta(OCH_3)$ 3.62 for the 1ß-CO_2CH_3 of **10**. It is not unexpected that the OCH_3 signal of **8** (δ 3.42) occurs at an intermediate value.

Despite an excess of methyl phenylpropiolate, the red color of **2a** did not vanish; an equilibrium of **8** with the reactants is probable. When the ^1H NMR spectrum was recorded again 24 h later, the signals of **8** had nearly disappeared; the isolation of **8** did not succeed.

For the preparation of **11**, the product of the hydrazo rearrangement, the dichloromethane solution of **2a** was reacted with ethyl phenylpropiolate for 2 d at room temp.; the crystalline **11** was obtained in 57% yield. Thus, the Fischer indole reaction again halts at the aminal stage. Both **8** and **11** are racemates; formula **8** and its nomenclature are based on the chiral molecule with 10b-H on the ß-side; this marker becomes position 5ß-H of **11**.

The molecular model (Dreiding) of **11** reveals a rigid bowl-shaped structure for rings B - D with 5-H, 6a-H, and 11b-H on the ß-side; rigid - except for the inversion at N6. The bond planes of the aromatic rings A and E form an angle of about 110°. In the ^1H NMR spectrum of **11**, the *cis-vic* 6a-H (δ 5.44) and 11b-H (δ 4.11) are coupled with 5.2 Hz. Due to the planar W shape of H-C5-N6-C6a-H, $^4J_{5,6a}$ = 1.5 Hz was observed (Table 1).



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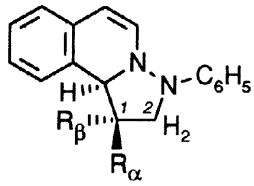
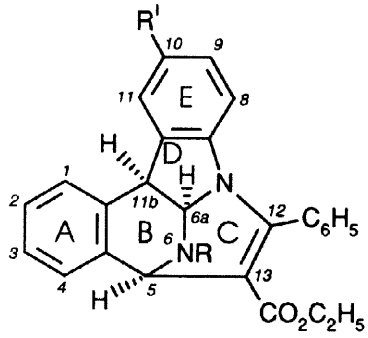


	R_α	R_β
9	CO_2CH_3	H
10	H	CO_2CH_3



	R	R'
11	H	H
12	CH_3	H
13	Ac	H
14	Ts	H
15	H	Cl
16	H	NO_2

The infrared NH band at 3295 cm^{-1} of **11** is consistent with a *sec*-amine. The strong coupled stretching frequencies for the C=C and C=O of enamine-ß-carbonyl compounds were found at 1585 and 1672 cm^{-1}; Dabrowski et al. refer to these as vinylogous amide I and amide II bands.[9]

The isoquinolinium *N*-(4-chlorophenyl)imide **2b** and the *N*-(4-nitrophenyl)imide **2d** reacted analogously with ethyl phenylpropiolate affording the 10-chloro derivative **15** (48% isolated yield) and the 10-nitro compound **16** (62%), respectively.

The rearrangement pathway of the primary cycloadducts closely parallels the one leading from **4** to **5**.[6] The [3.3]-sigmatropic reaction of **8** is followed by rearomatization to give **18**, the precursor of ami-

Table 1. Selected ^1H NMR Data (δ in ppm, J in Hz) in $CDCl_3$ (Substituents: E' = $CO_2C_2H_5$, E = CO_2CH_3, ME = $C(CO_2CH_3)=CHCO_2CH_3$)

No.	Substituents	δ	5-H	6a-H	11b-H	Other	J	5,6a	6a,11
	a. *6,6a,7,11b-Tetrahydro-5H-5,7-ethenoindolo[2,3-c]isoquinolines*								
11	12-C_6H_5, 13-E'		5.17	5.44	4.11	NH 2.78, 8-H 5.57		1.5	5.2
12	12-C_6H_5, 13-E', N-CH_3		4.90	5.13	4.15	NCH_3 2.76, OCH_2 3.91, 3.94		2.0	5.5
13A	12-C_6H_5, 13-E', N-Ac		6.05	6.88	4.26	CH_3CO 2.28, 8-H 5.51		2.0	5.9
13B	" " "		6.62	6.18	4.31	CH_3CO 2.29, 8-H 5.56		2.2	5.6
14	12-C_6H_5 13-E', N-Ts		6.04	6.23	4.33	Ar-CH_3 2.40, 8-H 5.57		2.0	5.5
15	12-C_6H_5, 13-E', 10-Cl		5.17	5.47	4.13	NH 2.81, OCH_2 3.92, 3.94		1.7	5.4
16	12-C_6H_5, 13-E', 10-NO_2		5.20	5.61	4.25	OCH_2CH_3 3.97, 0.93		1.5	5.4
17	12-C_6H_5, 13-E', N-ME		5.68	5.66	4.30	OCH_3 3.67, 3.95, =CH- 5.28			5.6
33	12-E, 13-E, N-ME		5.48	5.63	4.32	OCH_3 3.66, 3.81, 3.81, 3.92		2.4	5.8
34	12-E, 13-E		5.05	5.44	4.19	NH 2.76, 8-H 6.80, 10-H 7.07		1.8	5.5
43	13-CN		4.53	5.27	4.19	NH 2.81, 8-H 7.00			6.0
	b. *6,6a,7,11b-Tetrahydro-5H-5,7-ethenopyrido[3',2':4,5]pyrrolo[2,3-c]isoquinolines*								
37	12-E, 13-E		5.07	5.51	4.22	NH 2,84, OCH_3 3.75, 3.81			5.5
38A	12-E, 13-E, N-Ac		5.88	6.90	4.33	CH_3CO 2.23		2.2	5.6
38B	12-E, 13-E, N-Ac		6.52	6.22	4.39	CH_3CO 2.25		2.2	5.6
44	13-E		5.02	5.38	4.21	NH 2.85, OCH_3 3.67			6.0
45	13-E, N-Ac		5.77	6.12	4.24	CH_3CO 2.19, OCH_3 3.63		2.0	6.0

nal **11**. Here as in **5** excessive build-up of strain prohibits the indole formation, the concluding step of the Fischer reaction.[6]

On refluxing with formalin and formic acid, **11** was *N*-methylated affording **12** (Leuckart reaction). The *N6*-methyl shifts the proton signals of 5-H and 6a-H by 0.3 ppm to lower frequency (Table 1). The *N*-acetyl derivative **13** displays two sets of NMR signals as result of the hindered rotation about the amide C-N bond. The two rotamers **A** and **B** occur in an equilibrium ratio of 76:24, and the influence of *N*-acetyl on δ(5-H) and δ(6a-H) (Table 1) allows the conformational assignment. In **13A** the deshielding by the anisotropy effect of the C=O group is greater for 6a-H ($\Delta\delta$ 1.44 ppm) than for 5-H ($\Delta\delta$ 0.88 ppm); the opposite is true for **13B** where the carbonyl is located on the side of 5-H. In the *N6*-tosyl derivative **14**, 5-H and 6a-H are deshielded by 0.8 ppm. The δ(11b-H) of **11** is only marginally changed in **12** - **14**.

The NH of **11** reacted also with DMAD giving the crystalline 1:1 adduct **17**; primary and secondary amines add to DMAD furnishing derivatives of dimethyl 2-aminomaleate and 2-aminofumarate.[10,11]

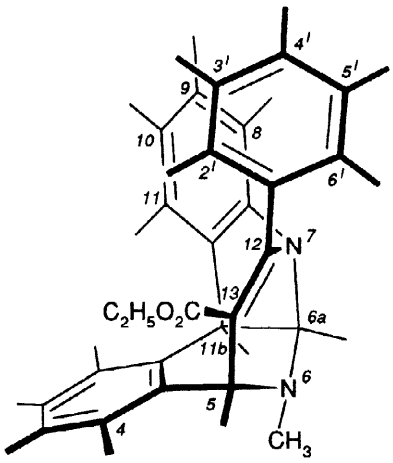


Figure 1. Structural Sketch of **12**, Based on Dreiding Model

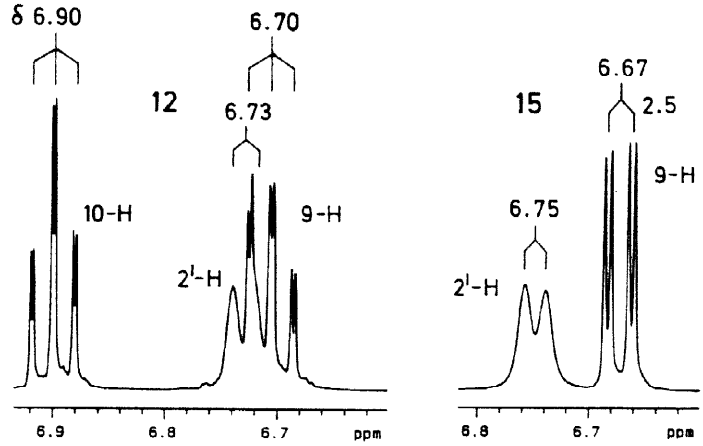


Figure 2. Sections of the ^{1}H NMR Spectra ($CDCl_3$, 400 MHz) of *N*-Methyl Compound **12** and 10-Chloro Compound **15**

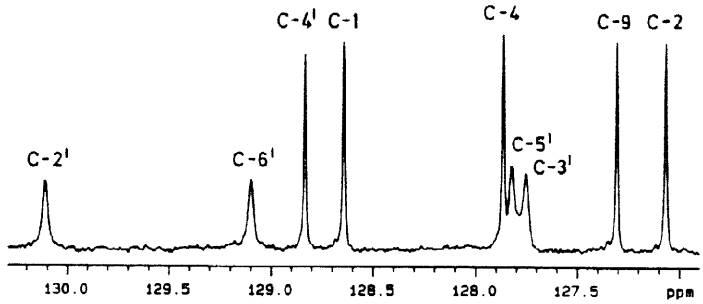


Figure 3. Section of the ^{13}C NMR Spectrum of **12** in $CDCl_3$ at 100 MHz

Surprising in the ^{1}H NMR spectra of **11** - **17** is the appearance of an aromatic proton signal in the region of the aliphatic H. The dd - sometimes a broadened d - at δ 5.43 - 5.57 belongs to the 8-H (Tables 1, 2); thus, the δ_H 7.26 of benzene is shifted to lower values by 1.7 - 1.8 ppm ! A minor part of

the effect results from the electron release by N7 (aniline-type resonance), but much larger is the shielding of 8-H by 12-phenyl. According to the Dreiding model, the distance from 8-H to the middle of the ring plane of the 12-phenyl is about 3.0 Å, less than the sum of the van der Waals radii (H 1.4 Å, half-thickness of benzene π-cloud 1.85 Å).[12,13] Thus, the 8-H is pressed into the shielding cone of the 12-phenyl.

Hindrance to phenyl rotation renders the five phenyl CH signals anisochronous. A DQF-COSY [14] experiment with the *N*-methyl compound **12** established the sequences of the aromatic hydrogens, and NOESY [15] anchored them by showing the proximity of 11-H, 11b-H, and 1-H. The shielding interaction of benzo ring E and 12-phenyl is mutual; two further high-field signals at δ 6.6 - 6.9 come from 2'-H and 9-H, the latter still being in the "pressure zone" (Fig. 1). For corroborating effects in the spectra of the 10-chloro compound **15** and the 10-nitro compound **16** see Table 2 and the experimental section.

Table 2. ^{1}H NMR Spectra (400 MHz, $CDCl_3$) of Ethyl 6,6a,7,11b-Tetrahydro-12-phenyl-5*H*-5,7-ethenoindolo[2,3-*c*]isoquinoline-13-carboxylates; Selected δ_H (in ppm) of Aromatic Protons; ME = $C(CO_2CH_3)=CHCO_2CH_3$

No.	Subst.	8-H	9-H	10-H	11-H	2'-H	3'-H	4'-H	5'-H	6'-H
12	N-CH_3	5.56	6.70	6.90	7.48	6.73	7.16	7.39	7.48	7.59
15	10-Cl	5.43	6.67	Cl	7.45	6.75	~7.18	7.40	7.49	7.58
16	10-NO_2	5.50	7.66	NO_2	8.34	6.83		7.46		~7.52
17	N-ME	5.50	6.74	6.94	7.39	6.78	~7.18	7.41	7.49	7.59

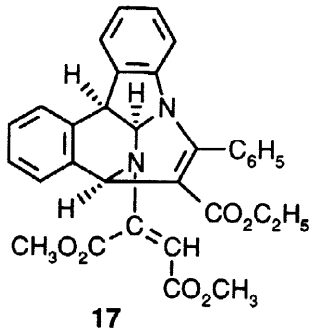
Is the rotation of 12-phenyl completely frozen ? Fig. 2 shows a broad d for 2'-H suggesting exchange with 6'-H. Four of the C_6H_5 protons give rise to broad signals; only the 4'-H signal - the only tt in the spectrum - is sharp. The phase-sensitive NOESY experiment with **12** reveals the exchange within the pairs 2'-H/6'-H and 3'-H/5'-H by a positive cross-peak, compared with the normal negative cross-peaks for NOE effects.

The ^{13}C NMR spectra display four aromatic CH signals which are broadened by exchange, shown for **12** in Fig. 3. According to the HETCOR [16] experiment, they belong to the *o*- and *m*-positions of C_6H_5. The mutual shielding of ring E and 12-C_6H_5 is not reflected in the δ_C values; CH-2' has the highest δ_C (130.1) and the lowest δ_H (6.73) among the four centers.

The inductive electron withdrawal by N7 and the mesomeric electron release are responsible for the big difference between the vinylic C-12 (155.5 ppm) and C-13 (107.9 ppm).

Acid Cleavage of Rearrangement Products

Notable for the rearrangement products **11-16** is their cleavage with acids. The treatment of **11** with hydrogen chloride in methanol at room temp. provided methyl benzoylacetate (58% yield) and a crystalline base $C_{15}H_{12}N_2$ (76%); the latter is an isomer of isoquinolinium *N*-phenylimide (**2a**). Methyl benzoylacetate is the formal hydration product of phenylpropiolic ester. The base was diazotized and coupled with 2-naphthol giving an orange azo dye, revealing a primary aromatic amine. The deamina-



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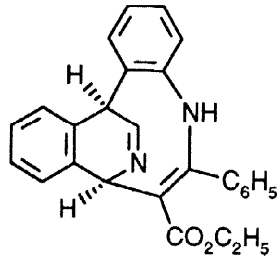

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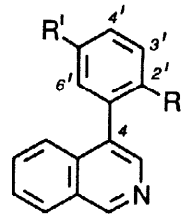
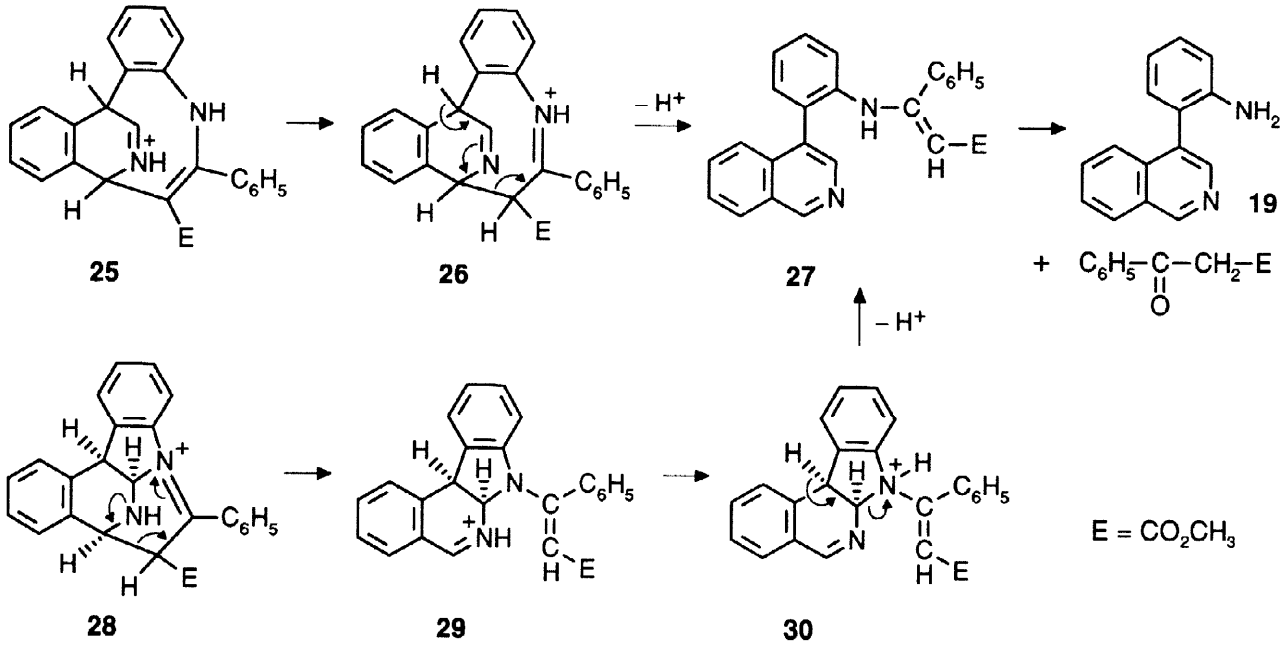


	R	R'
19	NH_2	H
20	NH-Ts	H
21	H	H
22	NH_2	Cl
23	H	Cl
24	NH_2	NO_2

tion of the diazonium ion by hypophosphorous acid afforded 4-phenylisoquinoline (**21**) which was identified with a specimen prepared by a Pictet-Gams synthesis.[17] Thus, the base $C_{15}H_{12}N_2$ must be 4-(2-aminophenyl)isoquinoline (**19**).

The 10-chloro compound **15** was amenable to the same cleavage by acid furnishing the isoquinoline derivative **22**. The ^1H NMR spectrum confirmed the substitution pattern of the 2'-amino-5'-chlorophenyl group in **22**. The AB spectrum of 3'-H and 4'-H was observed at δ 6.77 and 7.23 instead of δ 6.69 and 7.14, as calculated with substituent increments.[18]

The rearranged adduct of dimethyl fumarate, **5**, is resistant to 80% sulfuric acid at 100 °C.[6] In contrast, **11** underwent cleavage affording acetophenone (55%) and isoquinoline derivative **19** (47%); the benzoylacetic ester was converted to acetophenone under these conditions.



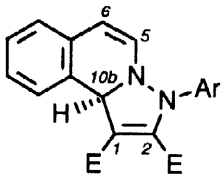
25 26 27 19 28 29 30

Several sequences of steps can be conceived for the fragmentation of **11** with HCl in methanol. The first of the two illustrated pathways combines the C-C cleavage as the key step with the aromatization of ring B. Protonation of **11** may give a small equilibrium concentration of **25**, and prototropy could provide **26**. The marked electron movements are conjectured to lead via **27** to the cleavage products. Transesterification of ethyl ester **11** takes place in the reaction course which is formulated above for the methyl ester.

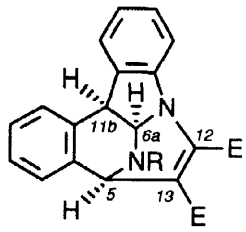
An alternative route starts with the C-protonated enamine **28**. The ring-opening **28** → **29** is the reversal of the electrophilic attack of an iminium ion on an enamine; then the tautomer **30** opens the aminal ring with concomitant aromatization. The forward reaction of iminium ions with enamines or vinylogous amides is known.[19-21] As for the reversal **28** → **29**, the analogy with various acid- or base-catalyzed reversions of Mannich reactions is pertinent.[22,23]

Dimethyl Acetylenedicarboxylate as a Dipolarophile

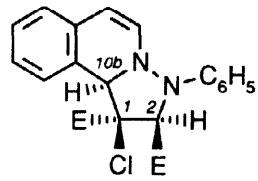
The initial cycloadduct **31** of the *N*-phenylimide **2a** to DMAD was not observable in the ^{1}H NMR spectrum, because secondary reactions - regrettably several - were too fast. A crystalline 1:2-product (19-21%) was isolated, when DMAD was applied in excess. The IR-spectrum displayed no NH, but the strong and broad absorptions of the enamine-ß-carboxylic ester suggested **33**. The ^{1}H NMR spectrum is in harmony (Table 1) with the structure; the 5-H at δ 5.48 is long-range coupled to 6a-H (δ 5.63), making it distinguishable from the s (δ 5.26) of the aminomaleic ester group attached to N6.



31 Ar = C_6H_5
32 C_5H_4N-(2)
E = CO_2CH_3



33 R = C(E)=CH-E
34 H
35 CHO



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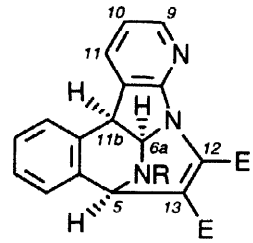


37 R = H
38 CO-CH_3

The dimethyl maleate group of **33** was removed with hydrochloric acid in aqueous methanol furnishing the 1:1-product **34** in 80% yield. Treatment of **33** with 2,4-dinitrophenylhydrazine in methanolic sulfuric acid gave the DNPH derivative of dimethyl oxaloacetate. On the other hand, **34** was reconverted to the 1:2-product **33** by DMAD.

The rearrangement product **34** shows the infrared N-H frequency at 3328 cm^{-1}. Besides the carbonyl absorption of the N-conjugated 13-CO_2CH_3 at 1696 cm^{-1}, that of the 12-CO_2CH_3 at 1739 cm^{-1} was observed. The aromatic 8-H (δ_H 6.80) is nearly normal for the *o*-position of an aniline derivative (Table 1). The electron release by N7 becomes noticeable in the ^{13}C NMR data, too; δ(C-8) 116.0 (115.6 ppm for **5**) is separated from the other aromatic C-signals. In a two-dimensional NMR analysis, all δ_H and δ_C of **34** were unequivocally assigned. The quaternary C-atoms were sorted out by their long-range C,H-couplings (COLOC-S),[24] mostly $^3J_{CH}$. The NOESY experiment reveals spatial interaction of 12-CO_2CH_3 with the aromatic 8-H.

The adduct **36**, prepared from **2a** and dimethyl 2-chlorofumarate,[4] does not undergo the acid-catalyzed hydrazo rearrangement. However, on treatment with sodium methanolate, the intermediate elimination product **31** was converted to **34**.

The diester **34** is not as susceptible to acid as the phenylpropiolic ester product **11**; **34** is stable under the conditions where **11** is cleaved by hydrogen chloride in methanol. It requires treatment with

80% sulfuric acid for the degradation of **34** to 4-(2-aminophenyl)isoquinoline (**19**).

The cycloadducts of isoquinolinium *N*-(2-pyridyl)imide (**2c**) to dimethyl fumarate and other electrophilic ethylenes did not enter into the acid-catalyzed hydrazo rearrangement.[6] However, the adducts to acetylenecarboxylic esters easily overcome this resistance. The fresh solution of equimolar amounts of **2c** and DMAD in $CDCl_3$ exhibited the ^1H NMR spectrum of the primary cycloadduct **32** with the AB pattern of 5-H and 6-H (δ 6.10, 5.73) and the s of 10b-H at δ 5.75. After 1 d at room temp., the spectrum indicated the complete rearrangement **32** → **37**. The broad s of NH and the signals of the ring protons follow closely those of **34** (Table 1).

The unstable **37** failed to crystallize, but the *N*-acetyl compound **38** (45%) was generated, when the rearrangement **32** → **37** took place in acetic anhydride and acetic acid. The hindered rotation of the acetamide group in **38** was responsible for double sets of ^1H and ^{13}C NMR signals, including even those of the aromatic rings; the two conformations A and B contribute with 58:42 to the equilibrium. The δ(5-H) of **37** is increased by 0.81 ppm in **38A** and by 1.45 ppm in **38B**, whereas the increase of δ(6a-H) is greater for **38A** (1.39 ppm) than for **38B** (0.71 ppm); see Table 1. The acetamide group is coplanar with the W shape of H-C5-N6-C6a-H, and the carbonyl group points in rotamer A to the side of 6a-H causing the greater deshielding; this was corroborated by NOESY experiments. Correspondingly, the δ_C values reflect the anisotropy effect of the amide group: δ(**38A**/**38B**) is 50.9/45.5 for C-5 and 66.3/71.1 for C-6a.

Although **5** originates from a hydrazo rearrangement of cycloadduct **4** (**2a** + dimethyl fumarate), the MS of **5** features the elimination of dimethyl fumarate as the major fragmentation pathway.[6] The products from acetylenic dipolarophiles behave differently. In the MS of the 10-chloro compound **15**, the molecular peak is the base peak. Neither ethyl phenylpropiolate nor its acylium ion appear among the cationic fragments of $\mathbf{15}^{+\cdot}$, but *m/z* 252 (23%, $C_{15}H_9ClN_2^+$) fits [M^+ - 2 H - ethyl phenylpropiolate]; among many possible structures, the aromatic indolo[2,3-c]isoquinoline **39** would require the least structural alteration. Major fragments of $\mathbf{15}^{+\cdot}$ are [M^+ - $CO_2C_2H_5$] (*m/z* 355, 45%), [355 - HCN] (22%), and [355 - C_6H_5] (21%)- The appearance of the isoquinolinium ion (*m/z* 130) is marginal.

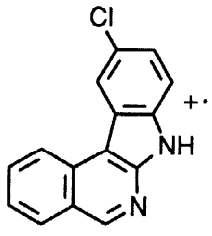
In the MS of **34**, the molecular peak appears with 81% and [M^+ - CO_2CH_3 - HCN] is the base peak. [M^+ - DMAD] (*m/z* 220) is missing; instead, *m/z* 217 (47%) [M^+ - DMAD - 3H] and 216 (38%) [M^+ - DMAD - 4H] appear. In the MS of the *N*-formyl derivative **35**, $M^{+\cdot}$ is the base peak, but many fragments reveal the easy loss of carbon monoxide.

Methyl propiolate

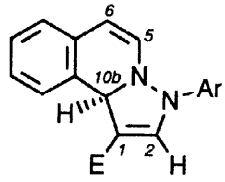
After **3**, the storage form of **2a**, was reacted with an excess of methyl propiolate at 0 °C, the ^1H NMR spectrum of the initial cycloadduct **40** was recorded at 0 °C. The vinylic 2-H (δ 7.82) shows an allylic coupling with 10b-H (δ 5.67, ^4J = 1.6 Hz). The signals of **40** were gone 30 min later; the new broad bands suggested a mixture.

We failed to isolate the carboxylic ester **42**, but the carbonitrile **43** was available by another route. The cycloadduct of **2a** to 2-chloroacrylonitrile was rearranged by picric acid furnishing **46**.[6] The elimination of hydrogen chloride by DBU afforded the crystalline **43**. The ^1H NMR spectrum of this formal cyanoacetylene adduct was in accordance with the expectation (Table 1).

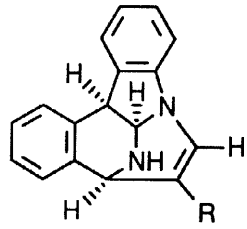
In contrast to **2a**, the *N*-(2-pyridyl)imide **2c** combined with methyl propiolate giving the crystalline cycloadduct **41**. The red-violet color of its solution indicated an equilibrium concentration of **2c** which



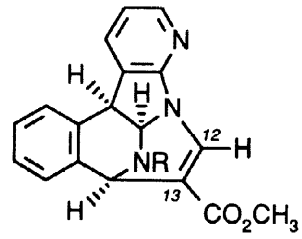
39



40 Ar = C_6H_5
41 C_5H_4N-(2)



42 R = CO_2CH_3
43 CN

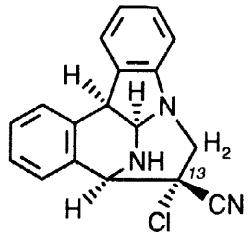


44 R = H
45 CO-CH_3

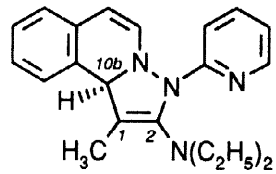
did not reach the analytical limit of the ^1H NMR spectrum. After 3 d, the ^1H NMR spectrum signaled the complete rearrangement, but we could not isolate **44** in pure form. The trick of running the rearrangement **41** → **44** in acetic anhydride and acetic acid provided the *N*-acetyl compound **45**, albeit in low yield.

1-Diethylaminopropyne

In correspondence with the nucleophilic-electrophilic character [25,26] of isoquinolinium *N*-arylimides, the *N*-(2-pyridyl)imide **2c** interacts with the electron-rich acetylenic bond of the ynamine. The rate appears to be markedly slower than for the cycloadditions to methyl propiolate or DMAD. After combining **2c** with 1.3 equiv. of 1-diethylaminopropyne in $CDCl_3$, the ^1H NMR spectrum, recorded after 15 min at room temp., agreed with the cycloadduct **47**. The 5-H and 6-H occur as d at δ 6.22 and 5.44 (J = 7.5 Hz). The 10b-H signal at δ 5.29 is a q and the 1-methyl signal a d with ^4J = 1.5 Hz; such long-range couplings via a sp^2-hybridized C-atom are known.[18]



46



47

We could not obtain **47** in pure form. Therefore, the assumption of a switch in regiochemistry (**41** vs. **47**) is tentative and based on the analogy with cycloadditions to enamines.[27] The NMR evidence is insufficient. In the framework of the opposite regiochemistry, the long-range coupling would be homoallylic.

EXPERIMENTAL

General.[6] All NMR spectra were taken in acid-free $CDCl_3$, if not otherwise stated. PLC is preparative thick-layer (2 mm) chromatography, and CC on silica gel is column chromatography. Melting points are uncorrected.

Phenylpropiolic Ester

Methyl (rel-10b-ßH)-(±)-3,10b-Dihydro-2,3-diphenylpyrazolo[5,1-*a*]isoquinoline-1-carboxylate (8): CS_2-adduct **3** (100 mg, 0.34 mmol) in 1 mL of $CDCl_3$ was reacted with 100 mg (0.60 mmol) of methyl phenylpropiolate. After 30 min, the ^1H NMR spectrum indicated only the signals of **8** and the excess of the dipolarophile (OCH_3 δ 3.73). **8**: δ 3.42 (s, OCH_3), 5.67 and 6.38 (AB, $J_{5,6}$ = 7.5 Hz, 6-H and 5-H), 5.88 (s, 10b-H); (C_6D_6): 3.12 (s, OCH_3), 5.60 and 6.36 (AB, J = 7.5 Hz, 6-H and 5-H), 5.93 (s, 10b-H). The signals of **3** have vanished. Due to the high extinction coefficient of **2a**, the solutions in $CDCl_3$ and C_6D_6 are deep-red without the NMR signals of a small equilibrium concentration of **2a** being observed. On the following day, the solution was light-yellow and turbid.

Ethyl (rel-5-ßH,6a-ßH,11b-ßH)-(±)-6,6a,7,11b-Tetrahydro-12-phenyl-5*H*-5,7-ethenoindolo[2,3-*c*]-isoquinoline-13-carboxylate (11). (a) *Preparation from* **1a**: *N*-Anilinoisoquinolinium bromide [2] (**1a**, 15.1 g, 50.1 mmol) was dissolved in 600 mL of water; the red precipitate after basifying with aqueous sodium carbonate was extracted with 250 mL of CH_2Cl_2. After quick drying with sodium sulfate, the deep-red solution was reacted with 10.4 g (59.7 mmol) of ethyl phenylpropiolate for 2 d at room temp.; the solution was concentrated to small volume and mixed with 25 mL of methanol. The rearrangement product **11** (11.3 g, 57%) was obtained in colorless crystals with mp 206.5-207.5 °C (acetonitrile). – IR (KBr): $\tilde{\nu}$ 702 cm^{-1} m, 760 st br (arom. CH out-of-plane def.), 1202 st (C-O); 1585, 1672 st (coupled vibr. of enamine-ß-carboxylic ester), 3295 (N-H). – UV ($CHCl_3$): λ_{max} (log ϵ) 327 nm (4.05), 245 (4.10). – ^1H NMR: Table 1. Further data: δ 0.87 (t, CH_3) and 3.93 (q, OCH_2) with J = 7.1 Hz; 6.60 - 6.97 (apparent td, 2 Ar-H), 7.00 - 7.80 (m, 10 Ar-H). – Anal. for $C_{26}H_{22}N_2O_2$: calcd C 79.16, H 5.62, N 7.10; found C 78.99, H 5.73, N 7.24. – *Picrate of* **11**: mp 176-178 °C (dec), rods from ethanol.

(b) *6-Methyl Derivative* **12**: 320 mg (0.81 mmol) of **11** was refluxed in a mixture of 5 mL of propanol, 2 mL of formic acid (98%) and 4 mL of formalin (35% aq. formaldehyde) for 2 h, poured into an excess of NaOH and extracted with CH_2Cl_2. Colorless needles (142 mg, 43%), mp 174-175 °C, came from ethanol. – IR (KBr): $\tilde{\nu}$ 700 cm^{-1}, 708, 735, 757 (arom. CH out-of-plane def.), 1115, 1207, 1221, 1247 st (C-O), 1470 st, 1606 w (arom. ring vibr.), 1571, 1582, 1672 st (vinylogous amide I and amide II) . ^1H NMR (400 MHz, Tables 1, 2). The above-mentioned NOESY experiment signaled the exchange process of 2'-H/6'-H and 3'-H/5'-H in the slowly rotating 12-C_6H_5. Interestingly, the vicinity of 2'-H/3'-H and 5'-H/6'-H (coupling is normal) is not indicated by NOESY signals. We ascribe this to the complex interplay of exchange together with internal and external relaxation. The close spatial relation of 2'-H with 8-H is likewise not indicated in the NOESY spectrum. DQF-COSY provides the sequence of 2'-H to 6'-H, but the direction of assignment relies solely on the low δ(2'-H) of 6.73 ppm (shielding cone of benzo ring E) whereas δ(6'-H) 7.59 suggests this hydrogen lies within the deshielding space of ring E. Further data: δ 0.88 (t, X_3 of ABX_3 for OC_2H_5), 3.91, 3.94 (AB of ABX_3, 12 lines visible, J_{vic} = 7.1 Hz, J_{gem} = -10.8 Hz, simulated by DavinX,[28] CH_2 of OC_2H_5). Ring A: δ 7.39 (1-H), 7.16 (2-H), 7.14 (3-H), 7.56 (4-H). - ^{13}C NMR (100 MHz, DEPT, HETCOR, Fig. 3): δ 13.7 (CH_3 of ethoxy), 41.1 (NCH_3), 45.8 (C-11b), 56.6 (C-5), 59.5 (OCH_2), 80.6 (C-6a), 117.6 (C-8), 124.3 (C-10), 124.8 (C-11), 126.3 (C-3), 127.1 (C-2), 127.3 (C-9), 127.75 (br, C-3'), 127.82 (br, C-5'), 127.9 (C-4), 128.6 (C-1), 128.8 (C-4'), 129.1 (br, C-6'), 130.1 (br, C-2'); the COLOC-S [24] experiment confirmed the assignment of the quaternary C atoms: 107.9 (C-13), 132.7 (C-11c), 137.6 (C-1'), 138.6 (C-11a), 139.9 (C-4a), 146.0 (C-7a),

155.5 (C-12), 168.3 (C=O). – Anal. for $C_{27}H_{24}N_2O_2$: N calcd 6.86, found 6.58.

(c) *6-Acetyl Derivative* **13**: Obtained with acetic anhydride, the colorless needles showed mp 195-197 °C. – IR (KBr): $\tilde{\nu}$ 680 cm^{-1}, 734 m, 763 st (arom. CH out-of-plane def.), 1123, 1222 st (C-O), 1442, 1470, 1567, 1583, 1606 (arom. ring vibr.), 1665 vst br (amide I, vinylogous amide). – ^1H NMR (400 MHz, Table 1): The integrals allowed the assignments of rotamers **A** and **B** (76:24). Further data for **13A/13B**: δ 0.85/0.95 (t, J = 7.1 Hz, CH_3 of OC_2H_5), 2.28/2.29 (s, CH_3CO), 3.95 (mc, 12 lines visible, AB of ABX_3, diastereotopic CH_2 of OC_2H_5), 5.51/5.56 (d br, J = 8.1 Hz, 8-H), 6.74/6.74 (d br, 2'-H), 6.72 (td, 9-H), 6.93/6.96 (td, 10-H). – Anal. for $C_{28}H_{24}N_2O_3$: calcd C 77.04, H 5.54, N 6.42; found C 76.53, H 5.46, N 6.42.

(d) *6-Tosyl Derivative* **14**: 920 mg (2.25 mmol) of **11** and 600 mg (3.15 mmol) of tosyl chloride in 20 mL of dry pyridine were refluxed for 2 h and worked up with water/CH_2Cl_2. 1.06 g (86%) of **14**, mp 203-204 °C, crystallized from CH_2Cl_2/ether. – IR (KBr): $\tilde{\nu}$ 666 cm^{-1}, 700, 758 st (arom. CH out-of-plane def.), 1168, 1228, 1243, 1356 st (C-O, SO_2N), 1584, 1672 st (coupled N-C=C-C=O). – ^1H NMR: Table 1. Further data: δ 0.81 and 3.85 (t and q, J = 7.2 Hz, OCH_2CH_3), 6.35 - 6.87 (apparent dd, 2 Ar-H), 6.90 - 8.00 (m, 14 Ar-H). – Anal. for $C_{33}H_{28}N_2O_4S$: calcd C 72.24, H 5.14, N 5.11, S 5.84; found C 71.92, H 5.05, N 5.12, S 5.94.

(e) *10-Chloro Derivative* **15**: As described above for **1a** → **2a**, 3.36 g (10.0 mmol) of salt **1b** was converted to **2b** in 150 mL of CH_2Cl_2. After reacting with 1.77 g (10.2 mmol) of ethyl phenylpropiolate for 2 d at room temp., the still raspberry-red solution was concentrated to ~ 10 mL. Addition of methanol provided in two fractions 2.07 g (48%) of **15** in colorless needles, mp 200-201 °C. – IR (KBr): $\tilde{\nu}$ 699 cm^{-1} m, 724, 750, 814 st (arom. CH out-of-plane def.); 1070, 1123, 1223, 1246, 1256 st (C-O, ClC_6H_3); 1464 st, 1488 w, 1608 w (arom. ring vibr.); 1584, 1677, 1687 st (vinylogous amide); 3341 m (N-H). – ^1H NMR (400 MHz, Tables 1, 2): δ 0.89 (t X_3 part of ABX_3, CH_3), 3.92, 3.94 (AB of ABX_3, 14 lines visible, simulation by DavinX,[28] J_{vic} = 7.1 Hz, J_{gem} = -10.7 Hz, CH_2 of OC_2H_5). The assignment of the Ar-H (Table 2) followed that of the signals of **12**; 9-H forms a dd with J = 8.5, 2.2 Hz, and 11-H is a d with J = 2.2 Hz. The influence of Cl on the δ_H in ring E is small as expected. The signals of 1-H to 4-H were not disentangled. – ^{13}C NMR (100 MHz, DEPT): Comparison with the confirmed δ_C assignments of **12** leaves little uncertainty. δ 13.7 (CH_3 of OC_2H_5), 45.1 (C-11b), 49.9 (C-5), 59.5 (O-CH_2), 74.9 (C-6a), 118.0 (C-8); 125.1, 126.5, 127.3, 127.4 (C-2, C-3, C-9, C-11); 128.3, 128.7 (C-4, C-1), 129.1 (C-4'); broadened by exchange: 127.95, 128.03 (C-3', C-5'), 128.8 (C-6'), 130.3 (C-2'); quaternary C atoms: 114.2 (C-13), 129.0 (C-10), 132.4 (C-11c), 137.5, 139.0, 139.9 (C-4, C-11a, C-11c), 144.8 (C-7a), 155.5 (C-12), 167.6 (C=O). – MS (170 °C); *m/z* (%): 428 (100) [M^+; ^{37}Cl + $^{13}C_2$ calcd. 36.1/found 36.1], 427 (21) [M^+ - H], 401 (10) [M^+ - HCN; ^{13}C 2.9/ 3.2), 399 (16) [M^+ - C_2H_5], 381 (11), 355 (45) [M^+ - $CO_2C_2H_5$; ^{13}C 12/14; ^{37}Cl 15/16], 328 (22) [355 - HCN], 327 (20), 326 (12), 325 (13), 324 (11), 293 (13), 292 (11), 291 (12), 278 (21) [$C_{17}H_{11}ClN_2^+$, M^+ - $CO_2C_2H_5$ - C_6H_5; ^{37}Cl + $^{13}C_2$ 7.0/7.5], 252 (23) [$C_{15}H_9ClN_2^+$, **39**; ^{37}Cl + $^{13}C_2$ 7.7/7.5], 217 (5) [252 - Cl], 130 (4) [Isoquinolinium$^+$]. – Anal. for $C_{26}H_{21}ClN_2O_2$: calcd C 72.80, H 4.94, N 6.53; found C 73.35, H 4.96, N 6.56.

(f) *10-Nitro Derivative* **16**: 265 mg (1.00 mmol) of the carmine-red **2d** in 25 mL of CH_2Cl_2 was reacted with 191 mg (1.10 mmol) of ethyl phenylpropiolate. By the same work-up as above, 272 mg (62%) of **16** was obtained in bright yellow crystals (CH_2Cl_2/methanol), mp 283-285 °C (dec.). – IR (KBr): $\tilde{\nu}$ 704 cm^{-1}, 722, 734, 752, 762, 831 st (arom. CH out-of-plane def.), 1088, 1228, 1242 (C-O, C-N), 1328, 1504, 1516 (NO_2); 1584, 1671 st (N-C=C-C=O), 3345 (N-H). – ^1H NMR (400 MHz, Tables 1, 2): δ

0.93 (t, CH_2 of OC_2H_5), 3.97 (q, J = 7.1 Hz, O-CH_2), 7.36 (dd, 1-H), 7.46 (tt, 4'-H), 7.66 (dd, 9-H), 8.34 (d, J = 2.4 Hz, 11-H). The 10-NO_2 group deshields 9-H by 0.96 ppm and 11-H by 0.86 ppm, compared with **12**; data tables give +0.95 ppm.[18] Signal overlap renders some assignments of ArH uncertain. - Anal. for $C_{26}H_{21}N_3O_4$: N calcd 9.56, found N 9.91.

(g) *DMAD Adduct* **17**: 395 mg (1.00 mmol) of **11**, dissolved in 25 mL of ether and 10 mL of CH_2Cl_2, was reacted with 156 mg (1.10 mmol) of DMAD for 24 h. Removal of the solvent left adduct **17** which was twice recrystallized from CH_2Cl_2/methanol: 374 mg (70%) of colorless crystals, mp 239-241 °C, was obtained. - IR (KBr): $\tilde{\nu}$ 701 cm^{-1}, 763 st (arom. CH out-of-plane def.); 1119 st, 1160 vst, 1120, 1160, 1228 st (C-O); 1372 st; 1598 vst, 1674, 1708, 1743 st (C=O and vinylogous amide). - ^1H NMR (400 MHz, Tables 1, 2): δ 0.91 (t, J = 7.1 Hz, CH_3 of OC_2H_5), 3.90 - 4.12 (m for diastereotopic OCH_2 of ABX_3), 4.30 (d br, $J_{6a,11b}$ = 5.6 Hz, 11b-H), 5.50 (dd, 8-H), 5.66 and 5.68 (higher order, simulated by DavinX,[28] $J_{6a,11b}$ = 5.6 Hz, $J_{5,6a}$ = 2.4 Hz, 6a-H and 5-H), 6.74 (td, 9-H), 6.78 (d br, 2'-H), 6.94 (td, 10-H), 7.16 - 7.24 (superimposed signals of 2-H, 3-H, 3'-H), 7.38 (dd, 1-H), 7.41 (tt, 4'-H), 7.49 (t br, 5'-H), 7.50 (d br, 11-H), 7.56 (partial overlap, 4-H), 7.59 (d br, 6'-H). The splitting pattern of aromatic H is similar to that observed for **12**. - ^{13}C NMR (100 MHz, DEPT): δ 13.7 (CH_3 of OC_2H_5), 44.9 (C-11b), 51.3, 53.3 (2 OCH_3), 52.4 (C-5), 60.0 (CH_2 of OC_2H_5), 74.8 (C-6a), 117.4 (C-8), 124.8, 124.9 (C-10, C-11), 126.9, 127.8, 127.9, 128.0 (C-2, C-3, C-4, C-9), 128.7 (C-4'), 129.4 (C-1); broadened by exchange: 127.7, 128.0 (C-3', C-5'), 129.5, 130.3 (C-2', C-6'); quaternary C-atoms: 92.7 (C-ß of side chain), 110.9 (C-13), 132.2 (C-11c), 136.4, 136.7, 137.4 (C-4a, C-11a, C-1'), 145.0 (C-7a), 151.7 (C-α of side chain), 156.2 (C-12), 165.4, 166.7, 167.4 (3 C=O). - Anal. for $C_{32}H_{28}N_2O_6$: calcd C 71.63, H 5.26, N 5.22; found C 71.74, H 5.53, N 5.33.

Acid Cleavage of 11 and Derivatives. (a) **11** (3.95 g, 10.0 mmol) in 50 mL CH_2Cl_2 was treated with 100 mL of conc. methanolic HCl. After 10 d at room temp., the volatile was removed in vacuo up to 30 °C (bath). The semisolid residue was shaken with water/CH_2Cl_2. From the organic phase, 1.03 g (58%) of *methyl benzoylacetate* distilled at 115-125 °C (bath)/10^{-3} Torr as a pale-yellow oil with n_D^{25} 1.5365 (n_D^{24} 1.53654).[29] The aqueous phase was made alkaline and the basic product extracted with ether. The base was distilled at 150 °C (bath)/0.005 Torr; it solidified on cooling, and 1.67 g (76%) of colorless *4-(2-aminophenyl)isoquinoline* (**19**), mp 110-112 °C, was obtained. Recrystallization from CH_2Cl_2/cyclohexane gave fine needles, mp 116-117 °C. - IR (CCl_4): $\tilde{\nu}$ 3387 cm^{-1}, 3475 (N-H), 3025 (arom. C-H). - Anal. for $C_{15}H_{12}N_2$: calcd C 81.79, H 5.49, N 12.72; found C 81.52, H 5.58, N 12.56. - The yellow *picrate* of **19**, mp 201-203 °C, has a low solubility in ethanol. - The *N-Tosyl Derivative* **20** was obtained from **19** with tosyl chloride in pyridine and recrystallized from CH_2Cl_2/methanol: colorless rhombs, mp 235-236.5 °C. - Anal. for $C_{22}H_{18}N_2O_2S$: N calcd 7.48; found N 7.71. - The reaction of **19** with benzoyl chloride in pyridine provided the *N-Benzoyl Derivative*, mp 139-140 °C (CH_2Cl_2/cyclohexane). - Anal. for $C_{22}H_{16}N_2O$: calcd C 81.46, H 4.97, N 8.64; found C 81.36, H 4.99, N 8.62.

(b) **11** (1.50 g, 3.80 mmol) was dissolved in 15 mL of 80% sulfuric acid; after 30 min at room temp. and 30 min on the steam-bath, the green solution was poured into water and extracted with CH_2Cl_2. The neutral product was *acetophenone*, purified by distillation (55%) and identified by its IR spectrum and the 2,4-dinitrophenylhydrazone, mp 248 °C (dec.). The aqueous layer was made basic with sodium carbonate; the organic base was isolated via the CH_2Cl_2 extract and consisted of **19** (395 mg, 47%), mp 214-216 °C (cyclohexane).

(c) The *10-Chloro Derivative* **15** was subjected to the same cleavage with methanolic HCl, as described above for **11**. The basic product, *i.e.*, *4-(2-amino-5-chlorophenyl)isoquinoline* (**22**) was distilled at 160 °C (bath)/10^{-3} Torr and crystallized from CH_2Cl_2/cyclohexane in colorless rods, mp 120-122 °C (35%). - IR (CCl_4): $\tilde{\nu}$ 3380 cm^{-1}, 3470 (N-H). - UV ($CHCl_3$): λ_{max} 321 nm (3.77), 310 sh (3.73), 274 sh (3.86). - ^1H NMR: δ 3.55 (s br, NH_2), 6.77 (A of AB, $J_{3',4'}$ = 8.0 Hz, 3'-H), 7.23 (B of AB, 4'-H), 7.15 (s, 6'-H), 8.01 (m, 8-H), 8.45 (s, 3-H), 9.25 (s, 1-H); unresolved were the m of 5-H to 7-H at 7.24 - 7.82. δ values of isoquinoline:[18] 1-H 9.15, 3-H 8.45, 8-H 7.87. - Anal. for $C_{15}H_{11}ClN_2$: calcd N 11.00; found N 11.06. - The *N-Tosyl Derivate of* **22** was prepared as described above. Colorless prisms, mp 171.0-171.5 °C, crystallized from CH_2Cl_2/cyclohexane. The solubility in 2 N NaOH and precipitation with acetic acid demonstrated NH-SO_2. - Anal. for $C_{22}H_{17}ClN_2O_2S$: calcd C 64.22, H 4.19, N 6.85, S 7.84; found C 64.46, H 4.15, N 6.89, S 7.90.

(d) The *10-Nitro Derivative* **16** was degraded by 80% sulfuric acid, as described under b. *Acetophenone* (44%) was isolated as 2,4-dinitrophenylhydrazone; the basic product, *i.e.*, *4-(2-amino-5-nitrophenyl)isoquinoline* (**24**), was isolated as a brown solid (30%) and analyzed as the picrate, mp 251-253 °C (acetone/ether). - Anal. for $C_{15}H_{11}N_3O_2 \cdot C_6H_3N_3O_7$: calcd N 17.00; found N 16.39.

Deamination of 4-(2-Aminophenyl)isoquinoline: (a) **19** (220 mg, 1.00 mmol) in 8 mL of 18% hydrochloric acid was diazotized with sodium nitrite at -5 to 0 °C. After 30 min, 3.1 mL of a 50% aqueous solution of hypophosphorous acid was added under stirring at 0 °C. The solution was kept for 24 h at ~5 °C and worked up with ammonia and CH_2Cl_2. At 110-120 °C (bath)/0.005 Torr, *4-phenylisoquinoline* (**21**, 104 mg, 51%) distilled and solidified; after sublimation in vacuo the mp was 78-80 °C (80 °C).[17] Anal. for $C_{15}H_{11}N$: calcd C 87.77, H 5.40, N 6.82; found C 87.98, H 5.40, N 6.82. - The picrate of **21** came from ethanol in yellow needles, mp 213-214 °C (209-210 °C).[17] Anal. for $C_{15}H_{11}N \cdot C_6H_3N_3O_7$: calcd N 12.90, found N 13.11. - The identity with the independently prepared specimen [17] was demonstrated by mixed mp of base and picrate, and by comparison of the IR spectra.

(b) *4-(3-Chlorophenyl)isoquinoline* (**23**) was analogously prepared from **22** by deamination. The oily **23** was distilled at 140 °C (bath)/0.01 Torr. - IR (KBr): $\tilde{\nu}$ 698 cm^{-1}, 726, 790 st, 894 m (arom. CH out-of-plane def.); 1504, 1565, 1577, 1596, 1620 m (arom. ring vibr.). - ^1H NMR (100 MHz): δ 8.45 (s, 3-H), 9.25 (s, 1-H); the m of 8 arom. H at δ 7.25 - 8.13 was not resolved.

Isoquinolinium N-Phenylimide and DMAD

Dimethyl 6,6a,7,11b-Tetrahydro-5*H*-5,7-ethenoindolo[2,3-*c*]isoquinoline-12,13-dicarboxylate (**34**). (a) *1:2-Product* **33**: The deep-red solution of **2a** in 300 mL of ether, prepared from 10.0 mmol of **1a** as above, turned light-red within 1 min upon addition of 3.12 g (22.0 mmol) of DMAD; subsequently, the clear solution darkened. After 20 h some undissolved material was discarded. The solvent was removed, the residue dissolved in a little CH_2Cl_2, and the crystallization was induced by adding methanol. In two batches 965 mg (19%) of **33** was obtained in colorless crystals, mp 241-243 °C (dec.) after recrystallization. - IR (KBr): $\tilde{\nu}$ 753 cm^{-1}, 760 st (out-of-plane def. for 4 adjacent arom. H), 1160, 1250 st br (C-O); 1590 sh, 1603, 1704 st (coupled N-C=C-C=O vibr.), 1741 st (C=O). - UV ($CHCl_3$): λ 282 nm (4.28). - ^1H NMR: Table 1. - MS (175 °C); *m/z* (%): 504 (100) [M^+; ^{13}C 30/31], 473 (23) [M^+ - OCH_3; ^{13}C 6.6/5.5], 445 (22) [M^+ - CO_2CH_3], 413 (29) [445 - CH_3OH], 276 (99) [M^+ - DMAD - CO_2CH_3 - HCN, $C_{18}H_{14}NO_2^+$], 244 (33) [276 - CH_3OH; ^{13}C 6/5], 217 (23) [$C_{15}H_9N_2^+$], 216 (22), 170 (14), 94 (79), 93

(79). – Anal. for $C_{27}H_{24}N_2O_8$: calcd C 64.28, H 4.80, N 5.55; found C 64.24, H 4.93, N 5.58. Mol. mass (cryoscop. camphor): calcd 504, found 496, 494. – In a second experiment with **2a**, prepared from 20 mmol of **1a** and 100 mmol of DMAD, 2.10 g (21%) of **33**, mp 240-242 °C (dec.) was isolated.

(b) ***1:1-Product* 34**: **33** (2.00 g, 3.96 mmol) was refluxed in 75 mL of methanol, 25 mL of CH_2Cl_2, and 10 mL of conc. aqueous HCl for 2 h, made basic with aqueous sodium carbonate, and extracted with CH_2Cl_2. Removal of the solvent gave 1.15 g (80%) of slightly yellow **34**, mp 176-178 °C; after recrystallization from CH_2Cl_2/methanol, the colorless platelets showed mp 181-182 °C. – IR (KBr): $\tilde{\nu}$ 762 cm^{-1} st (arom. CH out-of-plane def.), 1120 m, 1246 vst (C-O), 1463 m, 1604 w (arom. ring vibr.), 1586, 1696 st (enamine C=C-C=O vibr.), 1739 st (C=O of 12-CO_2CH_3), 3328 m (N-H, 3342 in CCl_4). – ^1H NMR (400 MHz, Table 1): δ 3.77 (s, 13-CO_2CH_3), 3.79 (s, 12-CO_2CH_3). DQF-COSY provided two sequences of four Ar-H each, and NOESY (interaction of 11-H, 11b-H, 1-H) showed the direction in which they should be read. δ 6.80 (d br, 8-H), 7.13 (td, overlap, 9-H), 7.07 (td, 10-H), 7.57 (td, 11-H); 7.40 (d br, 1-H), 7.18 (td, 2-H), 7.12 (td, overlap, 3-H), 7.44 (dd, 4-H). – ^{13}C NMR (100 MHz, DEPT; HETCOR and COLOC-S experiments confirmed the assignments): δ 44.7 (C-11b), 48.3 (C-5), 51.9 (OCH_3 of 12-ester), 52.7 (OCH_3 of 13-ester), 74.2 (C-6a), 116.0 (C-8), 125.3 (C-10), 125.5 (C-11), 126.4 (C-3), 127.5 (C-2), 127.9 (C-4), 128.2 (C-9), 129.0 (C-1); quaternary C atoms: 114.4 (C-13, $^2J_{CH}$ with 5-H), 132.9 (C-11c), 138.0 (C-4a), 138.3 (C-11a), 144.8 (C-7a), 147.5 (C-12, $^2J_{CH}$ with 5-H, 6a-H), 165.9 (C=O of 13-ester, $^2J_{CH}$ with 5-H), 166.0 (C=O of 12-ester). The δ_C are consistent with those of the saturated diester **5**, except for δ(C-5) which is lower than that of **5** (52.8 ppm) [6] despite allylic position; however, in cyclohexene, δ(C-3) 25.4 is not much different from δ(C-4) 23.0.[18] – MS (110 °C); *m/z* (%): 362 (81) [M^+, ^{13}C 19/18), 335 (5) [M^+ - HCN; ^{13}C 1.1/1.0], 331 (11) [M^+ - OCH_3; ^{13}C 2.4/2.4], 303 (17) [M^+ - CO_2CH_3, ^{13}C 3.6/4.2], 276 (100) [M^+ - CO_2CH_3 - HCN; ^{13}C 20/19], 271 (43) [M^+ - CO_2CH_3 - CH_3OH; ^{13}C 9/10], 244 (79) [276 - CH_3OH; $C_{17}H_{10}NO^+$, ^{13}C 15/15], 232 (10), 218 (10), 217 (47) [$C_{15}H_9N_2^+$], 216 (38), 165 (9) [Fluorenyl$^+$], 130 (2) [Isoquinolinium], 108.5 (3) [217^{++}]. – Anal. for $C_{21}H_{18}N_2O_4$; calcd C 69.60, H 5.01, N 7.73; found C 69.89, H 5.15, N 7.74.

(c) 3.30 g (6.54 mmol) of **33** was refluxed with 90 mL of conc. methanolic HCl; evaporation and trituration with ether left 1.96 g of **34**-hydrochloride in pale-green crystals. The yield of base **34** was 1.29 g (54%).

(d) *Reaction with 2,4-Dinitrophenylhydrazine*: 505 mg (1.0 mmol) of **33** was briefly refluxed with the reagent in methanolic sulfuric acid. The orange solid was recrystallized from CH_2Cl_2/methanol and gave 240 mg (73%) of *dimethyl oxaloacetate 2,4-dinitrophenylhydrazone* in yellow needles, mp 161-163 °C (dec.). The IR spectrum was identical with that obtained from DMAD and 2,4-dinitrophenylhydrazine.

(e) *Dehydrochlorination of Cycloadduct* **36**:[4] Treatment with 4 equiv. of $NaOCH_3$ in methanol at room temp. and work-up with CH_2Cl_2/water gave **34**, mp 181-182 °C, identified with the specimen above by mixed mp and ^1H NMR spectrum.

(f) *Cleavage by Sulfuric Acid*: **34** (710 mg, 1.96 mmol) was dissolved in 15 mL of 80% H_2SO_4; within 1 h, the color turned orange-red. Work-up with water, sodium carbonate, and CH_2Cl_2 furnished 235 mg (55%) of **19** which after recrystallization from cyclohexane showed mp 113-115 °C and was IR-identical with the 4-(2-aminophenyl)isoquinoline, obtained above from **11**.

(g) *Conversion of* **34** *to* **33**: The interrelations were clarified by reacting 362 mg (1.00 mmol) of **34** with 250 mg (1.76 mmol) of DMAD in 2 mL of CH_2Cl_2. After 2 d, methanol was added and the CH_2Cl_2

distilled off; 385 mg (76%) of 1:2-adduct **33** was obtained.

(h) *N-Formyl Derivative* **35**: 100 mg of **34** was converted by acetic formic anhydride to 88 mg of **35**, mp 196-197 °C (CH_2Cl_2/methanol). - IR (KBr): $\tilde{\nu}$ 1228 cm^{-1} st (C-O), 1474, 1614 m (arom. ring vibr.), 1436, 1594, 1685 st, 1708 sh (amide I and vinylogous amide bands), 1740 (C=O of 12-ester). - ^1H NMR: some signals are doubled, due to slow rotation about the formamide bond. The integrals of the CHO singlets at δ 8.22 and 8.36 suggest a ratio of 69:31 for the rotamers. - MS (130 °C); *m/z* (%): 390 (100) [M^+; ^{13}C 24/23], 276 (20) [$C_{18}H_{14}NO_2^+$; ^{13}C 4.0/5.0], 271 (23) [$C_{18}H_{11}N_2O^+$], 244 (18) [276 - CH_3OH], 217 (12), 216 (10), 165 (13) [Fluorenyl]. Most of the fragments coincide with those of **32**, *i.e.*, loss of CO from the formamide group is common. - Anal. for $C_{22}H_{18}N_2O_5$: calcd C 67.68, H 4.65, N 7.18; found C 67.80, H 4.78, N 7.04.

Isoquinolinium N-(2-Pyridyl)imide and DMAD

Dimethyl 3,10b-Dihydro-3-(2-pyridyl)-pyrazolo[5,1-*a*]isoquinoline-1,2-dicarboxylate (32): **2c** (100 mg, 0.45 mmol) was reacted with 64 mg (0.45 mmol) of DMAD in 1 mL of $CDCl_3$. The ^1H NMR spectrum of the fresh solution fitted the expectation for **32**: δ 3.57 (s, 1-CO_2CH_3), 3.88 (s, 2-CO_2CH_3), 5.73 and 6.10 (AB, $J_{5,6}$ = 7.5 Hz, 6-H and 5-H), 5.75 (s, 10b-H), 6.70 - 8.20 (8 arom. CH). Although the OCH_3 signal of DMAD had disappeared, the solution still showed the brown-red color of **2c**; a small equilibrium concentration of the reactants is supposed. - **32** was not isolable; another ^1H NMR spectrum recorded 24 h later indicated that the rearrangement to **37** was complete.

Dimethyl 6,6a,7,11-Tetrahydro-5*H*-5,7-ethenopyrido[3',2':4,5]pyrrolo[2,3-*c*]isoquinoline-12,13-dicarboxylate (37): (a) Although the ^1H NMR spectrum is fairly good, **37** could not be isolated and purified. ^1H NMR: Table 1. Further data: δ 7.73 (dd, 11-H), 8.03 (dd, 9-H).

(b) *6-Acetyl Derivative* **38**: **2c** (1.11 g, 5.02 mmol) and 0.71 g (5.00 mmol) of DMAD reacted in 10 mL of CH_2Cl_2. After 30 min at room temp., the solvent was removed on the rotary evaporator, and the residue was taken up in 9 mL of acetic anhydride and 1 mL of acetic acid. 24 h later, the volatile was removed at 1 Torr and the redbrown material was subjected to thick-layer chromatography on basic alumina (benzene/ethyl acetate/petroleum ether 2:2:1). The content of the UV-fluorescent zone crystallized from CCl_4/methanol; **38** (0.92 g, 45%) was obtained in colorless needles, mp 184-185 °C (dec.). - IR (KBr): $\tilde{\nu}$ 1252 cm^{-1}, 1280, 1314, 1353 (C-O), 1416, 1435 (pyridyl bands), 1590, 1606 (arom. ring and C=C vibr.), 1672 br (amide I), 1703 br (C=O of 13-ester), 1746 (C=O of 12-ester). - ^1H NMR (400 MHz): The double set of signals for conformations **A**/**B** (58:42) is given in Table 1. Further data: δ 3.81/3.80, 3.85/3.86 (2 s, 2 OCH_3), 7.30/7.30 (4-H), 7.50/7.57 (1-H), 7.82/7.82 (11-H), 8.14/8.11 (9-H). A NOESY experiment, performed with a mixing time of 100 ms, indicated the proximity of CH_3 ($COCH_3$) to 5-H in rotamer **A** and to 6a-H in rotamer **B**. - ^{13}C NMR (100 MHz, DEPT): The height ratio (58:42 on average) allowed the pairwise differentiation. δ (**A**/**B**) 21.7/21.8 (CH_3 of acetyl), 43.2/44.4 (C-11b), 50.9/45.5 (C-5), 52.3/52.2 and 52.9/52.9 (2 OCH_3), 66.3/71.1 (C-6a), 113.1/116.0 (C-13), 120.5/120.6 (C-10), 127.4 - 129.2 (8 CH of C-1 to C-4), 130.5/130.2 (C-11a), 132.3/131.7 and 136.4/136.5 (C-4a, C-11b), 133.33/133.29 (C-11), 146.1/144.8 (C-12), 148.1/148.4 (C-9), 158.3/158.0 (C-7a); 164.0/164.2, 165.2/165.0 (2 CO, ester), 168.4/167.5 (N-CO). - Anal. for $C_{22}H_{19}N_3O_5$: calcd C 65.18, H 4.72; found C 64.90, H 4.81.

Methyl Propiolate

Methyl 3,10b-Dihydro-3-phenylpyrazolo[5,1-*a*]isoquinoline-1-carboxylate (40): The solution of 100 mg (0.34 mmol) of **3** in 1 mL of $CDCl_3$ was cooled to 0 °C. After addition of 1.70 mmol of methyl propiolate, the ^1H NMR spectrum was recorded at 0 °C within several min. δ 3.59 (s, OCH_3), 5.71 and 5.94 (AB, $J_{5,6}$ = 7.5 Hz, 6-H and 5-H), 5.67 (d, $^4J_{2,10b}$ = 1.6 Hz, 10b-H), 6.8 - 7.6 (m, 8 arom. H), 7.82 (d, ^4J = 1.6 Hz, 2-H). Despite the excess of methyl propiolate (δ 2.83, 3.72), the solution showed the dark-red color of **2a**. After 30 min, the signals of **40** were gone; the new spectrum indicated a mixture. Attempts of isolating **40** were in vain.

6,6a,7,11b-Tetrahydro-5*H*-5,7-ethenoindolo[2,3-*c*]isoquinoline-13-carbonitrile (43): (a) **46** [6] (2.00 g, 6.50 mmol) and 1.00 g (6.60 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene in 60 mL of benzene were refluxed for 15 h under argon. After washing with water, PLC on basic alumina (benzene/ether 1:1) yielded two products with R_f 0.55 and 0.83. The first is **43**, a colorless oil (0.64 g, 36%) which came from $CHCl_3$/ether in fine needles, mp 170-171 °C. - IR (KBr): ν 755 cm^{-1} (arom. CH out-of-plane def.), 873 (olefin. CH out-of-plane def.), 1282; 1464, 1473, 1590 st (arom. ring vibr.), 1614 st (enamine-C=C), 2195 st (C≡N), 3330 m (N-H). - ^1H NMR: Table 1. - MS (130 °C); *m/z* (%): 271 (100) [M^+; ^{13}C 20/19], 270 (78) [M^+ - H], 244 (94) [M^+ - HCN], 243 (69) [244 - H], 218 (10) [M^+ - Acrylonitrile, $C_{15}H_{10}N_2^+$; HR 218.0844/.088], 217 (10), 165 (6) [Fluorenyl$^+$], 135.5 (9) [M^{++}], 130 (3) [Isoquinolinium], 77 (5) [$C_6H_5^+$]. - Anal. for $C_{18}H_{13}N$: calcd C 79.68, H 4.83, N 15.49; found C 79.48, H 4.88, N 15.35.

(b) The second fraction of the chromatography (R_f 0.83) provided 0.25 g (14%) of a pale-yellow oil which crystallized from $CHCl_3$/ether in colorless needles, mp 147-148 °C. It is an isomer of **43** which contains an additional aliphatic H and no NH. Tentatively, we assume the closing of an aziridine ring between N6 and C13. Although fairly consistent with the spectroscopic properties, the formation of such a structure would involve a nucleophilic substitution with front-side attack. - IR (KBr): ν 733 cm^{-1}, 750, 778 (arom. CH out-of-plane def.); 1472 st, 1495 m, 1607 w (arom. ring vibr.), 2240 m (C≡N). - ^1H NMR (C_6D_6): δ 2.28 (d, J = 9.6 Hz), 3.28 (d, J = 5.5 Hz), 3.41 (d, J = 9.5 Hz), 3.53 (s), 5.37 (d, J = 6.0 Hz), 6.4 - 7.2 (8 arom. CH). - Anal. for $C_{18}H_{13}N_3$: calcd C 79.68, H 4.83, N 15.49; found C 79.54, H 4.94, N 15.35.

Methyl 3,10b-Dihydro-3-(2-pyridyl)-pyrazolo[5,1-*a*]isoquinoline-1-carboxylate (41): **2c** (890 mg, 4.02 mmol) was reacted with 340 mg (4.04 mmol) of methyl propiolate in 10 mL of benzene. After 5 min at room temp., the solvent was removed, and the semisolid residue crystallized from $CHCl_3$/ether with exclusion of light; after 24 h 680 mg (55%) of **41** was isolated in colorless needles, mp 114-116 °C. On exposure to light, the crystals turn intensely blue. In the red-violet solution, **41** slowly rearranges to **43**. - Properties of **41**: IR (KBr): ν 682 cm^{-1}, 760, 772 (arom. CH out-of-plane def.), 1085, 1118, 1184, 1304, 1322 st (C-O, C-N), 1437, 1458 (pyridyl bands),[4] 1480, 1590 st, 1644 m, 1695 st br (vinylogous amide absorptions). - ^1H NMR: δ 3.60 (s, OCH_3), 5.74 and 5.92 (AB, $J_{5,6}$ = 7.8 Hz, 6-H and 5-H), 5.69 (d, $^4J_{2,10b}$ = 2.2 Hz, 10b-H), 6.7 - 8.3 (m, 8 arom. H), 8.33 (d, ^4J = 2.2 Hz, 2-H). - Anal. for $C_{18}H_{15}N_3O_2$: calcd C 70.80, H 4.95, N 13.76; found C 70.97, H 5.14, N 13.68.

Methyl 6,6a,7,11b-Tetrahydro-5*H*-5,7-ethenopyrido[3',2':4,5]pyrrolo[2,3-*c*]isoquinoline-13-carboxylate (44): (a) When the solution of **41** in $CDCl_3$ was stored for 3 d at room temp., the ^1H NMR

spectrum (Table 1) indicated the complete rearrangement to **44**; the isolation was not successful.

(b) *N-Acetyl Derivative* **45**: 6.11 g (20.0 mmol) of **41** was dissolved in 18 mL of acetic anhydride and 2 mL of acetic acid at 0 °C. After 48 h at 5 °C, the deep-redbrown solution was freed of the volatile at 0.1 Torr. The dark residue was separated by PLC on basic alumina (benzene/ethyl acetate/petroleum ether 2:2:1). The blue-fluorescent zone gave 1.08 g of pale-yellow product which crystallized from $CHCl_3$/ether; the colorless needles of **45** (0.97 g, 14%) were freed from solvent above 100 °C in vacuo and showed mp 180-185 °C (dec.): a good elementary analysis was not obtained. - IR (KBr): ν 1590 cm^{-1}, 1620, 1670, 1690 st br (amide I and vinylogous amide bands). - ^1H NMR: Some signals are doubled due to hindered rotation of the acetamide group. The data in Table 1 are those of the major isomer. - Anal. for $C_{20}H_{17}N_3O_3$: calcd C 69.15, H 4.93, N 12.10; found C 68.10, H 5.37, N 12.04.

1-Diethylaminopropyne

2-Diethylamino-3,10b-dihydro-1-methyl-3-(2-pyridyl)-pyrazolo[5,1-*a*]isoquinoline (47): The solution of **2c** and 1.3 equiv. of the ynamine in $CDCl_3$ was not decolorized, but remained yellow-brown, suggesting (as above) a cycloaddition-cycloreversion equilibrium. The unstable **47** could not be isolated. - ^1H NMR: δ 1.10 (t, J = 7.2 Hz, CH_3 of NC_2H_5), 1.47 (d, J = 1.5 Hz, 1-CH_3), 2.65 - 3.55 (m, CH_2 of NC_2H_5), 5.29 (q, not fully resolved, J = 1.5 Hz, 10b-H), 5.44 and 6.22 (AB, J = 7.5 Hz, 6-H and 5-H), 6.45 - 8.33 (m, 8 aromat. H); the excess of the ynamine gives rise to δ 1.03 (t, J = 7.0 Hz, CH_3 of NC_2H_5), 2.45 (s, CH_3).

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REFERENCES

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1. 1,3-Dipolar Cycloadditions, 105; Part 104: Ref. 6.
2. Bast, K.; Behrens, M.; Durst, T.; Grashey, R.; Huisgen, R.; Schiffer, R.; Temme, R. *Eur. J. Org. Chem.* **1998**, 379-385.
3. Zincke, Th.; Weißpfenning, G. *Liebigs Ann.* **1913**, *396*, 103-131.
4. Huisgen, R.; Temme, R. *Eur. J. Org. Chem.* **1998**, 387-401.
5. Huber, H.; Huisgen, R.; Polborn, K.; Stephenson, D. S.; Temme, R. *Tetrahedron* **1998**, *54*, 3735-3744.
6. Bast, K.; Durst, T.; Huisgen, R.; Lindner, K.; Temme, R. *Tetrahedron* **1998**, *54*, 3745-3764.
7. Eckell, A.; George, M. V.; Huisgen, R.; Kende, A. S. *Chem. Ber.* **1977**, *118*, 578-595.
8. Huisgen, R.; Gotthardt, H. *Chem. Ber.* **1968**, *101*, 1059-1071.
9. Dabrowski, J.; Dabrowska, U. *Chem. Ber.* **1968**, *101*, 2365-2374; 3392-3402.
10. Huisgen, R.; Herbig, K.; Siegl, A.; Huber, H. *Chem. Ber.* **1966**, *99*, 2526-2545. Herbig, K.; Huisgen, R.; Huber, H. *Chem. Ber.* **1966**, *99*, 2546-2555. Huisgen, R.; Giese, B.; Huber, H. *Tetrahedron Lett.* **1967**, *8*, 1883-1888.

11. Reviews: (a) Winterfeldt, E. *Angew. Chem.* **1967**, *79*, 389-400; *Angew. Chem. Int. Ed. Engl.*, **1967**, *6*, 423-434. (b) Baumgarth, M. *Chem. Ztg.* **1972**, *96*, 361-372; ibid. **1976**, *100*, 515-528.
12. Briegleb, G. *Fortschr. Chem. Forsch.* **1950**, *1*, 642-684.
13. Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8551-8566.
14. Piantini, U.; Sörensen, O. W.; Ernst, R. R. *J. Am. Chem. Soc.* **1982**, *104*, 6800-6801.
15. Jeener, J.; Meier, B. H.; Bachmann, P.; Ernst, R. R. *J. Chem. Phys.* **1979**, 71, 4546-4553.
16. Freeman, R.; Morris, G. A. *J. Chem. Soc., Chem. Commun.* **1978**, 684-686.
17. Krabbe, W.; Böhlk, H. H.; Schmidt, K. H. *Ber. Dtsch. Chem. Ges.* **1938**, *71*, 64-76.
18. Pretsch, E.; Clerk, T.; Seibl, J.; Simon, W. *Tabellen zur Strukturaufklärung organischer Verbindungen mit spektroskopischen Methoden*; Springer-Verlag, Berlin, 1976.
19. Nordmann, H. G.; Kröhnke, F. *Angew. Chem.* **1969**, *81*, 1004; *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 984.
20. Böhme, H.; Osmers, K.; Wagner, P. *Tetrahedron Lett.* **1972**, *13*, 2785-2786.
21. Hengartner, U.; Batcho, A. D.; Blount, J. F.; Leimgruber, W.; Larscheid, M. E.; Scott, J. W. *J. Org. Chem.* **1979**, *44*, 3748-3752.
22. Larramona, H.; Tchoubar, B. *Bull. Soc. Chim. Fr.* **1953**, C52-C58; Larramona, H. *Compt. rend.* **1954**, *238*, 488-490; **1955**, *240*, 96-98, 2544-2546.
23. Taber, D.; Becker, E. I.; Spoerri, P. E. *J. Am. Chem. Soc.* **1954**, *76*, 776-781.
24. Krishnamurty, V. V.; Casida, J. E. *Magn. Res. Chem.* **1987**, *25*, 837-842.
25. Sustmann, R. *Pure Appl. Chem.* **1974**, *40*, 569-593.
26. Huisgen, R. in *1,3-Dipolar Cycloaddition Chemistry*, Padwa, A., Ed.; J. Wiley & Sons, New York, 1984; vol. 1, pp. 99-128.
27. Huisgen, R.; Durst, T.; Temme, R. *J. Heterocyclic Chem.*, submitted.
28. Stephenson, D. S. *Encyclopedia of Nuclear Magnetic Resonance*; Grant, D. M.; Harris, R. K.; Eds.; John Wiley and Sons, Inc.: New York, 1996; pp 816-821.
29. von Auwers, K. *Liebigs Ann. Chem.* **1918**, *415*, 230.