The Astounding Chemistry of a 2-Amino-1,2-dihydroisoquinoline Derivative[1])

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Dedicated to Professor *Albert Eschenmoser* on the occasion of his 75th birthday

The cycloadducts of isoquinolinium *N*-phenyl imide **2** with C=C bonds are derivatives of 2-amino-1,2-dihydroisoquinoline. Their N^{β}-vinylphenylhydrazine system is amenable to an acid-catalyzed [3,3]-sigmatropic shift; the formation of pentacyclic aminals is exemplified by **6** → **8**. The dimethyl maleate adduct **11**, $C_{21}H_{20}N_2O_4$, is exceptional by being converted on treatment with acid to bright-yellow crystals, $C_{24}H_{22}N_2O_6$ (additional $C_3H_2O_2$). X-Ray crystal-structure analysis and NMR spectra reveal structure **13**, and mechanistic studies indicated an initial β-elimination at the N–N bond of **11** to yield **18**; this step is followed by a *retro-Mannich*-type cleavage that gives methyl isoquinoline-1-acetate (**14**) and methyl 2-(phenylimino)acetate (**15**), according to the sequence $C_{21}H_{20}N_2O_4$ (**11**) → **18** → $C_{12}H_{11}NO_2$ (**14**) + $C_9H_9NO_2$ (**15**). In the second act of the drama, electrophilic attack by **15**-H^+ on the ene-hydrazine group of a second molecule of **11** furnishes **13** by a polystep intramolecular redox reaction. All rate constants must be fine-tuned in this reaction cascade to give **13** in yields of up to 78% with an overall stoichiometry: 2 $C_{21}H_{20}N_2O_4$ (**11**) → $C_{24}H_{22}N_2O_6$ (**13**) + $C_{12}H_{11}NO_2$ (**14**) + aniline. Interception and model experiments confirmed the above pathway. A by-product, $C_{33}H_{31}N_3O_6$ (**62**), arises from an acid-catalyzed dimerization of **11** and subsequent elimination of **15**.

1. Introduction. – 'Isoquinoline *N*-aryl imides' of type **2** can be regarded as azomethine imines [2][3] that undergo *in situ* 1,3-dipolar cycloadditions to C=C bonds to furnish *N*-aryltetrahydropyrazolo[5,1-*a*]isoquinolines; *e.g.*, the reaction of *N*-phenyl imide **2** with dimethyl fumarate furnished the *trans*-diesters **4** and **5**[2]) in the ratio of 85:15 [4] (*Scheme 1*).

The adduct structures contain the bond systems of an N^{β}-vinylphenylhydrazine, which was subjected to a hydrazo rearrangement known as *Fischer*'s indole synthesis [5] (for a review, see [6]). Treatment of **2** with acid afforded the pentacyclic aminal **8** [7]. In formula **6**, *i.e.*, protonated **4**, the thicker bonds help one to recognize the initial [3,3]-sigmatropic shift (*Scheme 2*). The final indolization, **8** → **9**, does not take place because the gain in aromaticity cannot outweigh the increased ring strain; an (*E*,*Z*)-1,3-cyclooctadiene system is incorporated in the tetracyclic indole **9**.

This hydrazo rearrangement was observed for numerous cycloadducts of **2**, formed with α,β-unsaturated carboxylates and nitriles [7], with acetylenic carboxylates [8], enamines [9], and even ethylene [7]. Some cycloadducts undergo rearrangement in neutral media. Special precautions are often required to isolate the initial cycloadducts.

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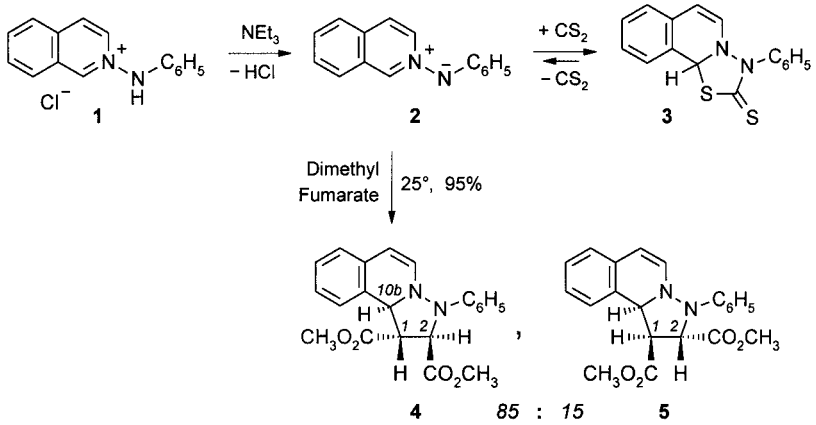
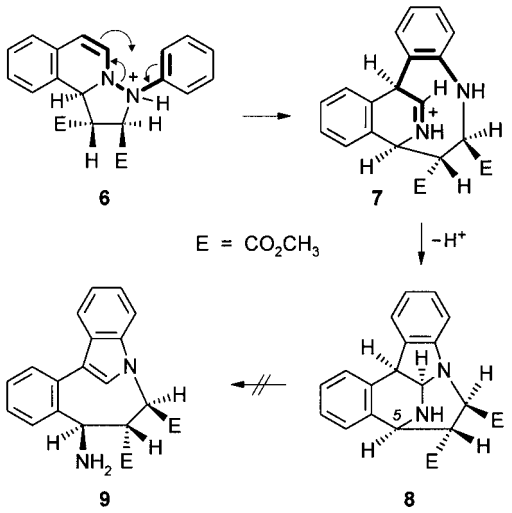
[1]) 1,3-Dipolar Cycloadditions, Part 118; Part 117: [1].

[2]) A representation was arbitrarily chosen, in which H–C(10b) appears on the β-side; this hydrogen becomes H_{β}–C(5) of **8**.

Scheme 1



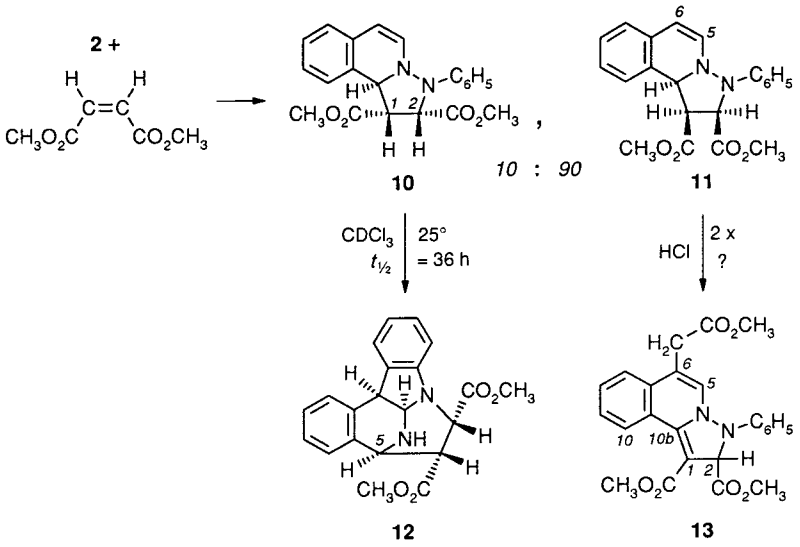
Scheme 2



The deep-red 1,3-dipole **2** is not isolable. When generated by slow addition of Et_3N to a solution of **1**, the triethylammonium chloride formed can catalyze the rearrangement of the cycloadduct. The adduct with CS_2, **3**, is a neutral source of **2**. The light-yellow crystals of **3** dissolve to give a solution with a deep-red color, showing a rapidly established dissociation equilibrium [10].

The cycloaddition of **2** with dimethyl maleate proceeded with retention of dipolarophile configuration, suggesting a concerted pathway [11]. The two crystalline *cis*-diesters **10** and **11** were obtained in the ratio of 10 : 90, and their structures were assigned on the basis of ^{1}H-NMR data (*Scheme 3*) [4]. The hydrazo rearrangement of the minor adduct **10** slowly afforded aminal **12** quantitatively, even in the absence of acid [7].

Scheme 3



2. Results and Discussion. – 2.1. *Exceptional Behavior of the Major Cycloadduct of Dimethyl Maleate.* '*There are no general reactions*' (*R. B. Woodward*) [12]. It came as a surprise that the major adduct **11**, on treatment with acid, followed a fundamentally different pathway. The bright-yellow crystalline product had the molecular formula $C_{24}H_{22}N_2O_6$, *i.e.*, $C_3H_2O_2$ more than **11** ($C_{21}H_{20}N_2O_4$). Since addition of dimethyl maleate during the acid treatment did not increase the yield of the C_{24} compound, the additional three C-atoms cannot come from the maleate, a conceivable equilibrium partner. When HCl was passed through the solution of **11** in CH_2Cl_2/MeOH at 0°, yields of up to 78% of the C_{24} compound were isolated, based on the participation of *two* C_{21} molecules (for a preliminary communication based on a lecture, see [13]).

Karle et al. established structure **13** for the yellow compound by X-ray analysis [14]. The ^{1}H-NMR spectrum shows three different ester Me groups, and the signal at lowest frequency (*s*, 3.57 ppm) corresponds to the CH_2 group of the acetate side chain; this CH_2 group is subject to H/D exchange with MeOD/MeONa. The allylic H–C(2) of **13** is deshielded by N(3) and an ester group: the *singlet* for this proton appears at 5.09 ppm. One aromatic H-atom resonates at 10.02 ppm as a *dd* and is ascribed to H–C(10); its high frequency suggests near-coplanarity with the MeOCO group [15] and a small distance to the carbonyl O-atom.

The visible absorption at 420 nm ($CHCl_3$, ε 7600) is responsible for the deep-yellow color of **13**. The mass spectrum confirmed the molecular mass; the base peak was $[M - CO_2CH_3]^+$, and peaks corresponding to $[M - 2\ CO_2CH_3]^+$ and $[M - 3\ CO_2CH_3]^+$ were also observed. The low-frequency C=O vibration (1677 cm^{-1}) comes from the enamine-β-carboxylate.

Yields for the conversion **11** → **13** by the procedure described above fluctuated. The use of defined HCl concentrations did, however, improve the reproducibility of the reaction. *Entries 2–5* of *Table 1* list variations in acidity and the ratio of CH_2Cl_2/

Table 1. *Acid Reactions of Cycloadduct* **11** *in CH_2Cl_2/MeOH* (conditions: 2 h 20°; acid: CF_3CO_2H in *Entry 1*, HCl in *Entries 2–9*)

Entry	Adduct **11**		Acid [N]	Vol-% MeOH	Products [mmol]				
	[mmol]	[M]			**13**	**14**	Aniline	**18**	$C_{33}H_{31}N_3O_6$
1	2.74	0.14	0.45	0	0.99	0.48	0.73		
2	2.74	0.14	0.55	10	0.56	0.47	1.07		
3	2.74	0.14	0.27	5	0.62	0.55	1.05		
4	2.74	0.14	0.14	3	0.43	0.66	0.22		
5	13.70	0.06	0.02	0.5	–	[a])	[a])	6.68	
6	2.74	0.14	0.55	25	0.53	0.41	0.52		0.21
7	2.74	0.14	0.55	50	0.58	[a])	[a])		0.32
8	2.74	0.14	0.55	75	0.52	[a])	[a])		0.26
9	2.74	0.14	0.55	100	0.59	0.37	0.35	0.09	

[a]) No workup by distillation.

MeOH; with 0.27N HCl the yield reached 45%. With CF_3COOH (0.45N) in CH_2Cl_2, 72% of **13** was isolated (*Entry 1*, *Table 1*).

Aniline and methyl isoquinoline-1-acetate (**14**) were identified as side-products. To avoid ambiguity, yields in *Table 1* are given in mmol rather than in percentages. Based on the consumption of 2 equiv. of **11**, 77% of aniline and 40% of **14** were isolated by distillation (*Entry 3*).

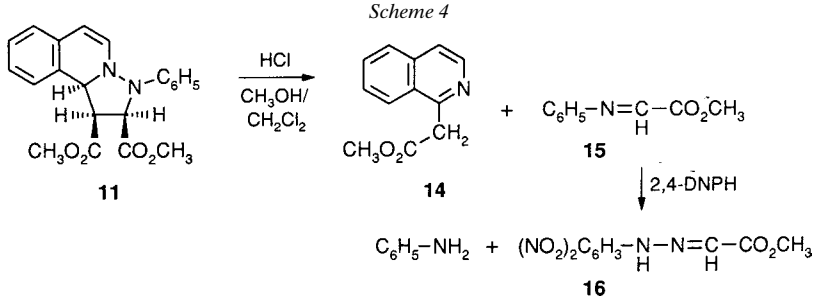
Exper. 6–9 in *Table 1* were conducted in solvents with higher MeOH contents. An additional crystalline product, $C_{33}H_{31}N_3O_6$, was observed, and its structure and mode of formation will be discussed in *Sect. 2.8*.

The high rate of the polystep sequence to give **13** is astonishing; under standard conditions (0.4N HCl in CH_2Cl_2/MeOH 3:1, 20°), 33% of **13** was detected after 5 min, and yields of 41 and 47% were obtained after reaction times of 20 and 120 min, respectively.

The structure of **13** did not *per se* suggest a formation pathway, and a number of questions arise regarding this aspect: how is the methyl-acetate group transferred to a second molecule of **11**, and how are two H-atoms removed from C(1) and C(10b) of **11**?

2.2. *Key Experiments in the Mechanistic Elucidation.* The breakthrough in this respect came from the reaction of **11** with 0.9N HCl in the presence of 2,4-dinitrophenylhydrazine (2,4-DNPH). Compound **13** was not formed, but 59% of the hydrazone **16** of methyl glyoxylate precipitated. Aniline and **14** were further products (*Scheme 4*).

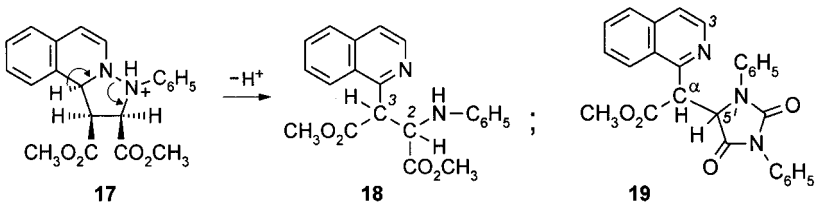
Scheme 4



Cycloadduct **11** appears to undergo fragmentation into **14** and methyl 2-(phenylimino)acetate (**15**) upon treatment with acid. It will be established in *Sect. 2.5* that protonated **15** is indeed the reagent that introduces the acetate side chain into **11**; in the presence of 2,4-DNPH, **15** is intercepted by conversion to **16**.

Another key experiment led to the elucidation of an intermediate in the aforementioned fragmentation. When a dilute solution of **11** in CH_2Cl_2 was treated with less than ⅓ equiv. of HCl, an isomer of **11** (49%) was obtained instead of the yellow compound **13** (*Entry 5*, *Table 1*). The IR NH absorption and the formation of hydantoin **19** with PhNCO revealed the presence of a *sec*-amino group. The UV spectrum was closely related to that of 1-methylisoquinoline, thus establishing the open-chain dimethyl 2-anilino-3-(isoquinolin-1-yl)succinate (**18**) and indicating a β-elimination at the N–N bond *via* the protonated species **17** (*Scheme 5*).

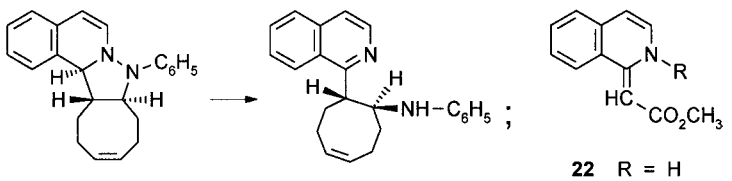
Scheme 5



When **18** was treated with a stronger acid, **14** and aniline were isolated, but compound **13** was not formed; nevertheless, **18** is the precursor of imino-acetate **15**. Acid cleavage of **18** in the presence of 2,4-DNPH afforded 76% of the hydrazone **16**, as well as **14** (66%) and aniline (77%). The acid-catalyzed process, **18** → **14** + **15**, resembles a *retro-Mannich* reaction. The configuration of **18** will reveal further insights into the processes that occur (*Sect. 2.4*).

Numerous cycloadducts of **2** undergo the hydrazo rearrangement in acidic medium, as mentioned above. Previously, we encountered an acid-catalyzed β-elimination only for the cycloadducts of **2** with (*E*)-cyclooctene and (*E*,*Z*)-cycloocta-1,5-diene [16], represented by **20** → **21** (*Scheme 6*). Treatment with AcOH at room temperature or adsorption onto silica gel proved sufficient to induce the ring-opening of **20**. Presumably, the *trans*-annulation of the eight- and five-membered rings in **21** generates strain in the transition state of the [3,3]-sigmatropic rearrangement.

Scheme 6



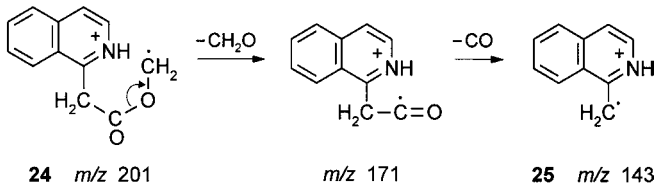
2.3. *Tautomerism of Methyl Isoquinoline-1-acetate* (**14**). Several groups (ours included) have reported on the methyl and ethyl isoquinoline-1-acetates [17][18]. However, two special features remained unnoticed: the facile H/D exchange of the CH_2 protons of **14** in *neutral* MeOD and the yellow color of its solution (λ_{max} 394 nm, $\varepsilon = 402$, EtOH).

The reaction of **14** with MeI and subsequent deprotonation with NH_3 provided the deep-yellow *N*-methyl enamine **23**, which shows a long-wavelength absorption at 394 nm ($\varepsilon = 12600$, EtOH). If equal extinction coefficients are assumed for **22** and **23**, then **14** is in equilibrium with 3.2% of enamine **22**.

Enamine-methylenimine tautomerism has been described for heteroaromatic compounds, *e.g.*, quinoline-2-methyl ketones and related compounds (for a review, see [19]). Basicity studies led *Jones* and *Katritzky* to estimate an enamine content of 10^{-6} M for ethyl pyridine-2-acetate [20].

The mass spectrum of **14** deserves brief consideration. The molecular ion M^+ appears with an intensity of 57%, and the peak at *m*/*z* 143, which corresponds to $[M - C_2H_2O_2]^+$, is the base peak instead of that at *m*/*z* 142 for the usual loss of CO_2CH_3. At our request, *Schwarz*[3]) established two metastable radical cations (*m*/*z* 201, 171) as precursors and proposed the fragmentation **24** → **25** (*Scheme 7*). The basic N-atom promotes the initial H migration to give **24**. In the mass spectrum of methyl naphthalene-1-acetate, a carbocyclic analog, $[M - CO_2CH_3]^+$ appears as the base peak, since favored distonic ions like **24** and **25** cannot be formed.

Scheme 7



2.4. *The Role of Dimethyl 2-Anilino-3-(isoquinolin-1-yl)succinate* (**18**). The ring-opened compound **18** has two stereogenic centers, and the *erythro* structure is expected to be formed from *cis*-diester **11**. To our surprise, the isolated sharp-melting compound **18** was a 4:1 mixture of *erythro*- and *threo*-forms, the assignment being unknown. The analytical HPLC displayed two peaks, but the preparative separation was unsuccessful. The H–C(2), H–C(3), and NH signals of the major component appear in the ^{1}H-NMR spectrum as an *AMX* pattern, which was simplified to *AM* by adding D_2O. The minor stereoisomer showed an A_2 spectrum for H–C(2) and H–C(3) after *N*-deuteration. The ^{13}C-NMR spectrum of **18** displayed a double set of signals.

Solutions of **18** are colorless, demonstrating the absence of an enamine tautomer, a situation in contrast to the equilibrium of **14** with **22**. H/D Exchange of H–C(2) and H–C(3) was not observed, when **18** was refluxed in MeOD; the diastereoisomer ratio remained 4:1. However, treatment with MeONa/MeOD gave [3,*N*-$^2H_2$]-**18**.

In the hope of separating the diastereoisomers, the dimethyl-maleate adducts **26** and **27** were subjected to the same treatment with 0.3 equiv. of HCl. According to NMR spectra, the *p*-toluidino compound **28** was obtained as 62:38 mixture of diastereoisomers. The *N*-(4-chlorophenyl) derivative **29** was homogeneous, but in all three cases, **18**, **28**, and **29**, the NMR data were insufficient for an *erythro*/*threo*-assignment.

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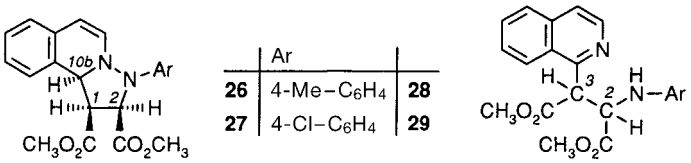
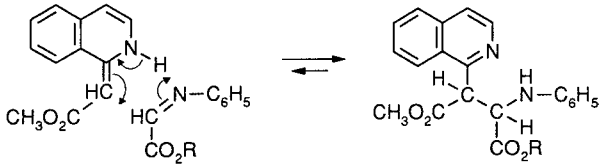
[3]) We express our deep gratitude to Prof. *Helmut Schwarz*, Technical University, Berlin, for his fine MS study.



The mass spectrum of **18** showed both imino-acetate **15**$^+$ (25%) and **24** (*i.e.*, **14**$^+$, 32%) as products of a *McLafferty* reaction; the base peak corresponds to [**15** – CO_2CH_3]$^+$, which is probably a nitrilium ion HC≡N$^+$–Ph. The mass spectra of **28**, **29**, and [$^2H_2$]-**18** helped to establish various fragmentation pathways.

Surprisingly, **14** and **15** reacted slowly in benzene to give again the *sec*-amine **18**. The lability of the synthetic specimen of **15** [21] may be responsible for the low yield (26%); the reaction of the butyl ester **30** with **14** furnished 67% of **31** (*Scheme 8*). The nucleophilic enamine tautomer **22** is the logical partner for the reaction with the electrophilic imino-acetate **15**; the cyclic electron shift indicates an ene reaction, the C=N bond being the enophile. Additions of enamines to imines or iminium salts have been reported [22] (for a review, see [23]).

Scheme 8



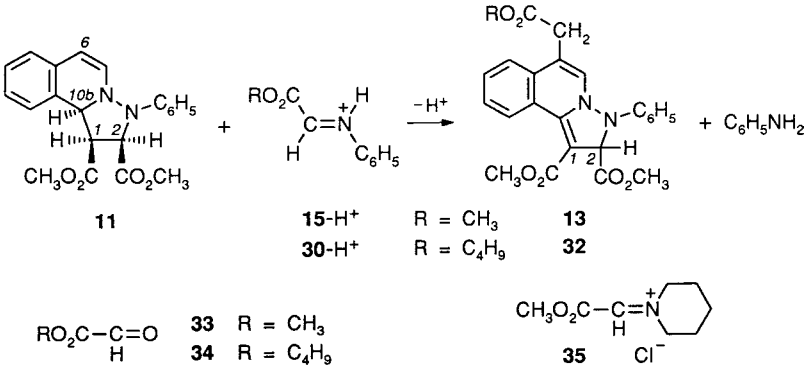
There is probably an equilibrium, **22** + **15** with **18**, in which the addition direction is favored. In acidic media, protonation of **22** and/or reaction of **15** with alcohol, H_2O *etc.* might well take place *via* dissociation.

Both the reaction of **14** (*via* **22**) with **15** and the treatment of **11** with 0.3 equiv. of HCl, *i.e.*, the buffer system of **11** + **11**-H$^+$, led to the same 4:1 *erythro*/*threo*-mixture of the *sec*-amine **18**. It is assumed that the dissociation-association equilibrium is already established during the acid treatment of **11**. The reaction of butyl ester **30** with **14** (*via* **22**) provided **31** as a liquid 1:1 *erythro*/*threo*-mixture.

2.5. *Introduction of the Acetate Group into Adduct* **11**. Ene-hydrazines like **11** harbor a nucleophilic β-C-atom, as do enamines. Whereas the electrophilic attack of **15** on enamine **22** takes place in a neutral medium, the reaction at C(6) of **11** (no longer an ene reaction) requires the stronger electrophilic reagent **15**-H$^+$ (*Scheme 9*).

Acid treatment of **18** produced **14** + **15** (see *Sect. 2.2*), but not the yellow compound **13**. However, **18** can transfer **15**-H$^+$ to the maleate adduct **11**. Equimolar amounts of **11** and **18** were converted, by treatment with 0.4N HCl at room temperature, to **13** in 60% yield, based on a 1:1 stoichiometry; the side products, **14** and aniline, were also isolated. In the presence of CF_3COOH, butyl 2-(phenylimino)acetate (**30**) reacted with **11** to afford the yellow C_{27} compound **32** in 75% yield; the trimethyl ester **13** was not found to

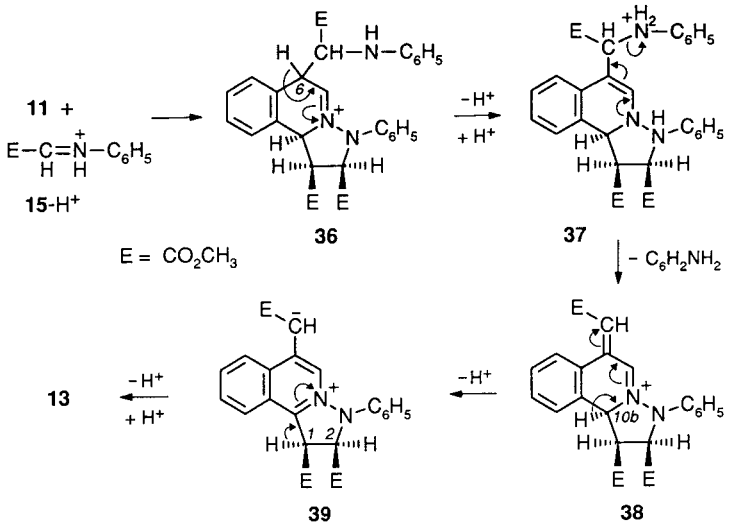
Scheme 9



be present alongside the butyl dimethyl ester **32**. In the absence of **30**, compound **11** alone was converted to **13** (72%, based on 2 equiv. of **11**; see *Sect. 2.1*) under the same conditions. Thus, the reaction of **11** with **30**-H^+ must be faster than its acid degradation.

Methyl or butyl glyoxylate, **33** and **34**, respectively, activated by HCl, were likewise capable of converting **11** to **13** (50%) and **32** (63%), respectively (*cf. Table 2*). The 1-[(methoxycarbonyl)methylidene]piperidinium chloride (**35**) was prepared by *Gross et al.* [24] and employed for aminoalkylations; a couple of enamines were among the reactants [25] (for reviews on aminoalkylations with iminium salts, see [26]). The rapid interaction of **35** and **11** can be visually followed by the deepening yellow color, and 76% of **13** was isolated.

Scheme 10

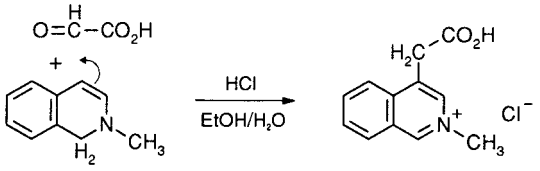


A new mechanistic problem arises: the oxidation state of an aldehyde in reagents **15**, **30**, and **33**–**35** is changed to that of an arylacetate in **13** and **32**. The H–C(1) and

H–C(10b) of the pyrazolidine ring in **11** are involved in an intramolecular redox process. Based on precedents (see below), a series of acid-base reactions with elimination of aniline is proposed. The addition of the electrophilic **15**-H^+ to C(6) of **11** produces iminium ion **36** (*Scheme 10*). By de- and reprotonation, H–C(6) is formally transferred to the anilino group in **37**. The loss of aniline affords the α,β-unsaturated iminium ion **38**, and deprotonation at C(10b) benefits from establishing the isoquinolinium resonance. A formal proton transfer from C(1) of **39** to the carbanionic side chain furnishes **13**. The electron flow from the lower to the upper part of the molecule demonstrates the redox process.

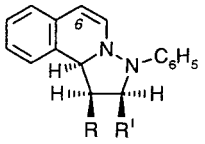
The reaction depicted in *Scheme 11* found precedence in the fine experiments described by *Dyke* and co-workers [27]. 1,2-Dihydro-2-methylisoquinoline (**40**) is attacked by glyoxylic acid and HCl, and the subsequent redox reaction, with loss of H_2O, yields the isoquinolinium salt **41**. A nice variation of this reaction has been described by *Minter* and *Re* [28].

Scheme 11

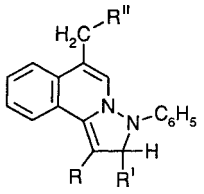


40 **41** (71%)

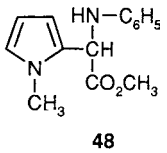
2.6. *Model Reactions with Varying Reagents.* Further electrophilic reagents are successful in attacking C(6) of adduct **11** as long as they exceed the rate of the β-elimination **11** → **18**. 4-Nitrobenzaldehyde, catalyzed by CF_3CO_2H, converted **11** to the deep-yellow nitrobenzyl compound **44** (47%; *Table 2*). Benzaldehyde failed to react, but *N*-benzylidenemethylamine furnished **45**, albeit in poor yield.



	R	R'
42	CN	CO_2CH_3
43	CN	H



	R	R'	R''
44	CO_2CH_3	CO_2CH_3	4-NO_2–C_6H_4
45	CO_2CH_3	CO_2CH_3	C_6H_5
46	CN	CO_2CH_3	CO_2CH_3
47	CN	H	CO_2CH_3



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All cycloadducts of **2** are ene-hydrazines; we reported cycloadditions of dimethyl acetylenedicarboxylate or mesitonitrile (=2,4,6-trimethylbenzonitrile) *N*-oxide to the electron-rich C(5)=C(6) bond of **4** and **11** [4]. Electrophilic substitution of the

Table 2. *Reactions of Cycloadducts with Electrophilic Reagents* (conditions: 20°, 2–3 h; *A:* 0.4–1.1N HCl in CH_2Cl_2/MeOH; *B:* 0.5N CF_3CO_2H in CH_2Cl_2; *C:* in CH_2Cl_2)

Cycloadduct	Electrophilic reagent	Conditions	Product		
			Formula	Yield [%]	M.p. [°C]
11	**18** (*via* **15**$^+$)	*A*	**13**	60	182–184
11	**30**-H$^+$	*B*	**32**	75	128–129
11	**30** + MeI	*C*	**32**	49	128–129
11	**35**	*C*	**13**	76	182–184
11	**33**	*A*	**13**	50	182–184
11	**34**	*A*	**32**	61	128–129
11	4-NO_2–C_6H_4CH=O	*B*	**44**	47	185–186
11	PhCH=NMe	*B*	**45**	26	152–153
4	**18** (*via* **15**-H$^+$)	*A*	**13**	26	182–184
4	**35**	*C*	**13**	46	182–184
4	**34**	*A*	**32**	16	128–129
42	**35**	*C*	**46**	24	122–124
43	**35**	*C*	**47**	44	154–155
N-Methylpyrrole	**18** (*via* **15**-H$^+$)	AcOH	**48**	67	82–83

dimethyl fumarate adduct **4** at C(6) will occur only when it is faster than the hydrazo rearrangement leading to **8**. Indeed, reaction of **4** with iminium salt **35** afforded the C_{24} compound **13** (*Table 2*); both **11** and **4** yielded **13** since the stereocenters C(1) and C(10b) were lost in the process.

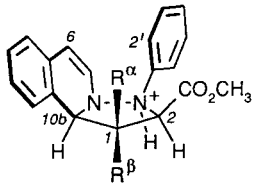
In contrast to the reaction of **11**, the substitution of **4** at C(6) by 4-nitrobenzaldehyde and HCl failed; 87% of the *Fischer* product **8** was isolated instead. Clearly, the [3,3]-sigmatropic shift, **6** → **7**, is more rapid than the cascade reaction **11** → **13** in an acidic medium. It is assumed that the hydrazo rearrangement of **11** is sterically hindered.

The acrylonitrile adduct **43** is also amenable to the *Fischer* reaction [7]. Nevertheless, **43** was converted to the yellow nitrile **47** (44%) with iminium salt **35** in CH_2Cl_2; the only protic acid present is the piperidinium chloride formed during the process. In its nucleophilic reactivity at C(2), *N*-methylpyrrole resembles a dienamine, and the substitution at C(2) by **15**-H$^+$ gave **48**.

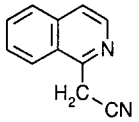
2.7. *Competing Reactions and Selectivity Problems.* Two pathways are open to our tetrahydro-3-phenylpyrazolo[5,1-*a*]isoquinolines in acidic media: the [3,3]-sigmatropic reaction that initiates the *Fischer* reaction, and the β-elimination that is the first-step in the conversion **11** → **13**. The origin of both reactions is the weakness of the N–N bond. Is the polystep sequence **11** → **13** unique, and which structural features are responsible?

Adducts **4** and **11** are C(1) epimers. Only *N*(3)-protonation *cis* to H–C(10b), *i.e.*, on the 'underside' of the perspective formula **49**, offers the close proximity of the *N*-phenyl and dihydroisoquinoline required for the [3,3]-sigmatropic shift. It is assumed that two vicinal ester groups in **49b** (**11**-H$^+$) impede the approach of the *ortho* position of Ph and C(6), whereas one ester group 'above' (2α-CO_2Me) in **49a** (**4**-H$^+$) is still tolerated. The hindrance by 1α-CO_2Me in **49b** can be ascribed to a buttressing effect. The presence of two ester groups 'below' in **49** leads to less hindrance; indeed, the minor maleate adduct **10** enters the [3,3]-sigmatropic rearrangement, even without acid (see *Introduction*).

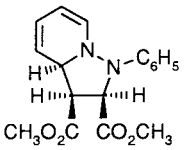
Closely related to maleate adduct **11** is **42**, which is the major regioisomer in the cycloaddition of **2** to methyl *cis*-3-cyanoacrylate [4]; it is the 1α-CO_2Me group of **11**



	R^{α}	R^{β}	
49a	H	CO_2CH_3	(**4**-H^+)
49b	CO_2CH_3	H	(**11**-H^+)



50

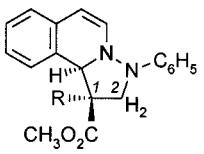


51

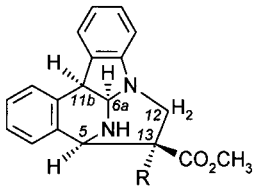
that is replaced by 1α-CN. Treatment of **42** with CF_3CO_2H rendered aniline (13%) and isoquinoline-1-acetonitrile (**50**, 12%), but neither **46** nor the *Fischer* aminal were isolated. A more successful reaction was that of **42** with HCl in MeOH in the presence of 2,4-DNPH, which furnished hydrazone **16** (30%), aniline (58%), and **50** (53%), a process that is still less clean than the conversion of **11** (see *Sect. 2.2*). The 'fine-tuning' in the polystep sequence appears to be disturbed. On the other hand, the reaction of **42** with iminium salt **35** provided the yellow compound **46** (24%; *Table 2*).

We reported recently on the cycloaddition of pyridinium *N*-phenylimide with dimethyl maleate; adduct **51** smoothly underwent the hydrazo rearrangement to give a tetracyclic aminal [29]. In the framework of structure **49b**, removal of the fused benzo ring reduces steric hindrance and allows the [3,3]-sigmatropic shift to proceed.

The replacement of the 2-CO_2Me group in structure **49b** by an H-atom should likewise relieve the hindrance, and this was confirmed experimentally. We treated adducts **52**–**54**, described in [4], with HCl and isolated aminals **55**–**57**. The structures established by ^{1}H-NMR spectra are in agreement with a previously reported investigation [7].



52 R = H **55**
53 R = CH_3 **56**
54 R = Cl **57**



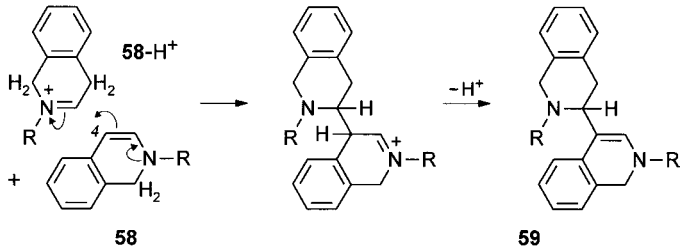
2.8. *Structure of the Side-Product $C_{33}H_{31}N_3O_6$ and its Mode of Formation.* The reaction of **11** with HCl in CH_2Cl_2/MeOH gave rise to $C_{33}H_{31}N_3O_6$ (see *Sect. 2.1*). The molecular formula was established by elemental analysis and mass determination. Based on the stoichiometry

$$2\ C_{21}H_{20}N_2O_4\ (\mathbf{11}) \rightarrow C_{33}H_{31}N_3O_4\ (\mathbf{62}) + C_9H_9NO_2\ (\mathbf{15}),$$

the yield of the C_{33} compound reached 23% (*Table 1*). A probable pathway will be discussed before the spectroscopic evidence is presented.

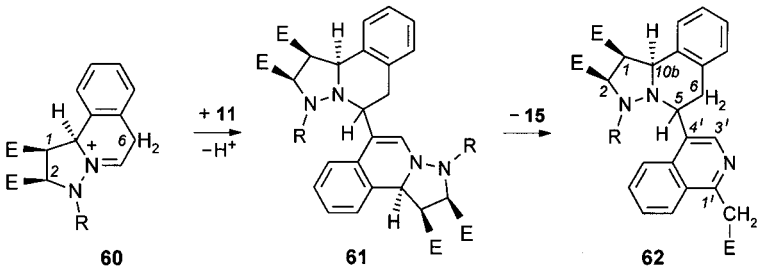
1,2-Dihydroisoquinoline derivatives show a propensity for dimerization [30][31]. On refluxing the hydrochloride of **58** in MeOH, *Brown* and *Dyke* obtained the bis-hydrochloride of **59** (75%) [30]. The electrophilic iminium ion **58**-H^+ attacks the nucleophilic C(4) of **58**, and subsequent deprotonation gives rise to **59** (*Scheme 12*).

Scheme 12



The dimethyl maleate adduct **11** has several basic centers. The *N*(3)-protonated species **17** undergoes β-elimination and initiates the cascade that produces **13**. Iminium ion **60**-H^+ is the result of *C*(6)-protonation and should share with imino-acetate **15** the capability of electrophilic substitution at C(6) of **11** (*Scheme 13*). The dimer **61** thus formed is an analog of **59** and still contains the intact ene-hydrazine system of **11** in the lower half. After *N*(3)-protonation, β-elimination at the N–N bond can initiate the same sequence of steps that converts **11** to **14** + **15**. Formally, the 1,2-dihydroisoquinoline system of **11** has undergone a disproportionation, since we find isoquinoline and tetrahydroisoquinoline rings in the lower and upper half of **62**.

Scheme 13



E = CO_2CH_3, R = C_6H_5

The configuration of the pyrazolidine ring in **11** probably remained unchanged in **62**. However, C(5) is a new stereogenic center created in the dimerization. Two diastereoisomers of **62** are conceivable, but the isolated C_{33} compound is homogeneous.

The UV/VIS spectrum of **62** is strikingly similar to that of the tautomeric system of methylisoquinoline-1-acetate (**14**) and enamine **22** (see *Sect. 2.3*). Comparison of the extinction at 400 nm (EtOH) with that of **23** indicates the presence of 2.0% of an enamine tautomer alongside **62**. Both H-atoms of CH_2–C(1′) of **62** are exchanged with neutral MeOD, demonstrating the mobility of the tautomeric equilibrium.

At first glance, the ^{1}H-NMR spectrum (400 MHz) of **62** reveals only two ester Me groups instead of three (*Fig.*). Tentatively, the MeO signal at 3.66 ppm is ascribed to the 1′-CH_2CO_2Me group (3.65 ppm in the parent compound **14**). The *singlet* at 3.32 ppm reaches only 56% of the height of the *singlet* at 3.66 ppm, and the third MeO signal is in coalescence. Changing from 400 MHz to 60 MHz at 25° affects the spectrum

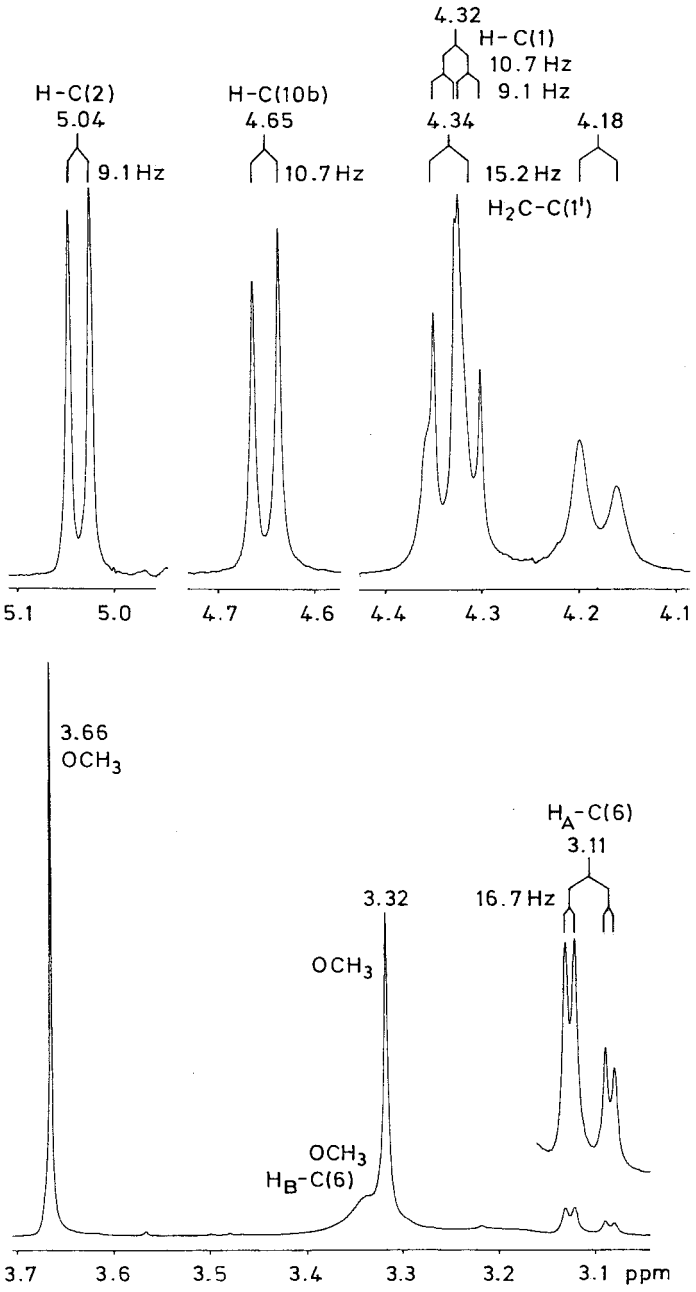


Figure. *Sections of the* ^{1}*H-NMR spectrum* (400 MHz, $CDCl_3$) *of product* $C_{33}H_{31}N_3O_6$ (**62**)

in a similar way as an increase in the temperature at constant field strength. In the 60-MHz spectrum of **62** the MeO signals at 3.32 and 3.66 ppm have nearly the same height, and the now well-defined *singlet* of the third MeO signal at 3.39 ppm stretches to half

the height of the other two signals. Hindered rotation of the ester groups at C(1) and C(2) appears to be responsible for the dynamic phenomenon.

The *AB* pattern at 4.18 and 4.34 ppm (the left branch overlapped), $J = 15.2$ Hz, disappears on deuteration and corresponds to the diastereotopic protons of $CH_2-C(1')$. The protons H–C(1) (*dd*), H–C(2) (*d*), and H–C(10b) (*d*) of **62** resonate at somewhat higher frequencies than those of **11** [4].

When the ^{13}C-NMR data of **62** are compared with those of **11** [32], isoquinoline, and aniline [33], all the saturated and many aromatic C-atoms can be assigned. On comparing the 100-MHz and 20-MHz ^{13}C-NMR spectra, partial coalescences can be observed; among others, the signals of C(6), C(5), and C(4′) are involved, suggesting hindered rotation about the C(4′)–C(5) bond.

Our thanks are due to the *Fonds der Chemischen Industrie*, Frankfurt, for the support of the research program. *T. D.* thanks the *National Research Council of Canada* for a stipend. We are greatly indebted to *Helmut Huber* for excellent NMR spectra, to *Reinhard Seidl* for the MS, and to *Helmut Schulz* for the elemental analyses.

Experimental Part

1. *General*. TLC: *Merck* silica gel *60 PF$_{254}$*. HPLC: *DuPont de Nemours 830*, *Zorbax-Sil* column. Mol. mass: *Mechrolab* vapor-phase osmometer. CC: *Woelm* silica gel (100–200 mesh), *Fluka* basic alumina. M.p.: uncorrected. UV/VIS: *Zeiss RPQ*; λ_{max} (log ε), wavelength in nm. IR: *Perkin-Elmer 125*, KBr pellets, if not otherwise stated; frequencies in cm^{-1}. NMR: *Varian A60*, *Bruker WP80 CW* (^{1}H: 80 MHz); *Bruker WP80 DS* (^{13}C: 20 MHz), and *Varian XR 400S* (^{1}H: 400 MHz, ^{13}C: 100 MHz); solvent $CDCl_3$ (stored over dry K_2CO_3), if not otherwise stated; *J* in Hz; chemical shifts, relative to TMS, were evaluated by first order except for *AB*; multiplicities in ^{13}C signals resulted from comparing H-decoupled and off-resonance spectra; DEPT for 100 MHz spectra. MS: *AEI*, Manchester, *MS902* and *Finnigan MAT90*; EI spectra with 70 eV (if not stated otherwise), *m*/*z* (%), intensities of ^{13}C isotope peaks in % calc./found; HR: high resolution.

2. *Dimethyl 2,3-Dihydro-6-[(methoxycarbonyl)methyl]-3-phenylpyrazolo[5,1-a]isoquinoline-1,2-dicarboxylate* (**13**). 2.1. *Without Isolation of* **11**. Dimethyl maleate (4.40 g, 30.5 mmol) was added to the red soln. of the CS_2 adduct **3** (9.00 g, 30.4 mmol) [10] in CH_2Cl_2 (60 ml). After 30 min at r.t., the solvent was removed, and **10**/**11** was taken up in CH_2Cl_2 (80 ml) and MeOH (20 ml). A slow stream of HCl was passed through the soln. at 0° for 15 min. After 2 h at r.t. and concentration on the rotary evaporator, the oily residue was dissolved in CH_2Cl_2 (50 ml) and shaken with aq. 2N NH_3. The brilliant-yellow org. phase was evaporated and portionwise subjected to CC (basic alumina; AcOEt/benzene/petroleum ether 1:2:1); the sensitivity of **13** to light required low light levels for CC and later operations; the fast-moving yellow zone crystallized from acetone/benzene: **13** (5.21 g, 78% based on 2 equiv. of **11** and 90:10 ratio of **11**/**10** [4]).

2.2. *Data of* **13**. M.p. 182–184°. UV/VIS ($CHCl_3$): 420 (3.88), 385 (sh, 3.81), 275 (4.09). IR: 690*m*, 758*s*, 767*s*, 782*m*, 926*m*, 1036*s*, 1095v*s*, 1167v*s*, 1206v*s*, 1288*s*, 1525v*s* (br.), 1600*w*, 1632*m*, 1677*s*, 1740v*s*, 2950*m*, 3070*w*. ^{1}H-NMR (400 MHz): 3.57 (*s*, $CH_2-C(6)$); 3.65, 3.69, 3.83 (3*s*, 3 MeO); 5.09 (*s*, H–C(2)); 6.98 (*s*, H–C(5)); 7.06 (*dt*, 2 arom. H); 7.19 (*tt*); 7.33 (*tt*, 2 arom. H); 7.52 (*td*); 7.53 (*d*, H–C(7)); 7.64 (*td*); 10.02 (*dd*, broadened, $J = 7.6$, 1.5, H–C(10)). ^{13}C-NMR (100 MHz, DEPT): 35.5 ($CH_2-C(6)$); 50.5, 52.3, 52.6 (3 MeO); 76.7 (C(2)); 86.0 (C(1)); 109.9 (C(6)); 118.7 (C(2′/6′)); 122.7 (C(4′)); 129.6 (C(3′/5′)); 125.3, 127.0, 128.5, 131.7, 132.2 (C(5), C(7)–C(10)); 123.7, 134.5, 147.0 (C(6a), C(10a), C(10b)); 151.3 (C(1′)); 164.4, 171.16, 171.23 (3 C=O). MS (175°): 434 (2.5, [M^+, ^{13}C 0.66/0.63]), 375 (100, [$M - CO_2Me$]$^+$; ^{13}C 24.5/23.8, $^{13}C_2$ 2.9/3.4), 316 (3.7, [$M - 2\ CO_2Me$]$^+$, $C_{20}H_{16}N_2O_2^+$; ^{13}C 0.81/0.82), 283 (7), 257 (8, [$M - 3\ CO_2Me$])$^+$, 256 (6), 255 (5), 163 (5), 104 (13, $C_7H_6N^+$, Ph–N≡CH$^+$; ^{13}C 1.02/1.15), HR-MS: 77.0400 (10, $C_6H_5^+$, calc. 77.0391). Anal. calc. for $C_{24}H_{22}N_2O_6$ (434.43): C 66.35, H 5.10, N 6.45; found: C 66.38, H 5.13, N 6.22.

2.3. *Adduct* **11** *and* CF_3CO_2H. Colorless crystalline **11** (1.00 g, 2.74 mmol) [4] in CH_2Cl_2 (20 ml) was treated with CF_3CO_2H (0.70 ml, 9.1 mmol). After 2 h at r.t. and dilution with CH_2Cl_2 (20 ml), the acid was extracted with 2N NH_3, whereupon the color changed to yellow. The solvent was removed, and the residue was recrystallized from acetone/pentane: **13** (430 mg, 72%). M.p. 182–184°. Distillation of the mother liquor at 90° (bath)/0.01 Torr gave aniline (68 mg, 53%), identified as *N*,*N*′-diphenylthiourea (m.p. 153–154°). At 140°/10^{-3} Torr, *methyl isoquinoline-1-acetate* (**14**, see *Sect. 4.2*) was distilled. M.p. 47–48° (Et_2O/pentane).

2.4. *Deuteration*. A small amount of MeONa was added to **13** (150 mg, 0.35 mmol) in MeOD (5 ml). After 15 h at r.t., neutralization with aq. AcOH and extraction with CH_2Cl_2 furnished 108 mg, m.p. 181–183°. The *s* of 2 H at 3.57 ppm was missing in the otherwise unchanged ^{1}H-NMR spectrum.

2.5. *Procedure with Defined HCl Concentrations* (*Entry 6* of *Table 1*). Methanolic HCl (2.3 ml, 4.8N) was added to **11** (1.00 g, 2.74 mmol) in CH_2Cl_2 (15 ml) and MeOH (2.7 ml), corresponding to 0.55N HCl and 0.14M **11** in CH_2Cl_2/MeOH 3:1 (*v*/*v*). After 2 h at r.t. and workup as described above, **13** (229 mg, 38%) crystallized from acetone/pentane. M.p. 180–183°. The solvent was removed, and the residue was dissolved in MeOH. At 5°, colorless crystals of **62** (117 mg, 15%) were obtained. M.p. 207–209°. For further data, see *Sect. 10*. Distillation of the mother liquor from a microflask afforded aniline (48 mg, 38%) and **14** (83 mg, 30%).

3. *Acid Cleavage of* **11** *in the Presence of 2,4-Dinitrophenylhydrazine*. 2,4-DNPH (2.20 g, 11.1 mmol) was briefly boiled with methanolic HCl (40 ml, 1.1N), filtered, and combined with **11** (2.00 g, 5.48 mmol) in CH_2Cl_2 (10 ml). In 2 d at −20°, the orange *methyl 2-(2,4-dinitrophenylhydrazono)acetate* (**16**, 856 mg, 59%) precipitated (leaflets from AcOEt). M.p. 164-165°. IR: 710*m*, 746*m*, 835*m*, 852*m*, 928*m*, 1108*s*, 1140*s*, 1323v*s*, 1345*s*, 1500*s*, 1577v*s* (NO_2), 1622*s*, 1732v*s* (C=N, C=O), 3295*s* (N–H). ^{1}H-NMR: 3.91 (*s*, MeO); 7.09 (*s*, N=CH); 9.13 (*d*, *J* = 9.5, H–C(6)); 9.35 (*dd*, *J* = 9.5, 2.3, H–C(5)); 10.16 (*d*, *J* = 2.3, H–C(3)). MS (120°): 268 (28, M^+), 189 (10), 59 (14, $[CO_2Me]^+$), 43 (100). Anal. calc. for $C_9H_8N_4O_6$ (268.19): C 40.30, H 3.01, N 20.89; found: C 40.59, H 2.84, N 20.89. A sample of **16** was prepared from methyl dimethoxyacetate and 2,4-DNPH in methanolic H_2SO_4. M.p. 164–165°; mixed m.p. without depression.

The mother liquor from the experiment with **11** was diluted with ice water, basified with 2N NH_3 and extracted with CH_2Cl_2. Distillation of the org. phase furnished aniline (205 mg, 40%) at 100–110° (bath)/12 Torr and **14** (263 mg, 24%) at 170–180°/10^{-2} Torr.

4. *Methyl Isoquinoline-1-acetate* (**14**). 4.1. *Synthesis*. 1-Methylisoquinoline (3.54 g, 24.7 mmol) in abs. THF (20 ml) was treated under Ar at −78° with LDA (30 mmol) in Et_2O (20 ml). The dark-red suspension was stirred at −78° for 15 min, then methyl chloroformate (2.34 g, 24.8 mmol) was introduced dropwise. After stirring for 30 min at r.t., H_2O and benzene was added, the org. phase was extracted with 2N HCl, and worked up with 2N NH_3 and CH_2Cl_2. At 130–140° (Kugelrohr)/10^{-3} Torr, **14** (1.99 g, 40%) distilled as a light-yellow oil, which solidified. M.p. 47–48° ([18]: 47–48°), identical with the side-product of **13** (see *Sect. 2.3*).

4.2. *Data of* **14**. UV/VIS (EtOH): 'triplet' at 415 (2.46), 394 (2.60), 372 (2.46); 322 (3.56), 308 (3.46), 272 (3.69), 218 (4.71). IR: 750*s*, 797*m*, 806*s*, 1006*m* (br.), 1168*s* (br.), 1258*s* (br.), 1332*s*, 1388*s*, 1434*s*, 1560*s*, 1628*s*, 1739v*s*. ^{1}H-NMR: 3.65 (*s*, MeO); 4.32 (*s*, CH_2–C(1)); 7.47–8.21 (*m*, 5 arom. H); 8.45 (*d*, *J* = 5.2, H–C(3)); after dissolving in MeOD and evaporation, the CH_2 signal had disappeared. MS (30°): 201 (57, M^+, **24**), 186 (5, $[M - Me]^+$), 170 (16, $[M - MeO]^+$), 143 (100, $[M - C_2H_2O_2]^+$, **25**), HR-MS: calc. 143.07349, found: 143.07343; 142 (56, $[M - CO_2Me]^+$), 129 (13, $C_9H_7N^+$), 128 (22), 115 (82), 89 (8), 59 (8, $[CO_2Me]^+$); a high-voltage scan of *m*/*z* 143 established *m*/*z* 171 and 201 as metastable precursors. Anal. calc. for $C_{12}H_{11}NO_2$ (201.22): C 71.62, H 5.51, N 6.96; found: C 71.51, H 5.52, N 7.37.

Picrate of **14**. From MeOH. M.p. 183–184° (dec.). Anal. calc. for $C_{18}H_{14}N_4O_9$ (430.32): C 50.24, H 3.28, N 13.02; found: C 50.64, H 3.26, N 12.84.

4.3. *Methyl 2-(1,2-Dihydro-2-methylisoquinolin-1-ylidene)acetate* (**23**). Compound **14** (1.23 g, 6.11 mmol) and MeI (1.85 g, 13.1 mmol) in benzene (3 ml) were reacted at 40° for 15 h. After cooling, the light-yellow *1-[(methoxycarbonyl)methyl]-2-methylisoquinolinium iodide* (1.88 g, 90%) was filtered. M.p. 183–184°. Anal. calc. for $C_{13}H_{14}INO_2$ (343.16): C 45.50, H 4.11, N 4.08; found: C 45.29, H 4.15, N 3.89.

The *N*-methyl iodide (370 mg, 1.08 mmol), suspended in CH_2Cl_2 (10 ml), was shaken with 2N NH_3 (10 ml), whereby the org. phase became deep-yellow. Bulb-to-bulb distillation at 110°/10^{-3} Torr afforded **23** (227 mg, 98%) as a brilliant-yellow oil. UV/VIS (EtOH): 394 (4.09), 289 (4.00), 258 (sh, 3.74), 219 (4.48); the 'triplet' fine structure of the long-wave absorption is weaker than in tautomer **22**, but recognizable, and the extinction of **23** at 394 nm is 31 times higher than that of the tautomeric mixture **15** ⇌ **22**. ^{1}H-NMR: 3.53 (br. *s*, MeN); 3.70 (*s*, MeO); 5.27 (*s*, HC=C(1)); 6.28, 6.78 (2*d*, *J* = 7.0, H–C(4), H–C(3)); 7.0–7.6 (*m*, 4 arom. H). Anal. calc. for $C_{13}H_{13}NO_2$ (215.24): C 72.54, H 6.09, N 6.51; found: C 72.79, H 6.30, N 6.79.

5. *Dimethyl 2-Anilino-3-(isoquinolin-1-yl)succinate* (**18**). 5.1. *By Acid-Catalyzed Ring Opening of* **11**. Methanolic HCl (1.0 ml, 4N) was added to **11** (5.00 g, 13.7 mmol) in CH_2Cl_2 (200 ml); by this HCl concentration 29% of **11** was converted to the hydrochloride. After 2 h at r.t., the soln. was shaken with aq. NH_3. The residue of the yellow-brown org. phase crystallized from benzene: **18** (2.43 g, 49%) as colorless powder. M.p. 140–141°. Anal. HPLC with AcOEt/hexane 6:1 at 40 bar and 1 ml/min showed two substances with t_R of 22.5 and 23.5 min; no full separation at the basis. The ^{1}H-NMR integrals of MeO groups indicate a 4:1 mixture of *erythro*- and *threo*-form; fractional crystallization and prep. HPLC failed to separate the stereoisomers.

5.2. *Data of* **18**. UV (EtOH): 322 (3.59), 308 (3.57), 282 (sh, 3.84), 218 (4.79); the range of 270–340 nm closely resembles that of 1-methylisoquinoline. IR: 695*m*, 754*s*, 1230*s* (br.), 1275*s* (br.), 1502*s*, 1562*w*, 1603*s*, 1740v*s* (br.). IR (CCl_4): 3410*w* (br., N–H). ^{1}H-NMR (400 MHz, C_6D_6): major isomer (*ca.* 80%): 3.24, 3.26 (2*s*, 2 MeO); *AMX* at 4.64 (*d*, slightly broadened, J(N,2) = 10.3, NH); 5.54 (*d*, J(2,3) = 7.8, H–C(3)); 5.73 (*dd*, J = 7.8, 10.3, H–C(2)); 6.63–6.78 (*m*, H–C(2″/6″), H–C(4″)); 7.00–7.36 (3*m*, 6 arom. H of both isomers); 8.20 (*m*, H–C(8′)); 8.39 (*d*, J = 7.3, H–C(3′)); with D_2O the *AMX* spectrum simplifies to MX; minor isomer (*ca.* 20%): 3.21, 3.22 (2*s*, 2 MeO); 5.56–5.65 (*m*, 3 H; with $D_2O \rightarrow A_2$ spectrum at 5.56 ppm); 7.89 (*m*, H–C(8′)); 8.31 (*d*, J = 5.5, H–C(3′)). ^{1}H-NMR ($CDCl_3$): 3.58, 3.65 (2*s*, 2 MeO of major isomer); 3.52, 3.58 (2*s*, 2 MeO of minor isomer). ^{13}C-NMR (20 MHz; 28 lines visible of 38 expected, major/minor, where separated): 52.2, 52.4 (2*q*, 2 MeO); 50.9, 58.2/58.5 (3*d*, C(2), C(3)); 113.9/114.0, 118.5/118.3 (4*d*, C(2/6), C(4) of anilino); 120.0, 120.6, 124.2, 127.5, 127.7, 129.1, 130.9 (7*d*, 6 arom. CH); 141.4/141.3 (2*d*, C(3′)); 129.0/127.2 (2*s*, C(8′)); 136.5 (*s*, C(4a′)); 146.5/147.2 (2*s*, C(1) of anilino); 154.1/155.0 (2*s*, C(1′)); 170.8, 172.4, 172.8 (3*s*, 2 C=O). MS (80°): 364 (1, M^+), 271 (8, $[M - PhNH_2]^+$), 201 (32, $C_{12}H_{11}NO_2^+$, **24**), 169 (13), 163 (25, $C_9H_9NO_2^+$, **15**$^+$), 143 (50, **25**), 115 (50), 104 (100, $C_7H_6N^+$, $HC{\equiv}N{-}C_6H_5^+$). HR-MS: 104.0495 (calc. 104.0499), 93 (27, $C_6H_5NH_2^+$), 77 (87, $C_6H_5^+$). Anal. calc. for $C_{21}H_{20}N_2O_4$ (364.39): C 69.22, H 5.53, N 7.69; found: C 69.41, H 5.66, N 7.72. Mol. mass: 365 (osmometr., C_6H_6, 37°).

5.3. *Mono-Deuteration of* **18**. Refluxing in MeOD (5 h) gave the N-deuterated compound with unchanged diastereoisomer ratio. IR: 2510*w* (br., N–D).

Bis-Deuteration. Compound **18** (0.56 mmol) and MeONa (0.11 mmol) in MeOD (3 ml) were refluxed for 2 h. Workup with D_2O/CH_2Cl_2 afforded a red residue, which crystallized from benzene: colorless [$^2H_2$]-**18**. M.p. 133–136°. ^{1}H-NMR (80 MHz, C_6D_6): 3.21, 3.25 (2*s*, 4 MeO); 5.52, 5.69 (2 br. *s*, probably H–C(2)); the MS points to exchange at H–C(3) and NH; the signal ratios suggest 55:45 for the stereoisomers, further clarification required. MS (120°): 271 (10, $[M - C_6H_5ND_2]^+$), 203 (25, $C_{12}D_2H_9NO_2^+$, [$^2H_2$]-**24**), 202 (40 [$^2H_2$]-**24**), 163 (40, **15**$^+$), 104 (100, $C_7H_6N^+$), 95 (55, $C_6H_5ND_2^+$), 94 (67, C_6H_5NHD).

5.4. *Methyl α-(2,4-Dioxo-1,3-diphenylimidazolidin-5-yl)isoquinoline-1-acetate* (**19**). Compound **18** and PhNCO (1.34 mmol each) in CH_2Cl_2 (3 ml) reacted for 4 weeks at r.t.: colorless crystals of **19** (425 mg, 70%). M.p. 224–225°. IR: 642*m*, 693*m*, 754*s*, 762*s*, 827*m*, 1184*s* (br.), 1198*s* (br.), 1262*s* (br.), 1412v*s*, 1498*s*, 1562*m*, 1717v*s*, 1779*m*. ^{1}H-NMR: 3.73 (*s*, MeO); 5.21, 5.64 (2*d*, J = 5.0, H–C(α), H–C(5′)); 6.9–7.8 (*m*, 15 arom. H); 8.39 (*d*, J = 5.5, H–C(3)). MS (200°): 451 (19, M^+), 392 (100, $[M - CO_2Me]^+$), 104 (20, $C_7H_6N^+$), 77 (15, $C_6H_5^+$). Anal. calc. for $C_{27}H_{21}N_3O_4$ (451.46): C 71.83, H 4.69, N 9.31; found: C 72.03, H 4.66,N 9.49.

5.5. *Cleavage of* **18** *with 0.4*N *HCl*. Compound **18** (500 mg, 1.37 mmol) in CH_2Cl_2 (15 ml) and MeOH (3 ml) was reacted with methanolic HCl (2.0 ml, 4N) for 2 h at r.t.; workup with 2N NH_3 and more CH_2Cl_2, and distillation at 10^{-3} Torr furnished aniline (92 mg, 72%) and **14** (218 mg, 79%).

5.6. *Treatment with HCl in the Presence of 2,4-Dinitrophenylhydrazine*. Compound **18** (1.37 mmol) was added to 2,4-DNPH (1.37 mmol) in methanolic 4N HCl. After 30 min at r.t. and 15 h at 5°, the yellow platelets of **16** (278 mg, 76%), m.p. 163–164°, were filtered. The usual workup gave aniline (98 mg, 77%) and **14** (181 mg, 66%).

5.7. *Preparation of* **18** *from* **14** *and Methyl 2-(Phenylimino)acetate* (**15**). Compound **14** (1.17 g, 5.82 mmol) and **15** (15 ml of 0.5M soln. in benzene [21]) were reacted for 5 d at r.t. and 4 h at 60°. After washing with H_2O and evaporation, **18** (551 mg, 26%) crystallized from MeOH, m.p. 140–141°; mixed m.p. and spectra showed the identity with the product from *5.1*.

5.8. *Butyl 2-Anilino-3-(isoquinolin-1-yl)-3-(methoxycarbonyl)propionate* (**31**). *Butyl glyoxylate* (**34**) [34] was analogously converted to the less sensitive anil **30**. Compound **30** (1.00 mmol) in benzene (1 ml) was added to **14** (1.00 mmol) in benzene (10 ml) and refluxed for 3 h under Ar. CC (silica gel; AcOEt) furnished **31** (275 mg, 67%) as a colorless oil (*erythro*/*threo ca.* 1:1). IR (CCl_4): 1501*s*, 1603*s*, 1737v*s*, 3400*w* (br., N–H). ^{1}H-NMR (80 MHz): 0.52–1.81 (*m*,C_3H_7); 3.57, 3.62 (2*s* of equal height, 2 MeO); 3.8–4.1 (*m*, 2 diastereotopic CH_2O); 5.11–6.10 (*m*, 2 *ABC*); 6.51–8.15 (*m*, 2 × 10 arom. H); 8.48 (*d*, J = 6.0, 2 × H–C(3′)). MS (130°): 406 (3, M^+), 347 (6, $[M - CO_2Me]^+$), 337 (11), 313 (6, $M - C_6H_5NH_2]^+$), 309 (11), 221 (11), 205 (15) [$C_{12}H_{15}NO_2^+$, **30**$^+$], 201 (44) [**24**], 169 (20), 143 (26) [**25**], 142 (20), 115 (22), 104 (68, $C_7H_6N^+$), 93 (100, $C_6H_5NH_2^+$), 77 (33, $C_6H_5^+$). Anal. calc. for $C_{24}H_{26}N_2O_4$ (406.46): C 70.91, H 6.45, N 6.89; found: C 70.82, H 6.90, N 7.21.

6. N-*Aryl Analogs of* **18**. 6.1. *Dimethyl (±)-[1α,2α,*rel-*10bβ]-1,2,3,10b-Tetrahydro-3-*p-*tolylpyrazolo-[5,1-*a*]isoquinoline-1,2-dicarboxylate* (**26**). Aq. Na_2CO_3 was dropped into the stirred two-phase system of *N*-(*p*-toluidino)isoquinolinium chloride [10] (5.00 g, 18.5 mmol) in H_2O (25 ml) and dimethyl maleate (2.67 g, 18.5 mmol) in CH_2Cl_2 (30 ml), until the red color of the 1,3-dipole was no longer generated. Compound **26** (3.41 g, 49%) was isolated from the org. phase. M.p. 130–132° (Et_2O/pentane). ^{1}H-NMR: 2.32 (*s*, Me–C(4′));

3.13, 3.68 (2*s*, 2 MeO); 3.79 (*dd*, *J* = 8.9, 7.3, H–C(1)); 4.29 (*d*, *J* = 8.9, H–C(10b)); 4.78 (*d*, *J* = 7.3, H–C(2)); 5.31, 6.38 (2*d*, *J* = 8.0, H–C(6), H–C(5)); 6.68–7.26 (*m*, 8 arom. H); assignments based on a previous study [4].

6.2. *Dimethyl 3-(Isoquinolin-1-yl)-2-(*p*-toluidino)succinate* (**28**). Compound **26** (1.03 g, 2.72 mmol) in CH_2Cl_2 (40 ml) and methanolic HCl (0.2 ml, 4N) reacted 2 h at r.t.; workup with 2N NH_3 gave **28** (440 mg, 43%). M.p. 116–125 (Et_2O). Anal. HPLC (AcOEt/hexane 1:6, 50 bar, flow 1 ml/min) indicated two peaks of *ca.* 55:45 ratio (t_R 27.5, 28.5 min.); solubility was too low for prep. HPLC separation. The NMR spectra were taken from another crystal fraction of **28** and showed a diastereoisomer ratio of 62:38. IR: 749*m*, 827*s*, 998*s*, 1165*s*, 1202*s*, 1274*s* (br.), 1435*s*, 1522v*s*, 1562*w*, 1618*s*, 1735v*s* (br.), 3392*w* (sharp, N–H). IR (CCl_4): 3400*w* (br., N–H). ^{1}H-NMR (400 MHz; major/minor isomer, where separated): 2.191/2.198 (*s*, Me–C(4″)); 3.57/3.54, 3.67/3.62 (2*s*, 2 MeO); 4.40 (br. *s*, in coalescence, NH; disappears with D_2O); 5.21, 5.25 (*AB*, *J* = 7.2, H–C(2), H–C(3), major); 5.17, 5.36 (br. *AX*, *J* = 6.5, H–C(2), H–C(3), minor; signals get sharp with D_2O, coupling with NH stronger than for major isomer); 6.60, 6.92 (2*m*, *AA′BB′*, C_6H_4); 7.56/7.57 (*d*, *J* ≈ 6.1/5.6, H–C(4′), broadened by 4,8-coupling); 7.61/ *ca.* 7.60, 7.67 (2*td*, *J* ≈ 8.2, 1.2, H–C(7′), H–C(6′)); 7.81 (*d*, *J* ≈ 8.1, H–C(5′)); 8.15/8.03 (*d*, *J* = 8.1, H–C(8′)); 8.46/8.48 (*d*, *J* = 6.1/5.6, H–C(3′)); NMR parameters of isoquinoline and *N*-methyl-*p*-toluidine [33] helped the assignments of ^{1}H- and ^{13}C-NMR data. ^{13}C-NMR (100 MHz, DEPT; major/minor isomer): 20.38/20.40, *Me*–C(4″); 52.26 (MeO); 52.52/52.56 (MeO); 52.36, 51.08 (C(3)); 58.67/59.13 (C(2)); 114.27/114.42 (C(2″/6″)); 120.66/120.71 (C(4′)); 124.32/124.29, 127.59/127.63, 127.77/127.69 (C(5′), C(7′), C(8′)); 127.93/127.32, (C(8a′)); 129.66/129.58 (C(3″/5″)); 130.07/130.04 (C(6′)); 136.43/136.41 (C(4a′)); 141.57/141.40 (C(3′)); 144.17/144.95 (C(4″)); 154.18/155.15 (C(1′)); 170.91/170.97, 172.76/173.13 (2 C=O). MS (18 eV, 100°): 378 (0.5, M^+), 271 (13, $[M - C_7H_7NH_2]^+$), 201 (77, **24**), 177 (66, $[C_7H_7N{=}CH{-}CO_2Me]^+$), 143 (91, $C_{10}H_9N^+$, **25**), 142 (18), 118 (100, $HC{\equiv}N{-}C_7H_7^+$), 107 (91, $C_7H_7NH_2^+$), 106 (52), 91 (24, $C_7H_7^+$). Anal. calc. for $C_{22}H_{22}N_2O_4$ (378.41): C 69.82, H 5.86, N 7.40; found: C 69.76, H 5.86, N 7.55.

6.3. *Dimethyl (±)-[1α,2α,*rel*-10bβ]-3-(4-Chlorophenyl)-1,2,3,10b-tetrahydropyrazolo[5,1-*a*]isoquinoline-1,2-dicarboxylate* (**27**). Reaction of 2-(4-chloroanilino)isoquinolinium chloride [10] and dimethyl maleate, as described for **26**, furnished **27** (67%). M.p. 168–169° (MeOH). ^{1}H-NMR (80 MHz): 3.19, 3.74 (2*s*, 2 MeO); 3.83 (*dd*, partially superposed, H–C(1)); 4.26 (*d*, *J* = 9.0, H–C(10b)); 4.76 (*d*, *J* = 6.8, H–C(2)); 5.28, 6.31 (2*d*, *J* = 7.9, H–C(6), H–C(5)); 7.4–6.8 (*m*, 8 arom. H).

6.4. *Dimethyl 2-(4-Chlorophenyl)-3-(isoquinolin-1-yl)succinate* (**29**). Analogous to *6.2*, **27** was converted to **29** (63%). M.p. 139–140° (MeOH). IR (CCl_4): 1550*s*, 1568*w*, 1606*m*, 1741v*s*; 3415*m* (br., N–H); with D_2O 2540*m* (br., N–D). ^{1}H-NMR (90 MHz): 3.61, 3.68 (2*s*, 2 MeO); 4.63 (br. *d*, *C* of *ABC*, NH); 5.06–5.33 (*m*, 6 lines visible, *AB* of *ABC*, H–C(1), H–C(2)); 6.50–6.67, 6.94–7.08 (*AA′BB′*, C_6H_4); 7.25–8.47 (*m*, 6 arom. H); with *N*–D: 5.17, 5.28 (*AB*, *J* = 7.5, H–C(1), H–C(2)). ^{13}C-NMR (20 MHz): 52.1, 52.4 (2*q*, 2 MeO); 52.5, 58.3 (2*d*, C(2), C(3)); 115.0, 120.7, 124.1, 127.6, 127.8, 128.9, 130.1, 141.5 (8*d*, 10 arom. CH); 5*s* of arom. C_q at 123.1, 127.1, 136.4, 145.2, 153.9; 170.8, 172.5 (2*s*, 2 C=O). MS (18 eV, 150°): 398 (1, M^+), 339 (1.4, $[M - CO_2Me]^+$), 271 (4, $[M - ClC_6H_4NH_2]^+$), 201 (100, **24**), 197 (26, $C_9H_8ClNO_2^+$, *p*-Cl derivative of **15**$^+$), 169 (18), 143 (48, [**25**]), 142 (29, [**14** – $CO_2Me]^+$), 138 (59, $[HC{\equiv}N{-}C_6H_4Cl]^+$), 127 (14, $ClC_6H_4NH_2^+$), 111 (11, $ClC_6H_4^+$). Anal. calc. for $C_{21}H_{19}ClN_2O_4$ (398.84): C 63.24, H 4.80, N 7.02; found: C 63.26, H 4.78, N 7.13.

7. *Introduction of Acetate Group into Adduct* **11**. 7.1. *With* **18** *as Source of Imino-acetate* **15**. Compounds **11** and **18** (1.37 mmol each) in CH_2Cl_2 (15 ml) were mixed with methanolic HCl (5 ml, 1.6N). After 2 h at r.t., CH_2Cl_2 (20 ml) was added, and the acid was removed by shaking with 2N NH_3. Compound **13** (354 mg, 60%) crystallized from acetone/pentane, m.p. 182–184°, ^{1}H-NMR identified with the material from *2.1*. Distillation at 10^{-3} Torr gave aniline (1.46 mmol) and **14** (1.12 mmol).

7.2. *With Methyl Glyoxylate and HCl.* Freshly prepared **33** [35] (2.43 g, 27.6 mmol) and **11** (1.00 g, 2.74 mmol) in CH_2Cl_2 (10 ml) were treated with methanolic 4N HCl (4 ml) for 2 h at r.t. under N_2. Workup as above furnished **13** (595 mg, 50%), m.p. 182–184°.

7.3. *With Butyl 2-(Phenylimino)acetate* (**30**) *and* CF_3COOH. Compound **30** in benzene (10 ml) was added to **11** (5.48 mmol) and CF_3CO_2H (1.5 ml, 20.2 mmol) in CH_2Cl_2 (20 ml). After 2 h at r.t. under Ar, workup gave *dimethyl 6-[(butoxycarbonyl)methyl]-2,3-dihydro-3-phenylpyrazolo[5,1-*a*]isoquinoline-1,2-dicarboxylate* (**32**, 1.96 g, 75%) as yellow crystals. M.p. 128–129° (from acetone/pentane). ^{1}H-NMR (60 MHz): 0.61–1.21 (*m*, 7 H); 3.50 (*s*, CH_2–C(6)); 3.58, 3.75 (2*s*, 2 MeO); 4.03 (*t*, *J* = 6.5, CH_2O); 5.08 (*s*, H–C(2)); 6.90–7.68 (*m*, 8 arom. H). Anal. calc. for $C_{27}H_{28}N_2O_6$ (476.51): C 68.05, H 5.92, N 5.88; found: C 67.61, H 5.88, N 5.78. Without acid catalysis, no **32** was found after 2 h at 25°.

7.4. *With Butyl Glyoxylate and HCl.* Compound **34** (28 mmol) and **11** (2.74 mmol) in CH_2Cl_2 (10 ml), and methanolic 4N HCl (4 ml) afforded **32** (1.72 mmol, 63%). M.p. 128–129°.

7.5. *With* N-*[(Methoxycarbonyl)methylidene]piperidinium Chloride.* Compound **35** [24] is a colorless hygroscopic powder, which was applied without purification. From **35** (1.90 g, 9.95 mmol) and **11** (5.48 mmol) in

CH_2Cl_2 (20 ml), a deep-yellow soln. was obtained within 5 min. After 24 h at r.t., workup provided **13** (1.80 g, 76%). M.p. 182–184°.

8. *Variation of Reactants.* The data of *Table 2* are supplemented by spectra and elemental analyses.

8.1. *Dimethyl 2,3-Dihydro-6-(4-nitrobenzyl)-3-phenylpyrazolo[5,1-*a*]isoquinoline-1,2-dicarboxylate* (**44**). IR: 1094*s*, 1200*s* (br., C–O); 1345*s*, 1521v*s* (br., NO_2); 1678*s*, 1744*s*. ^{1}H-NMR: 3.63, 3.83 (2*s*, 2 MeO); 4.00 (*s*, CH_2–C(6)); 5.08 (*s*, H–C(2)). Anal. calc. for $C_{28}H_{23}N_3O_6$ (497.49): C 67.60, H 4.66, N 8.45; found: C 67.70, H 4.66, N 8.30.

8.2. *Dimethyl 6-Benzyl-2,3-dihyro-3-phenylpyrazolo[5,1-*a*]isoquinoline-1,2-dicarboxylate* (**45**). ^{1}H-NMR: 3.61, 3.78 (2*s*, 2 MeO); 3.98 (*s*, CH_2–C(6)); 5.08 (*s*, H–C(2)). Anal. calc. for $C_{28}H_{24}N_2O_4$ (452.49): C 74.32, H 5.35, N 6.19; found: C 74.28, H 5.41, N 6.32.

8.3. *Methyl 1-Cyano-2,3-dihydro-6-[(methoxycarbonyl)methyl]-3-phenylpyrazolo[5,1-*a*]isoquinoline-2-carboxylate* (**46**). IR: 698*m*, 764*s*, 772*s*, 1170*s* (br.), 1205*s* (br.), 1496*s*, 1558v*s*, 1634*s*, 1740v*s*, 1756*s*, 2185*s*. ^{1}H-NMR: 3.45 (*s*, CH_2–C(6)); 3.58, 3.76 (2*s*, 2 MeO); 4.80 (*s*, H–C(2)). Anal. calc. for $C_{23}H_{19}N_3O_4$ (401.41): C 68.82, H 4.77, N 10.47; found: C 68.65, H 5.00, N 10.41.

8.4. *Methyl 1-Cyano-2,3-dihydro-3-phenylpyrazolo[5,1-*a*]isoquinoline-6-acetate* (**47**). ^{1}H-NMR: 3.47 (*s*, CH_2–C(6)); 3.65 (*s*, MeO); 4.62 (*s*, CH_2(2)). Anal. calc. for $C_{21}H_{17}N_3O_2$ (343.37): C 73.45, H 4.99, N 12.24; found: C 73.63, H 5.13, N 12.25.

8.5. *Methyl α-Anilino-2-methylpyrrole-2-acetate* (**48**). Compound **18** (5.48 mmol), *N*-methylpyrrole (10 ml), and AcOH (2 ml) were reacted for 3 h at r.t.; workup with aq. NH_3/CH_2Cl_2 and distillation gave **48** (903 mg, 67%) as a light-yellow oil, which crystallized from Et_2O/pentane. M.p. 82–83°. IR: 695*m*, 712*s*, 758*s*, 972*m*, 1120*m*, 1216*s*, 1501*s*, 1604*s*, 1741v*s* (br.). ^{1}H-NMR (80 MHz): 3.48 (*s*, MeN); 3.60 (*s*, MeO); 4.42 (br. *s*, NH); 5.07 (*s*, H–C(α)); 5.9–7.2 (*m*, 8 arom. H). ^{13}C-NMR: 33.7 (*q*, MeN); 52.3 (*q*, MeO); 53.9 (*d*, C(α)); 107.1, 108.2 (2*d*, C(3), C(4)); 113.3 (*d*, C(2′/6′)); 118.5 (*d*, C(4′)); 123.5 (*d*, C(5)); 127.4 (*s*, C(2)); 129.2 (*d*, C(3′/5′)); 146.3 (*s*, C(1′)); 171.8 (*s*, C=O); assignments on the basis of pyrrole and *N*-methylaniline [33]. MS (50°): 244 (32, M^+), 185 (100, $[M-CO_2Me]^+$), 152 (100, $[M-C_6H_5NH]^+$), 104 (16, $[HC{\equiv}N-C_6H_5]^+$), 92 (22, $C_6H_5NH^+$), 82 (25), 77 (15, $C_6H_5^+$). Anal. calc. for $C_{14}H_{16}N_2O_2$ (244.28): C 68.83, H 6.60, N 11.47; found: C 68.73, H 6.72, N 11.31.

9. *Competing Reactions of Cycloadducts with Acid.* 9.1. *Adduct* **42** *of Methyl (Z)-3-Cyanoacrylate. a*) Compound **42** [4] (6.03 mmol) and CF_3CO_2H (2.0 ml, 27 mmol) in CH_2Cl_2 (40 ml) were reacted 2 h at r.t. Bulb-to-bulb distillation afforded aniline (13%) and, at 170°/10^{-3} Torr, *isoquinoline-1-acetonitrile* (**50**, 12%). ^{1}H-NMR: 4.29 (*s*, CH_2–C(1)); 6.5–8.05 (*m*, 5 arom. H); 8.43 (*d*, *J* = 5.5, H–C(3)). MS (40°): 168 (100, M^+), 129 (12, $C_9H_7N^+$), 128 (25, $C_9H_6N^+$). The picrate of **50** crystallized from EtOH. M.p. 127–129°. Anal. calc. for $C_{17}H_{11}N_5O_7$ (397.30): C 51.39, H 2.79, N 17.63; found: C 51.97, H 2.88, N 17.72.

b) 2,4-DNPH (550 mg, 2.78 mmol) and **42** (907 mg, 2.74 mmol) were reacted in methanolic 1.8N HCl (45 ml); after 12 h at 4°, hydrazone **16** (217 mg, 30%) was filtered. The mother liquor was worked up, and distillation provided aniline (147 mg, 58%) and **50** (246 mg, 53%).

9.2. *Adduct* **52** *of Methyl Acrylate.* Compound **52** [4] (500 mg, 1.63 mmol) in CH_2Cl_2 (5 ml) and methanolic 2.7N HCl (2 ml), 2 h at r.t., yielded *methyl (±)-(6aβ,11bβ,13α,*rel-*5β)-6,6a,7,11b-tetrahydro-5,7-ethano-5*H*-indolo[2,3-*c*]isoquinoline-13-carboxylate* (**55**, 49%). Colorless crystals. M.p. 134–135° (Et_2O). IR: 744*s*, 770*m*, 778*m*, 800*m*, 1173*s*, 1212*s*, 1473*s*, 1726v*s*, 3315*m*, 3335*m* (sharp, N–H). ^{1}H-NMR: 2.57 (br. *s*, NH; disappears with D_2O); 2.33–3.77 (*m*, CH_2(12), H–C(13)); 3.53 (*s*, MeO); 4.02, 4.87 (2*d*, *J* = 5.8, H–C(11b), H–C(6a)); 4.65 (*d*, *J* = 3.8, H–C(5)); 6.73–7.71 (*m*, 8 arom. H). Anal. calc. for $C_{19}H_{18}N_2O_2$ (306.35): C 74.49, H 5.92, N 9.15; found: C 74.61, H 5.81, N 8.99.

9.3. *Adduct* **53** *of Methyl Methacrylate.* Compound **53** [4] (3.12 mmol) was analogously treated with HCl and gave **56** (13α-methyl-**55**; 2.18 mmol, 70%). M.p. 159–160° (Et_2O). ^{1}H-NMR (60 MHz): 1.58 (*s*, Me–C(13)); 2.73 (br. *s*, NH); 3.09 (*s*, MeO); 3.15, 3.20 (*AB*, *J* = 12.0, CH_2(12)); 4.00, 5.03 (2*d*, *J* = 6.3, H–C(11b), H–C(6a)); 4.10 (*s*, H–C(5)); 6.7–7.6 (*m*, 8 arom. H). Anal. calc. for $C_{20}H_{20}N_2O_2$ (320.38): C 74.97, H 6.29, N 8.74; found: C 74.66, H 6.51, N 8.72.

9.4. *Adduct* **54** *of Methyl 2-Chloroacrylate.* Treatment of **54** with HCl as described above furnished aminal **57** (83%). M.p. 126° (Et_2O/pentane). IR: 747*s*, 752*s*, 1243*s*, 1263*s*, 1464*m*, 1605*w*, 1748v*s*, 3340*w* (sharp, N–H). ^{1}H-NMR (80 MHz): 3.10, 3.67 (*AB*, *J* = 13.5, left branch split by *J*(12,6a) = 1.5, CH_2(12)); 3.52 (*s*, NH, MeO); 4.02, 4.90 (*AB*, *J* = 5.8, H–C(11b), H–C(6a)); 4.53 (br. *s*, H–C(5)); 6.35–7.63 (*m*, 8 arom. H). Anal. calc. for $C_{19}H_{17}ClN_2O_2$ (340.80): C 66.96, H 5.03, N 8.22; found: C 66.96, H 5.09, N 8.13.

10. *Dimethyl (±)-(1α,2α,*rel-*10bβ)-1,2,3,5,6,10b-Hexahydro-5-{1-[(methoxycarbonyl)methyl]isoquinolin-4-yl}-3-phenylpyrazolo[5,1-*a*]isoquinoline-1,2-dicarboxylate* (**62**). *Entry 6* of *Table 1* was described in *Sect. 2.5*, and *Entry 7* gave the highest yield of **62** (23%). UV/VIS (EtOH): 'triplet' at 424 (2.28), 400 (2.40), 380 (2.32),

328 (3.83), 313 (3.76), 289 (sh., 3.84), 279 (3.88); the three long-wave absorptions resemble those of **14**. IR ($CHCl_3$): 1174*s*, 1378*m*, 1440*m*, 1489*s*, 1603*s*, 1732v*s*, 1766*s*. ^{1}H-NMR (400 MHz; *Fig.*): 3.11 (*dd*, $J = 16.7$, 3.8, $H_A-C(6)$; $H_B-C(6)$ at 3.32 is superimposed); 3.32 (br. *s*, MeO; superimposed by *ca*. 3.37 ppm, MeO in coalescence); 3.66 (*s*, MeO); 4.18, 4.34 (2*d*, left branch overlapped by H–C(1), $J_{gem} = 15.2$, diastereotopic $CH_2-C(1')$; disappear with D_2O); 4.32 (*dd*, $J = 10.7$, 9.1, H–C(1)); 4.65 (*d*, $J = 10.7$, H–C(10b)); 5.04 (*d*, $J = 9.1$, H–C(2)); 6.02 (*m*, not resolved, H–C(5)?); 6.86 (*m*, 1 arom. H); 7.08–7.25 (*m*, 8 arom. H); 7.59,7.72, 8.08, 8.25 (4*m*, 4 arom. H); 8.82 (br. *s*, probably H–C(3′)). ^{1}H-NMR (60 MHz): 3.32, 3.39, 3.66 (3*s*, 3 MeO). ^{13}C-NMR (100 MHz)[4]): 39.5* (*t*, C(6)); 42.1 (*t*, $CH_2-C(1')$); 51.8, 52.1, 52.4 (3*q*, 3 MeO); 53.8* (*d*, C(5)); 58.3 (*d*, C(1)); 65.3 (*d*, C(10b)); 73.1 (*d*, C(2)); *d* of arom. CH: 115.2, 121.0, 125.7 (C_6H_5), 123.8*, 126.6, 127.54, 127.63 (2×), 127.93, 129.5*, 140.8*; *s* of C_q: 127.0, 131.3, 132.4, 134.5, 134.9, 152.0, 152.5* (C(1″)); 171.0, 171.93, 172.00 (3*s*, 3 C=O); MS (200°): 565 (3, M^+), 506 (3, $[M - CO_2Me]^+$), 271 (7), 269 (8), 151 (10), 144 (13, $C_6H_8O_4^+$, dimethyl fumarate$^+$), 129 (10, $C_9H_7N^+$, isoquinoline$^+$), 113 (60, $C_5H_5O_3^+$, $MeO_2C-CH=CH-C\equiv O^+$), 93 (100, $C_6H_5NH_2^+$), 85 (20), 77 (13, $C_6H_5^+$), 59 (25, $MeO-C\equiv O^+$). Anal. calc. for $C_{33}H_{31}N_3O_6$ (565.60): C 70.07, H 5.52, N 7.43; found: C 69.87, H 5.62, N 7.56.

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