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Can the Progress of Fischer's Indole Synthesis Be Stopped ? [1]

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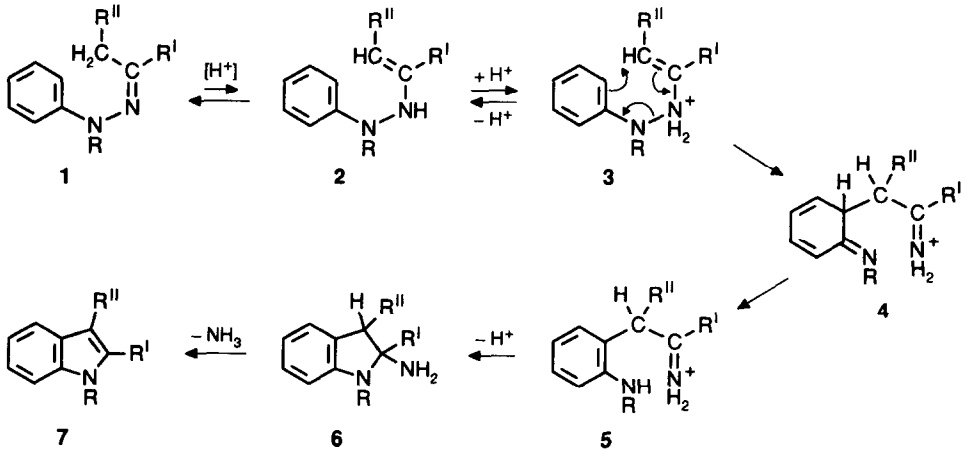
Abstract: The cycloadducts of isoquinoline *N*-phenylimide and ethylenic dipolarophiles are a new class of ene-phenylhydrazines. Their hydrazo rearrangement corresponds to the key step of Fischer's indole synthesis, but the reaction stops at the 2-aminoindoline stage, *e.g.*, **16**, because too much strain would build up in the 8-membered ring on indole formation. The model **23**, lacking the medium-sized ring, smoothly undergoes indolization. The structures of type **16a** aminals - besides the *all*-H parent mainly the diastereoisomeric 12,13-dicarboxylic esters and 13-carbonitriles - were clarified by X-ray and NMR analyses as well as by conversions. The pentacyclic aminals form a rigid bowl; the boat *vs.* chair conformation of the hydropyrimidine ring C is discussed.

Introduction

When Emil Fischer and Jourdan treated the *N*-methylphenylhydrazone of pyruvic acid with hydrochloric acid in 1883, a compound $C_{10}H_9NO_2$ was isolated as "a representative of an odd class of compounds for which analogies are missing." [2,3] Shortly after, Fischer and Hess identified the product as *N*-methylindole-2-carboxylic acid [4] and realized the connection with A. Baeyer's indigo studies.[5] In 1982, a 923-page monograph by B. Robinson [6] testified to the importance of Fischer's indole synthesis.



The mechanistic breakthrough was achieved by G. M. Robinson and R. Robinson (1918) who recognized the N,N-cleavage as a hydrazo rearrangement and formulated the sequence **1** → **7**.[7,8] Today, the key step **3** → **4** is regarded as a [3.3]-sigmatropic reaction, related to the Claisen and Cope rearrangements. The low bond energy of the N–N single bond (39 kcal mol^{-1}) constitutes the major driving force, whereas the aromaticity of the final product **7** can be dispensed with. Among the numerous variations

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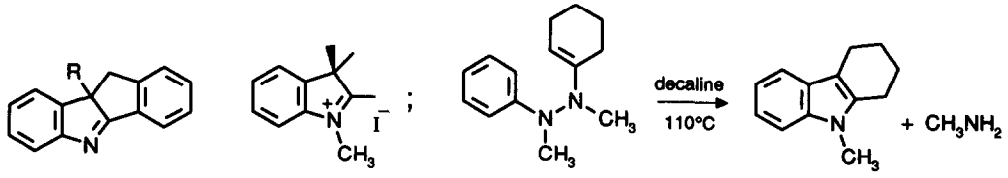
– their name is legion – many are known in which the polystep sequence is halted or diverted.[6]

3*H*-Indoles are formed in the final step when the 3-position is quaternary; compounds **8** were obtained from the phenylhydrazones of 2-substituted indane-1-ones by treatment with acid.[9] When the *N*-methylphenylhydrazone of 3-methylbutane-2-one was treated with hydrogen iodide, the 1,2,3,3-tetramethyl-3*H*-indolium salt (**9**) was the product, as known since 1898.[10]



8 R = C_2H_5, C_6H_5 **9** **10** **11**

Blocking of the aromatic *o*-positions by methyl or by ring annellation does not prevent the [3.3]-sigmatropic step, but the stabilization of the nonaromatic intermediates of type **4** requires loss or migration of alkyl.[11] The apparent 1,4 alkyl shifts initiated mechanistic studies by Fusco and Sannicolò;[12] many details of the fascinating cationic rearrangements have still not been elucidated.[13]

The conversion of arylhydrazones to indoles is subject to acid catalysis. The acid-catalyzed tautomerization of **1** to ene-phenylhydrazines **2** is sometimes the bottleneck of the polystep reaction and can be avoided by N^{β}-alkylation.[14,15] Usually, the isolation of the enehydrazines requires precautions because of their high tendency to enter the rearrangement step. The conversion **10** →**11** proceeds in neutral medium, but strong acceleration by dichloroacetic acid was demonstrated by Schiess and Grieder.[15]

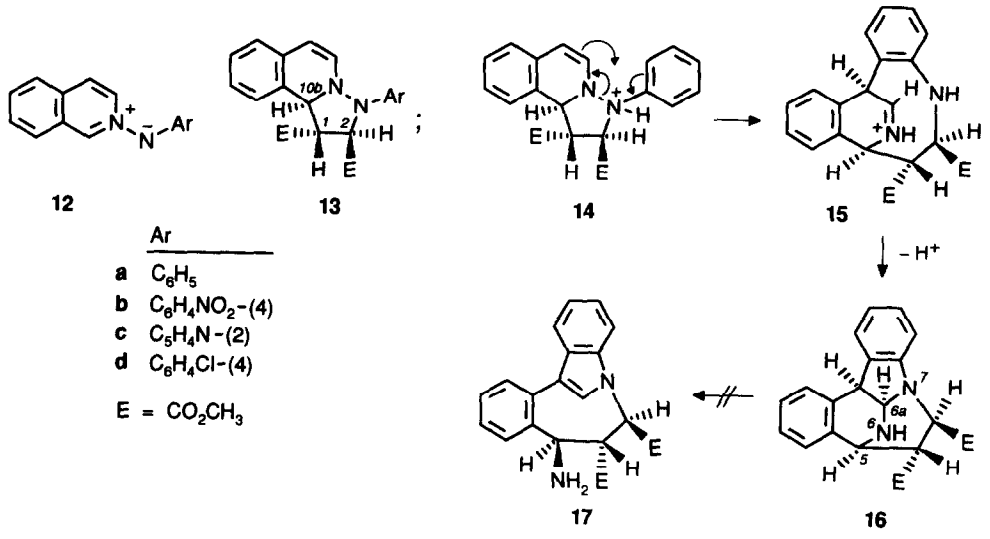
Hydrazo Rearrangement of a New Type of Ene-phenylhydrazine

The easily available isoquinolinium *N*-arylimides **12** [16] combine at room temp. with electron-deficient C=C bonds affording cycloadducts, *e.g.*, **13** with dimethyl fumarate as a dipolarophile.[17] The *N*-aryltetrahydropyrazolo[5,1-*a*]isoquinolines of type **13** represent new isolable N^{β}-aryl-enehydrazines capable of hydrazo rearrangement. Before we succeeded in crystallizing **13a**, we attempted the purification of the crude adduct as a picrate; the salt (75%, based on **12a**) was derived from a rearranged product. The base that was released was a secondary amine,[18] and its structure elucidation by ^{1}H NMR spectroscopy (next section) led to the pentacyclic **16**.[19]

The isolated cycloadduct **13a** required acid catalysis for the rearrangement, either picric acid (78% yield of **16**) or hydrochloric acid (84%). The protonated species **14** undergoes the [3.3]-sigmatropic reaction; the subsequent rearomatization of the intermediate of type **4** is achieved by prototropy. The iminium ion **15** accepts the secondary amine function furnishing **16**. The last step of the Fischer reaction, the formation of the indole **17**, could not be forced.

The nitrogen atoms of **16** are bonded in an aminal group. Such *N,N*-acetals are notorious for their sensitivity to acids. Aminal **16**, however, does not react with 2,4-dinitrophenylhydrazine and is even resistant to strong sulfuric acid; after 15 h in 80% H_2SO_4 at room temp., 87% of **16** was recovered. The inertness of **16** to hydrogen on platinum is also noteworthy.

Why is the intramolecular indolization, **16** → **17**, blocked ? The central ring of **17** is formally de-



rived from the highly strained *(E,Z)*-cycloocta-1,3-diene, whereas the corresponding perimeter in **16** is that of *(Z)*-cyclooctene. Comparison of the standard heats of formation with strainless models provided strain energies of 8.8 kcal mol^{-1} for *(Z)*-cyclooctene and 21.9 kcal mol^{-1} for *(E,Z)*-cycloocta-1,3-diene.[20,21] Thus, the additional strain energy for introducing the *trans*-double bond is 13.1 kcal mol^{-1}.

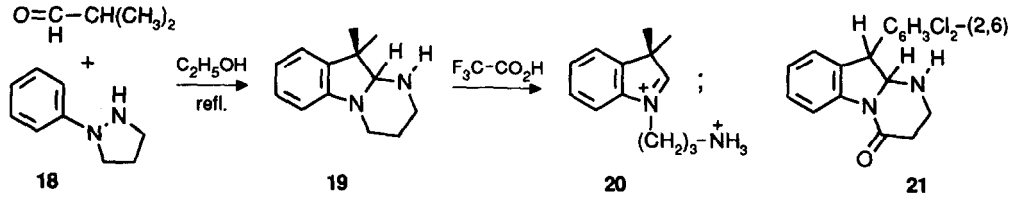
However, the extra strain accompanying the conversion **16** → **17** must be higher, because *three* members of the new pyrrole ring, the adjacent saturated C-atom, and the benzene ring are forced into coplanarity. Only two sp^3-hybridized C-atoms are left to span the distance between the terminal centers in the 8-membered ring. Even when conjugation between benzene and indole ring is not maintained, the 8-membered ring would suffer from oversize strain.

A *stereoelectronic* reason may contribute to the barring of the indolization step **16** → **17**, although it is difficult to separate it from the thermodynamic factor. The central tricyclic system of **16** has the shape of a rigid bowl. After protonation at N7, the ionization of the bond N6-C6a should give rise to an iminium ion. Inspection of the molecular model reveals, that the conditions for a planar bond system at C6a-N7 are very unfavorable.

Treatment with picric acid did not induce rearrangement of the 4-nitrophenyl or α-pyridyl compounds, **13b** or **13c**; however, the 4-chlorophenyl diester **13d** was amenable to the reaction. Thus, the hydrazo rearrangement appears to require a low HOMO energy in the aromatic moiety. On the other hand, the cycloadducts of **12a** to dimethyl maleate and acrylonitrile as well as the formal ethylene adduct rearrange at room temp. *without acid catalysis* (vide infra).

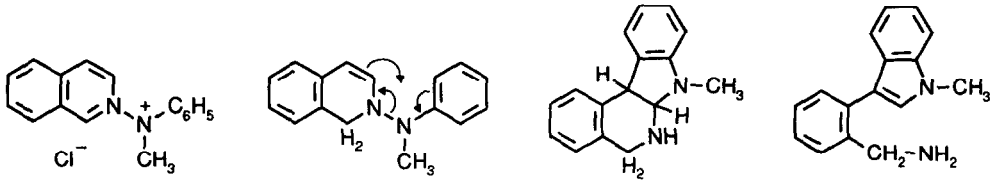
Aminals as products of the Fischer reaction have been reported by Eberle et al.;[22,23] *e.g.*, 1-phenylpyrazolidine (**18**) and isobutyraldehyde furnished **19** which, on dissolving in trifluoroacetic acid, opened the hydropyrimidine ring to give the dication **20** of 3*H*-indolium type. The aminal **21** was described as an isolated example which still could formally produce an indole. The stability of **21** was ascribed to steric hindrance by the 2,6-dichlorophenyl group, and the *N*-acylation diminishes the sensitivity to acid.[24]

If the inability of **16** to form the indole **17** is correctly interpreted, then a system without the C_2 tether between positions 5 and 7 of **16** should be prone to indole formation. In a model experiment,



18 19 20 21

2-(*N*-methylanilino)isoquinolinium chloride (**22**) [25] was reduced by sodium borohydride to the 1,2-dihydroisoquinoline derivative **23** which harbors the unsaturated hydrazo system of the cycloadducts **13**. Since **23** showed a slow ß-elimination, furnishing isoquinoline and *N*-methylaniline, probably base-catalyzed, **23** was treated with picric acid and gave the indole **25** in 80% yield. The *N*-methyl signal at δ_H 3.70 compares well with δ_H 3.60 of *N*-methylindole.[26] To distinguish **25** from its aminal precursor **24**, the primary amino group was characterized as the *N*-acetyl-*sec*-amide and as *N*-(4-nitrobenzylidene) derivative. The UV spectrum of the latter was fairly well simulated by superposition of the absorption curves of *N*-(4-nitrobenzylidene)methylamine and 1-methyl-3-phenylindole.



22 23 24 25

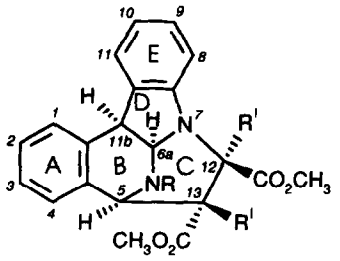
Structure and Reactions of the Pentacyclic Aminal* 16*: 12α,13ß-Dicarboxylic Esters

The X-ray structure of the trans-diester **16**, carried out by Karle and Flippen-Anderson, revealed a bowl-shaped nucleus of the rings B - D with the benzo rings A and E having the appearance of wings.[27] Compound **16** is a racemate; for Figure 1 and the projection formulae, the chirality was arbitrarily chosen. Three of the five stereocenters are dependent on each other: 5-H, 6a-H, and 11b-H are on the ß-side, and the α-side is the *concave* surface.

Ring B of **16** is a *half-chair* with a torsion angle of 64° for N6-C6a (60° for C4-C5 of cyclohexene). Ring C has a *boat* conformation which is slightly deformed towards the twist-boat. The molecular model (Dreiding) discloses substantial angle strain for the tricyclic system B - D, and the strain is increased by converting ring C into the *chair*. Both boat and chair conformations of ring C are flattened. When the N6-H is at a flagpole, the distance to 12ß-H, the flagpole partner, is 2.10 Å, compared with 1.84 Å for the regular cyclohexane boat (sum of van der Waals radii 2.4 Å).[28] The X-ray analysis of 1977 [27] did not locate the H atoms. The mentioned flagpole position N6-H at ring C would be *pseudo-equatorial* at the half-chair B. The *pseudo-axial* N6-H at ring B (shown in Figure 1) appears to be more favorable, especially for the *N*-methyl derivative **27**.

The assignment of the NMR data of **16** profited from the availability of the 12ß,13α-dideuterio compound **26**; the D content was not diminished during the rearrangement of [D_2]-**13a**, catalyzed by

picric acid. Furthermore, the ^{1}H NMR signals of **16** can be correlated with those of the substituent-free parent compound (Table 2 and later section). The correspondence of the *J* values with the dihedral angles of *vic*-CH bonds within the Karplus function [29] confirms the correctness of the assignments (Table 1). The H atoms were added to the X-ray structure by the program SHELXL-93.[30]



	R	R'
16	H	H
26	H	D
27	CH_3	H
28	CO-CH_3	H
29	CHO	H

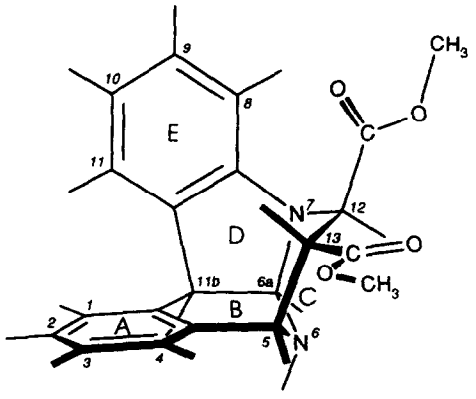


Figure 1. Structure of the 12α,13β-Dicarboxylic Ester (Based on the Atomic Coordinates of Ref. 27)

The deshielding by a *vic*-N function is stronger than that by a neighboring aryl group. The coupling constant between 6a-H (δ 5.62) and 11b-H (δ 4.33) is 7.9 Hz; the dihedral angle at this bond is 23°. 5-H and 6a-H are located in a planar W shape and couple with ^4J = 1.2 Hz. The dd of 5-H (δ 4.14) becomes a broadened s in the D_2 compound **26**. The bonds 12ß-H and 13α-H are nearly *diaxial* (ϕ 173°) and display the large $J_{12,13}$ = 11.8 Hz, whereas 114° for the dihedral angle between 5ß-H and 13α-H is still not far from the minimum of the Karplus-Conroy curve ($J_{5,13\alpha}$ = 4.2 Hz). Considering the decrease of J_{vic} with increasing substituent electronegativity, [31] the mentioned J = 11.8 Hz *is* a big value.

The N6-H stretching frequency occurs at 3368 cm^{-1} (CCl_4). The reaction of **16** with formalin and sodium cyanoborohydride in acetonitrile furnished the *N*-methyl derivative **27** (75% yield). Compared with the δ_H of **16**, the *N*-methyl of **27** shields its 5-H ($\Delta\delta$ -0.20 ppm), 6a-H (-0.36 ppm) and 11b-H (-0.20 ppm); all three constitute *pseudo-equatorial* positions at half-chair B with NCH_3 being *axial*. *a*-Methyl at the cyclohexane chair shields *e*-2-H by -0.20 ppm and *a*-3-H by -0.26 ppm.[26]

The *N*-acetyl derivative **28** was prepared from **16** and acetic anhydride as well as by treating the primary cycloadduct **13a** with acetyl chloride. The *N*-formyl compound **29** was available from **16** and the mixed acetic formic anhydride at room temperature. All proton signals - the aromatic H included - were doubled in the well-resolved 400 MHz spectrum. The partial double bond character raises the rotational barrier of amides, making the passage slow on the NMR time scale. The conformations A and B were present in a 77:23 equilibrium ($CDCl_3$).

The planar W structure of H-C5-N6-C6a-H was mentioned above. In **29** the formamide group is coplanar, as illustrated by the partial structure **30** of ring C. The bonds 5-H and 6a-H are oriented parallel to the C=O and C-H bonds of the formyl group, respectively. As a result of being in the deshielding cone of the amide system, δ(5-H) of **16** is increased by 1.48 ppm and δ(6a-H) by 0.38 ppm in **29A**; the size of the increase is reversed in **29B** (depicted in sketch **30**): +0.63 ppm for δ(5-H) and

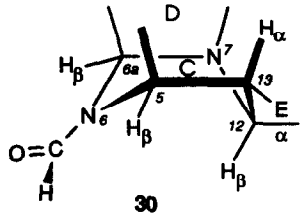
Table 1. ^{1}H NMR Spectra (400 MHz) of Dimethyl 6,6a,7,11b-Tetrahydro-5*H*-5,7-ethanoindolo-[2,3-*c*]isoquinoline-12,13-dicarboxylates in $CDCl_3$ (E = CO_2CH_3, ester methyls interchangeable)

No.	Substituent	δ	5-H	6a-H	11b-H	12α-H	12ß-H	13α-H	13ß-H	Other	
	12α,13β-Dicarboxylic Esters										
16	-		4.14	5.62	4.33	E 3.76	4.63	2.88	E 3.89	NH	2.89
27	N6-CH_3		3.94	5.26	4.13	E 3.75	5.03	2.86	E 3.86	NCH_3	2.38
29A	N6-CHO		5.62	6.00	4.43	E 3.79	4.33	3.05	E 3.88	CHO	8.34
29B	N6-CHO		4.77	6.72	4.41	E 3.80	4.39	3.11	E 3.89	CHO	8.37
	12β,13β-Dicarboxylic Esters										
36	-		4.84	5.45	4.21	4.38	E 3.70	2.73	E 3.86	NH	2.30
38	N6-CH_3		4.60	5.10	4.16	4.41	E 3.71	2.64	E 3.84	NCH_3	2.97
39A	N6-CHO		6.16	5.91	4.47	4.56	E 3.74	2.90	E 3.79	CHO	8.19
39B	N6-CHO		5.53	6.56	4.42	4.53	E 3.73	2.89	E 3.82	CHO	8.10

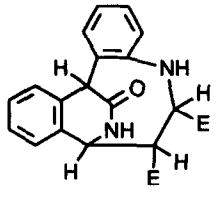
	J (Hz)	5ß,6aß	5ß,13α	6aß,11bß	12ß,13α	12α,13α
16		1.2	4.2	7.9	11.8	-
27		1.5	4.0	7.5	11.5	-
29A		2.0	4.2	8.3	11.7	-
29B		2.0	3.9	8.1	11.6	-
36		1.1	5.2	7.8	-	5.1
38		1.6	5.6	7.8	-	4.4
39A		1.9	5.7	8.4	-	5.1
39B		1.9	5.7	8.5	-	5.0
φ H-C-C-H	*boat*		114°	23°	173°	56°
	chair		60°	40°	75°	45°

+1.10 ppm for δ(6a-H) (Table 1). The coupling constants of **16** are virtually unchanged in **29A,B** and render the signal assignments unequivocal.

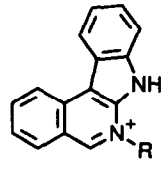
The aminal **16** is resistant to catalytic hydrogenation or to zinc in acetic acid. In an attempt of dehydrogenating **16** by chloranil in refluxing xylene, a crystalline product, richer by one oxygen atom, was isolated. The tentative structure **31** was based on preliminary spectroscopic observations. **31** did not react with acetic anhydride at low temp., but afforded a diacetyl compound at reflux temperature.



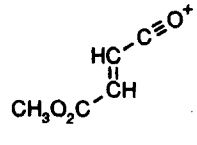
30
E = CO_2CH_3



31



32 R = H
33 R = CH_3



34

Whereas the initial cycloadduct **13a** eliminates dimethyl fumarate at 150°C, the rearrangement product **16** is not prone to cycloreversion. In contrast, the radical cation of **16** easily loses the former dipolarophile moiety. The [M^+ - Dimethyl fumarate] (*m/z* 220) fragment has an intensity of 95%, and *m/z* 219 is the base peak. The latter, $C_{15}H_{11}N_2^+$, could be the indolo[2,3-*c*]isoquinolinium cation (**32**). Not dimethyl fumarate, but $C_5H_5O_3^+$ (*m/z* 113, **34**), the result of CH_3O loss, was observed with 31%; it becomes *m/z* 115 in the MS of the D_2-compound **26**. The strong molecular peak (*m/z* 364, 90%) is accompanied by [M^+ - CO_2CH_3] (*m/z* 305, 71%); down the way, the fluorenyl cation (*m/z* 165, 11%) and the isoquinolinium ion (*m/z* 130, 28%) appear as fragments.

In the MS of the methyl derivative **27**, [M^+ - Dimethyl fumarate], *i.e.*, **33** + H (*m/z* 234, 100%), and the *N*-methylisoquinolinium ion (*m/z* 144, 36%) were observed.

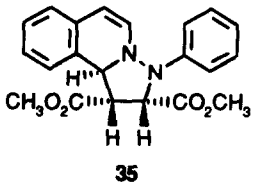
The 12ß,13ß-Dicarboxylic Esters and Their Conformations

When the *trans*-dicarboxylic ester **16** was refluxed with sodium methanolate in methanol, an isomer was obtained (81%) which was crystalline like **16**; $NaOCH_3$ in CH_3OD converted **16** to the 12,13-D_2 derivative of the new isomer. An independent pathway leaves no doubt that we are dealing with the 12ß,13ß-dicarboxylic ester **36** and its D_2-derivative **37**.

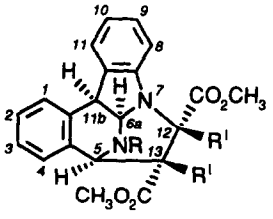
The 1,3-dipole **12a** combined with dimethyl maleate to give diastereoisomeric cycloadducts in a 90:10 ratio.[17] The major cycloadduct, *i.e.*, the colorless $C_{21}H_{20}N_2O_4$, was converted by acid catalysis into bright yellow crystals of $C_{24}H_{22}N_2O_6$; the clarification of the adventurous pathway will be the subject of a later report.[32]

The minor isomer **35** like **13a** underwent the hydrazo rearrangement; acid catalyzed the reaction, but was not mandatory. In acid-free $CDCl_3$ at 25 °C, the conversion **35** →**36** proceeded with a half-life of 36 h; after 20 d the ^1H NMR spectrum showed only the signals of the pure **36**. The mild conditions and the retention of configuration during the [3.3]-sigmatropic shift strongly suggest structure **36**.

The rapid reaction of **12a** with maleic anhydride furnished the 12ß,13ß-dicarboxylic anhydride (63%) which was converted into the diester **36**. Conceivably, the maleic anhydride acted as an electrophilic catalyst for the skeletal rearrangement.



35



	R	R'
36	H	H
37	H	D
38	CH_3	H
39	CHO	H

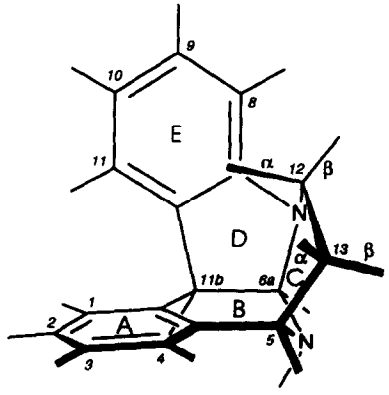


Figure 2. Structural Sketch of the Pentacyclic System with Chair Conformation of Ring C

The *N*-methyl-*trans*-diester **27** showed the same propensity for base-catalyzed stereoisomerization as **16**; treatment with sodium methanolate led to **38**. Furthermore, there is an acid-catalyzed variant too. The formylation of **16** at room temp. furnished **29**. However, the *N*-formyl-*cis*-diester **39** was the product when **16** was refluxed in formic acid for 30 h. Of course, the reaction with formic acetic anhydride at room temp. was sufficient for the conversion of **36** to the same **39**; the rotamers **A** and **B** are found in a 48:52 ratio.

Important information comes from the ^{1}H NMR data of the aromatic protons which reveal a striking difference between the two diester series. A two-dimensional analysis (see below), the splitting pattern, and the evaluation of the "roof effect" helped in assigning all eight δ(Ar-H). They are in the range of 7.0 - 7.4 ppm, except for 8-H and 10-H which are shielded by the resonance effect of N7.

	δ(8-H)	δ(9-H)	δ(10-H)
12α,13ß-Diesters **16, 27 - 29**	6.36 - 6.40	6.97 - 7.02	6.81 - 6.90
12ß,13ß-Diesters **36 - 39**	6.90 - 6.96	7.10 - 7.15	6.86 - 6.94
N,N-Dimethylaniline	2-H 6.60	3-H 7.08	4-H 6.59

In the rigid ring structure of **16**, the bond system of N7 is pyramidalized, as an angle sum of 347° discloses;[27] a smaller electron release to the aromatic ring E is anticipated than that found in *N,N*-dimethylaniline. The data of the diesters **36 - 39** confirm the expectation, but the δ(8-H) values for the 12α,13ß-diesters are disproportionally low. The X-ray structure of **16** indicates a distance of 2.73 Å between the carbonyl oxygen of the 12α-CO_2CH_3 and 8-H (Figure 1); 8-H is *not* located *in the plane* of the trigonal carbonyl C atom. According to the anisotropy function calculated by Jackman and Sternhell,[33] 8-H lies in the *shielding* cone of the carbonyl function. This additional effect brings δ(8-H) of the 12α,13ß-diesters down to 6.36 - 6.40 ppm.

The mentioned distance of 2.73 Å between the carbonyl oxygen and 8-H falls short of the sum of the van der Waals radii (2.9 - 3.0 Å).[34,35] If ring C flips to the chair conformation, even more van der Waals pressure would be generated between 12α-CO_2CH_3 and aromatic ring E, as Figure 2 suggests. It should be mentioned that all $\delta(OCH_3)$ values of the ester groups are "normal", *i.e.*, outside the shielding cone of aromatic rings. Moreover, the properties of the *all*-H parent **44** point to a flat boat form which appears here to be inherently more stable than the flattened chair.

The ^{1}H NMR data of the 12ß,13ß-diesters also support the boat conformation of ring C rather than the chair. In the chair (Figure 2), 13α-H would leave the shielding range of the aromatic rings, but δ(13α-H) 2.73 for **36** is even lower than 2.88 ppm for **16**. In contrast to the chair form, the 12ß-CO_2CH_3 of **36** contributes in the boat to the deshielding of the 5-H by +0.70 ppm. This value is higher than expected and observed in similar size for **38/27** and **39/29**. Each of the two ester groups moves in a rotation cone, and it is hard to predict the preferred conformations and their anisotropy effects.

The molecular model for the chair form of ring C (Figure 2) allows a rough estimate of the dihedral angles which are listed at the bottom of Table 1. $J_{5ß,13α}$ is in **36** (5.2 Hz) slightly higher than in **16** (4.2 Hz), whereas ϕ = 60° in the chair should decrease it. The large $J_{12ß,13α}$ of the 12α,13ß-diester series is replaced by a middle value of $J_{12α,13α}$ (4.4 - 5.1 Hz), expected for either conformation.

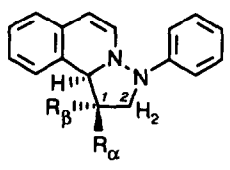
The $\delta(NCH_3)$ 2.38 of **27** is increased to 2.97 ppm in **38**, again pointing to the additional deshielding by 12ß-CO_2CH_3 which only the boat form offers. On the other hand, the 12ß-CO_2CH_3 occupies a

flagpole position in the boat. This disadvantage is abated by the flattening and twisting of the boat (see preceding chapter); only the unshared electron pair of N6 is at the second flagpole.

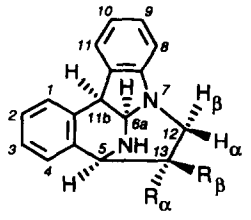
What makes the 12ß,13ß-diester **36** more stable than the 12α,13ß-diester **16** ? The nonbonded interaction between 12α-CO_2CH_3 and 8-H in **16** (Figure 1) appears to outnumber various adverse effects in **36** which, however, cannot be quantified.

Cycloadducts of Ethylene and Acrylonitrile: Hydrazo Rearrangement

The 1,3-dipole **12a** did not accept ethylene, but the formal ethylene adduct **40** was accessible via the cycloadduct of vinyltriphenylphosphonium bromide.[17] **40** spontaneously entered into the Fischer reaction; after 2 d in acid-free $CDCl_3$ at room temp., the ^1H NMR spectrum indicated the complete rearrangement affording **44**.



	R_α	R_β	
40	H	H	**44**
41	H	CN	**45**
42	CN	H	**46**
43	CN	Cl	**47**



In the ^1H NMR spectrum (100 MHz) of **44** the signal groups of the aliphatic protons are neatly separated, except for those of 5-H and 11b-H. The computer program LAME [36] reproduced the signals well and furnished the six δ and ten J values (Table 2). The δ at highest field must belong to 13α-H and 13ß-H; the others are deshielded as benzyl positions and/or by the vicinity of the nitrogen functions. The J data serve as a straitjacket, providing consistency in the form of a *boat conformation* for the hydropyrimidine ring C.

In contrast to 13ß-H (δ 1.87), the 13α-H (δ 1.43) is in the shielding cone of the aromatic rings A and E, mainly of the latter. As for the second *gem*-H_2 pair, 12α-H (δ 2.85) and 12ß-H (δ 3.37) are deshielded by N7, the 12ß-H also by the flagpole partner, the n-orbital at N6.

The coupling constants are set against the approximate torsion angles (ϕ of H–C–C–H) for boat and chair conformation of ring C in Table 2. The J values show a reasonable dependence on ϕ(boat). The negative sign of J_{gem} resulted from the LAME iteration.

The rapid cycloaddition of **12a** to *acrylonitrile* afforded the 1α- and 1ß-carbonitrile in a 56:44 ratio.[17] The separated nitriles **41** and **42** were treated with methanolic picric acid and smoothly converted to the pentacyclic 13-carbonitriles **45** and **46**. The configuration of the cycloadducts was fully retained during the [3.3]-sigmatropic reaction. Both **41** and **42** slowly rearrange in acid-free $CDCl_3$ at room temp., the less reactive **42** with a half-life of about 100 h at 25 °C.

Which structural features determine the rate of the hydrazo rearrangement ? For the compounds **35**, **40-42** the use of acid was not mandatory, although acid catalyzed strongly. 1ß-Substituents in the cycloadducts appear to be detrimental to the rate. The adduct of **12a** to dimethyl 2-chlorofumarate, a trisubstituted ethylene, turned out to be acid-resistant.[17] On the other hand, the cycloadduct **43**, obtained from **12a** and α-chloroacrylonitrile, rearranged to **47** by the picric acid procedure. [3.3]-Sigmatropic

Table 2. ^{1}H NMR Spectra (δ in ppm, J in Hz) of 6,6a,7,11b-Tetrahydro-5*H*-ethanoindolo[2,3-c]-isoquinoline and its Carbonitrile Derivatives in $CDCl_3$ at 400 MHz (100 MHz for **44**)

No.	Substituents	δ	5-H	6a-H	11b-H	12α-H	12ß-H	13α-H	13ß-H
44	*all*-H		3.96	5.10	4.00	2.85	3.37	1.43	1.87
45	13ß-CN		4.40	5.38	4.28	3.53	3.70	2.66	CN
46	13α-CN		4.49	5.01	4.15	2.85	3.73	CN	3.35
47	13α-CN, 13ß-Cl		4.52	5.19	4.22	3.64	3.82	CN	Cl

	$^3J_{cis}$				$^3J_{trans}$			$^2J_{gem}$	
No.	5,13ß	6a,11b	12α,13α	12ß,13ß	5,13α	12α,13ß	12ß,13α	12α,12ß	13α,13ß
44	9.0	7.7	5.9	4.7	4.0	4.5	10.4	-13.5	-13.6
45	-	7.9	5.5	-	4.0	-	11.1	-13.9	-
46	5.2	6.1	-	5.1	-	9.8	-	-12.2	-
47	-	6.7	-	-	-	-	-	-14.0	-
ϕ boat	5°	23°	56°	54°	114°	63°	173°		
ϕ chair	60°	40°	45°	50°	60°	170°	75°		

reactions proceed via chair- or boat-like transition states;[37] both are dense and may be subject to *steric hindrance* by substituents.

The δ_H differences between the *all*-H parent **44** and the 13ß-carbonitrile **45** can be ascribed to the effect of the cyano substituent (Table 2); *e.g.*, δ(13α-H) moves from 1.43 to 2.66 ppm, fairly consistent with the increment of *gem*-cyano (+1.13 ppm).[17] The J values of **45** closely correspond to those of **44**, to which the boat conformation of ring C was assigned.

On correlating the δ_H of the 13α-carbonitrile **46** with those of the *all*-H parent **44**, a striking deviation is observed: δ(12α-H) 2.85 is the same for **44** and **46**, notwithstanding the expectation that the *cis-vic*-CN of **46** should deshield the 12ß-H by ca. 0.6 ppm. In a *chair* conformation of ring C, however, the 12α-H would project into the shielding range of aromatic ring E (Figure 2); a cancelling of the two effects on δ(12α-H) of **46** offers a rationale. $J_{12\alpha,13\beta}$ = 4.5 Hz in **44** is increased to 9.8 Hz in **46**, incompatible with a torsion angle H–C–C–H of 63° in the boat (Table 2). In the chair, however, 12α-H and 13ß-H are nearly *diaxial*; ϕ = 170° argues for a large J value.

What is the reason for the *chair* conformational preference in ring C of the 13α-carbonitrile **46** ? In the boat, the 13α-CN juts out in front of aromatic ring C, parallel to it at a distance of about 2.6 Å and obviously creating intolerable van der Waals pressure. The van der Waals radius of the π cylinder of the cyano group is 1.6 Å, and 1.85 Å is given for the half-thickness of the benzene ring.[34] In the chair conformation, however, the 13α-CN is *axial* and towers over the 4-H of aromatic ring A at a distance of ca. 3.0 Å (see Figure 2).

The ^{1}H NMR spectra (400 MHz) reveal significant differences in the δ(Ar-H) of **45** and **46**. The δ_H of 8-H to 11-H in **46** exceed those of **45** by 0.08 - 0.22 ppm. At first glance we conjectured a deshielding of aromatic ring E by the π-cylinder of the cyano group in the *boat* conformation; apart from the

δ	8-H	9-H	10-H	11-H	1-H	2-H	3-H	4-H
13ß-CN (**45**)	6.76	7.10	6.83	7.37	7.41	7.29	7.15	7.09
13α-CN (**46**)	6.97	7.18	7.05	7.58	7.47	7.32	7.21	7.25

van der Waals strain, the $\Delta\delta$ would be much too small. A rationalization may come from the effect of conformational change on the direction of the n-orbital at N7. The shielding of Ar-H in ring E by electron release from N7 was discussed above. Model inspection intimates that the conjugation between N7 and ring E is slightly diminished in converting the boat to the chair; a net increase of δ(Ar-H) would be the outcome. A moderate increase of δ(4-H) in **46** is notable, too, and points to the deshielding by the *a*-CN in the *chair*.

In the MS of the 13ß-carbonitrile **45**, the molecular peak is large (88%), and acrylonitrile is lost in the major fragmentation : *m/z* 220 for [M^+ - Acrylonitrile] is the base peak; together with *m/z* 219 (Indoloisoquinolinium ion **32**, 97%), we are encountering the same doublet of fragments as in the MS of the dicarboxylic esters **16**, **26-29**. The isoquinolinium ion (*m/z* 130, 14%) appears here, too, and *m/z* 109.6 (12%) could well be the *dication* $C_{15}H_{11}N_2^{++}$.

^{13}C NMR Spectra and Two-Dimensional NMR Correlation

By comparing of the ^{13}C NMR spectra of the dicarboxylic esters **16** and **36** with those of the dideuterio derivatives **26** and **37**, the C-12 and C-13 signals could be assigned; the higher of the two must be that of C-12, due to the N7 vicinity (Table 3). For **45** - **47** the DEPT counting of bonded H atoms facilitated assignment.

The introduction of the N6-CH_3 leads to the deshielding of the *vicinal* C-5 and C-6a in both diester series by 5-7 ppm, whereas C-11b, located in ß-position to N6, is shielded by 4.5 and 3.7 ppm. The *N*-methyl is *axial* on the half-chair of ring B. In the cyclohexane chair conformation, an *a*-methyl group shifts δ(C-2) by +5.4 ppm and δ(C-3) by -6.4 ppm.[26] In the *N*-methylation of piperidine, even more pertinent, the δ(α-C) is shifted by +9.3 ppm and δ(ß-C) by -1.4 ppm.[26]

Table 3. ^{13}C Chemical Shifts of Substituted 6,6a,7,11b-Tetrahydro-5*H*-5,7-ethanoindolo[2,3-c]isoquinolines in $CDCl_3$ at 100 MHz (E = CO_2CH_3)

No.	Substituents δ	C-5	C-6a	C-11b	C-12	C-13	Other
16	12α-E, 13ß-E	52.8	73.6	44.3	58.2	47.7	OCH_3 52.2, 52.4
27	12α-E, 13ß-E, N6-CH_3	58.1	79.2	39.75	59.7	48.5	NCH_3 39.79
36	12ß-E, 13ß-E	48.7	71.7	43.3	61.7	48.3	OCH_3 52.1, 52.7
38	12ß-E, 13ß-E, N6-CH_3	55.6	77.3	39.6	62.0	49.5	NCH_3 39.2
45	13ß-CN	52.6	70.9	44.1	46.3	31.0	CN 120.4
46	13α-CN	50.4	72.2	43.9	49.3	32.9	CN 117.1
47	13α-CN, 13ß-Cl	60.8	70.9	44.1	56.2	57.7	CN 117.5

The HETCOR experiment [38] provided the two-dimensional correlation, and (assisted by further techniques) a complete assignment of the δ_C and δ_H values of the 13α-carbonitrile **46** (Table 4) was

achieved. Despite the substitution by the cyano group, δ(C-13) 32.9 is the lowest value by far; a *gem*-CN effect of only 4.2 ppm was observed for the hydrazo precursor **42**. The aminal C-6a shows with δ_C 72.2 the highest deshielding among the tetrahedral centers of **46**. The comparison of the 13ß-chloro-13α-cyano compound **47** with **46** ($\Delta\delta_C$) discloses the substituent effect of Cl: +25 ppm for *gem*-Cl, and 7 or 10 ppm for *vic*-Cl were observed.

The electron release from N7 to the aromatic ring E causes a strong shift to lower frequency. δ(C-8) 117.1 and δ(C-10) 124.1 stand out as the lowest among the aromatic CH of **46**; the other δ_C values follow in closely (Table 4).

A DQF-COSY experiment furnished two sequences of connectivities for the eight aromatic CH. The δ_H sequences based on the roof effect of *cis-vic*-H,H coupling patterns were confirmed here. The clue to the direction came from a NOESY experiment which pointed to the vicinity of 4-H and 5-H (ca. 2.4 Å); their U-shape relation does not favour direct coupling. The NOESY chart disclosed a phenomenon that we had long overlooked: 1-H, 11b-H, and 11-H are not engaged in mutual coupling, but form a nearly equilateral triangle with sides of 2.5 - 2.7 Å, close enough for positive NOESY signals. In the Karle structure of Figure 1, the σ-planes of the aromatic rings cut at an angle of 102°, *i.e.*, the arrangement is not far from orthogonality.

Table 4. Two-Dimensional NMR Correlation of 6,6a,7,11b-Tetrahydro-5*H*-5,7-ethanoindolo[2,3-*c*]isoquinoline-13α-carbonitrile (**46**) in $CDCl_3$

δ_C ppm	Position No.	δ_H ppm	Multiplicity	DQF-COSY	NOESY
49.3	12 (α)	2.85	dd	13ß,12ß	12
	12 (ß)	3.73	dd	12α > 13ß	12α > 13ß
32.9	13 (ß)	3.35	ddd	12α > 12ß, 5	5 > 12ß
43.9	11b	4.15	d	6a	6a > 1, 11
50.4	5	4.49	d	13ß	13ß, 4
72.2	6a	5.01	d	11b	11b
117.1	8	6.97	dt	9	9
124.1	10	7.05	td	9, 11	11 > 9
128.5	9	7.18	td	8, 10	8, 10
126.3	3	7.21	tq	2, 4	2
128.4	4	7.25	dd	3	3 > 5
128.8	2	7.32	td	1 > 3	1, 3
128.0	1	7.47	d, br.	2	2, 11 > 11b
128.5	11	7.58	dt	10	1, 10 > 11b

Does the NOESY experiment shed light on the vexing conformational assessment of ring C ? The chair form was proposed above as highly probable for the 13α-carbonitrile **46**. The 13ß-H of **46** "sees" the 12ß-H, but not the 12α-H (Table 4), the *diaxial* partner in the flattened chair. In the regular chair of cyclohexane, *diaxial* H atoms are apart by 3.06 Å.[28] In the flattened chair of the hydropyrimidine ring C,

the estimated torsion angle of 170° should correspond to a distance of 2.9 - 3.0 Å for 12α-H and 13ß-H which was beyond the sensitivity of our NOESY experiment. In contrast, $\phi = 63°$ for this dihedral angle in the boat form (Table 2) should have warranted "vicinity". Thus, the chair conformation of ring C in the 13α-carbonitrile **46** finds support here.

On comparing the δ_C of the α-carbonitrile **46** with those of the ß-isomer **45**, the additional deshielding of the aromatic ring E (see preceding chapter) is noticeable in the ^{13}C shifts, too: δ_C (**46**/**45**) 153.0/149.5 (C-7a), 117.1/114.6 (C-8), 124.1, 122.0 (C-10).

EXPERIMENTAL

General. IR spectra were recorded with a Perkin-Elmer 125 instrument and, later, with a Bruker FT model IFS 45 and a Perkin-Elmer FT-IR Spectrum 1000. Because the work stretched over three decades, the NMR equipment changed on the way: Varian A60, Bruker WP80 CW, and Varian XL 100 for ^1H NMR; Bruker WP80 DS (20 MHz) for ^{13}C NMR. Many of the NMR spectra were repeated with a Varian XR400S instrument, 400 MHz for ^1H and 100 MHz for ^{13}C; these spectra are marked. Acid-free $CDCl_3$ was the solvent, if not otherwise mentioned; TMS was the internal standard. The MS were EI spectra with 70 eV, recorded on an AET instrument MS902 and, later, on a Finnigan MAT 90; isotope effects are given in the mode ^{13}C % calcd/% found; HR is high resolution. - CC is column chromatography. Melting points are uncorrected.

Hydrazo Rearrangement of 2-(N-Methylanilino)-1,2-dihydroisoquinoline

2-(*N*-Methylanilino)isoquinolinium Chloride (22): [25,39] The crude product was purified by CC on silica gel; $CHCl_3$ and acetone eluted the 2,4-dinitroaniline, and **22** followed with methanol. Addition of acetone to the concentrated methanolic solution gave 55% of crystals, mp 190-191°C. - ^1H NMR (CH_3OD): δ 2.47 (s, NCH_3), 9.15 (s br, 1-H). - Anal. for $C_{16}H_{15}ClN$: calcd C 70.97, H 5.54, N 10.30; found C 70.97, H 5.58, N 10.30.

2-(*N*-Methylanilino)-1,2-dihydroisoquinoline (23): 300 mg (1.11 mmol) of **22** was reduced with sodium borohydride in methanol at 0 °C. Workup with water/CH_2Cl_2 and removal of the organic solvent at the rotary evaporator afforded the oily **23** which contained small amounts of isoquinoline and *N*-methylaniline. - IR (film): $\tilde{\nu}$ 693 cm^{-1}, 753, 766, 859 (arom. CH out-of-plane deform.), 1495 st, 1572 m, 1603, 1623 st (arom. ring vibr.). - ^1H NMR: δ 2.97 (s, NCH_3), 4.35 (s, 1-H_2), 5.33, 6.28 (2 d, $J_{3,4}$ = 7.6 Hz, 4-H and 3-H). - A slow decomposition of **23** yielding isoquinoline and *N*-methylaniline at room temp. was observed.

1-Methyl-3-(2-aminomethyl-phenyl)indole (25): (a) **23**, freshly prepared from 300 mg of **22**, was heated with 300 mg (1.31 mmol) of picric acid in 20 mL of methanol to 65 °C for 15 min under stirring. After cooling, the workup with dilute aqueous ammonia and CH_2Cl_2 furnished oily **25** which was colorless after 2 distillations at 170 °C/0.001 Torr (210 mg, 80%, based on **22**). - IR (film): $\tilde{\nu}$ 743 cm^{-1} st, 775 m (arom. CH out-of-plane def.); 1329, 1378 st; 1470, 1488 st, 1550, 1604 m (arom. ring vibr.); (CCl_4, 1 cm): 3390 (N-H, free), 3300 (N-H assoc.). - ^1H NMR: δ 1.38 (s, NH_2, disappears with D_2O), 3.70 (s, NCH_3), 3.83 (s, CH_2), 7.0 - 7.7 (m, 9 arom. H). - ^{13}C NMR (25.2 MHz, H-decoupled and off-resonance): δ 32.8 (q, NCH_3), 44.7 (t, CH_2), 109.2 (d, 6'-H), 114.7 (s, C-3); 119.5, 119.6, 121.8, 126.6, 126.9, 127.2, 128.0, 131.3 (8 d, 8 arom. CH); 127.6, 133.5, 136.6, 141.8 (4 s, 4 arom. C_q). - MS (70 °C); *m/z* (%): 238 (64) [M^+ + 2], 236 (100) [M^+], 218 (64), 159 (15), 129 (83) [*N*-Methylindole$^+$ - H], 107

(48) [$C_6H_5CH_2NH_2^+$], 106 (42), 77 (34) [$C_6H_5^+$].

(b) *N-Acetyl Derivative*: **25** (100 mg, 0.42 mmol) in 2 mL of acetic anhydride reacted for 2 d. From $CHCl_3$/ether crystallized 98 mg (83%), mp 104-105 °C, which turned brown on exposure to air. – ^1H NMR: δ 1.74 (s, $COCH_3$), 3.72 (s, N-CH_3), 4.42 (d, J = 5.0 Hz, CH_2; s after D_2O treatment), 5.96 (s br, NH, disappears with D_2O), 7.00 - 7.58 (m, 9 arom. CH).

(c) *N-(4-Nitrobenzylidene) Derivative*: 120 mg of **25** in 10 mL of ethanol was briefly refluxed with 80 mg of 4-nitrobenzaldehyde; on cooling, 120 mg (64%) was obtained as pale yellow needles, mp 122-124 °C. – UV ($CHCl_3$): λ_{max} 355 nm (log ϵ 3.00), 285 (4.41). Comparison with *N*-(4-nitrobenzylidene)methylamine: 342 sh (3.13), 283 (4.17), and with 1-methyl-3-phenylindole: 282 sh (4.06), 270 (4.11). – ^1H NMR: δ 3.71 (s, NCH_3), 4.85 (s, CH_2), 8.02 (s, -CH=N, occurs in the AA'BB' of $C_6H_4NO_2$). – Anal. calcd for $C_{23}H_{19}N_3O_2$: C 74.78, H 5.18, N 11.38; found C 75.01, H 5.25, N 11.37.

Isoquinoline N-phenylimide and Dimethyl Fumarate

Dimethyl 6,6a,7,11b-Tetrahydro-5*H*-5,7-ethanoindolo[2,3-*c*]isoquinoline-12α,13ß-dicarboxylate (16): (a) *N*-Anilinoisoquinolinium bromide [16] (300 mg, 1.00 mmol) was dissolved in 20 mL of water (+ a drop of acetic acid), basified with aqueous sodium carbonate, and extracted with 40 mL of ether. After short drying of the ethereal phase with Na_2SO_4, 156 mg (1.08 mmol) of dimethyl fumarate was added; the red color of **12a** disappeared in 5 min. After removal of the solvent, the oily residue was treated with picric acid in 10 mL of methanol. The yellow picrate of **16** (376 mg, 75%, based on the **13a**-content [17] of the primary cycloadducts) showed mp 190-192 °C (dec) after recrystallization from methanol. – Anal. calcd for $C_{27}H_{23}N_5O_{11}$: C 54.64, H 3.91, N 11.80; found C 54.74, H 3.85, N 11.50. – The picrate (11.2 g, 18.9 mmol) was shaken with dilute aqueous ammonia and CH_2Cl_2. The organic phase was evaporated to a small volume, and the crystallization was completed by adding 5 mL of ether: 5.94 g (86%) of **16** was obtained in pale yellow crystals, mp 140-143 °C. The colorless rhombs of the pure specimen (CH_2Cl_2/CH_3OH) melt at 144-146 °C.

(b) *From Isolated* **13a** *and Picric Acid*: The crystalline adduct **13a** [17] (6.80 g, 18.7 mmol) and 6.80 g (29.7 mmol) of picric acid were refluxed in 150 mL of methanol under stirring for 15 min. The picrate which precipitated on cooling was split by aqueous ammonia and CH_2Cl_2 as above. The yield of the free base, mp 143-145 °C, was 5.46 g (78%). – Anal. for $C_{21}H_{20}N_2O_4$: calcd C 69.20, H 5.53, N 7.69; found C 69.21, H 5.56, N 7.79. The analytical specimen was dried at 80 °C in vacuo; crystals obtained from methanol contain 1/3 mol equiv. of CH_3OH (^1H NMR spectrum): calcd C 68.32, H 5.69; found C 68.03, H 5.74. The crystal used for the X-ray analysis [27] likewise contained methanol.

(c) *Rearrangement by Hydrochloric Acid*:[39] **13a** (1.00 g, 2.74 mmol) was refluxed in 20 mL of methanol and 1 mL of conc. aqueous HCl. After several min, the hydrochloride of **16** precipitated (0.92 g, 84%); the IR spectrum (KBr) showed the broad absorption of ammonium salts at 2210 cm^{-1}. **16**, set free by triethylamine in CH_2Cl_2, was identified by mixed mp and IR spectrum.

(d) *Spectra of* **16**. IR (KBr): $\tilde{\nu}$ 755 cm^{-1} st (arom. CH out-of-plane def.); 1118, 1170, 1198, 1224, 1242 st (C-O, C-N); 1437, 1461 m, 1478 st, 1597 w (arom. ring vibr.); 1725, 1740 vst (C=O); (Nujol): 3292 w (N-H); (CCl_4): 3368 (N-H). – UV (ethanol): λ_{max} 301 nm (3.28), 255 (3.73); slight bathochromic shift compared with *N*-methylindoline: 294 (3.25), 251 (3.77). – ^1H NMR (400 MHz): Table 1. The aromat. CH show J_{vic} = 7.4 - 8.1 Hz, and ^4J = 1.0 - 1.8 Hz. The high-field signals of 8-H and 10-H allowed to disentangle the two sequences of Ar-H: δ 6.36 (d br, 8-H), 6.81 (apparent td, 10-H), 6.98 (td, 9-

H), 7.38 (d br, 11-H); 7.09 (td, 4-H), 7.14 (td, 3-H), 7.27 (td, 2-H), 7.41 (d br, 1-H). – ^{13}C NMR (100 MHz, DEPT): Table 3. Further data: δ 115.6 (C-8), 122.2 (C-10); 125.2, 125.7, 126.3, 127.7, 128.1, 128.3 (6 arom. CH); 135.5, 135.5, 139.6 (3 s, 3 arom. C_q), 147.1 (s, C-7a); 171.0, 174.1 (2 C=O). The ^{13}C data of **26** (see below) and the two-dimensional NMR spectrum of **46** confirmed the assignments. – MS (110 °C); *m/z* (%): 364 (90) [M^+; HR calcd 364.1418, found .1424; ^{13}C 21/20], 333 (8) [M^+ - OCH_3], 305 (71) [M^+ - CO_2CH_3; HR .1286/.1281; ^{13}C 14/15], 288 (36) [305 - NH_3; HR .1021/.1020; ^{13}C 7.8/8.8], 273 (47) [305 - CH_3OH; HR .1025/.1026; ^{13}C 9.4/10.5], 256 (19), 245 (25) [$C_{17}H_{15}N_2^+$, 305 - HCO_2CH_3], 231 (34) [245 - CH_2], 220 (95) [$C_{15}H_{12}N_2^+$, M^+ - Dimethyl fumarate, **32** + H; HR .0998/.0993; ^{13}C 16/15], 219 (100) [$C_{15}H_{11}N_2^+$; HR .0920/.0921; **32**], 218 (36), 217 (27), 204 (22), 165 (11) [$C_{13}H_9^+$, Fluorenyl$^+$], 153 (14), 143 (14), 130 (28) [$C_7H_8N^+$, Isoquinolinium$^+$; HR .0655/.0657], 113 (31) [$C_5H_5O_3^+$, **34**], 107 (11), 89 (21), 85 (18) [113 - CO], 78 (19) [$C_6H_6^+$], 77 (43) [$C_6H_5^+$], 55 (21).

(e) *12β,13α-Dideuterio Compound* **26**: [1α,2ß-D_2]-**13a** [17] (133 mg, 0.36 mmol) reacted with 130 mg (0.57 mmol) of picric acid in 10 mL of refluxing methanol for 15 min. After 2 h at room temp., 164 mg (77%) of the picrate was filtered. The free base was liberated as above. ^1H NMR: The $CDCl_3$ spectrum corresponds to that of **16**; the integrals of the dd at δ 2.88 (13α-H) and the d at δ 4.63 (12ß-H) are small. – ^{13}C NMR (100 MHz, DEPT): At δ 47.4 and 52.7, small CH signals besides the low-intensity CD triplets buttress the assignments of C-13 and C-12. – The MS (110 °C) of **26** was recorded under the same conditions as that of **16**. The comparison provides the number of D-atoms in each fragment; all *m/z* down to 258 are by 2 units higher. *m/z* 232 (17) indicates [M^+ - CO_2CH_3 - HCO_2CH_3 - CHD]. *m/z* 115 (16) is consistent with [CH_3O_2C-CD=CD-C≡O^+] and confirms the origin of *m/z* 113 in the MS of **16**, but, interestingly, its product of CO loss, *m/z* 86 (15) contains only 1 D, pointing to a more complex pathway for the loss of CO_2CH_3 from dimethyl fumarate.

Reactions of Rearrangement Product 16

6-Methyl Derivative 27: Formalin (0.5 mL) was added to a solution of 364 mg (1.00 mmol) of **16**, and 100 mg (1.6 mmol) of sodium cyanoborohydride was introduced portionwise. After 10 min the solution was neutralized by dropwise addition of acetic acid and kept at room temp. for 2 h. The residue after evaporation was worked up with 2 N KOH and CH_2Cl_2. The *N*-methyl compound **27** (282 mg, 75%) crystallized from methanol, mp 172-174 °C. – IR (KBr): ν 756 cm^{-1} st (arom. CH out-of-plane def.), 1150, 1169 st (C–O); 1480 st, 1598 m (arom. ring vibr.), 1740 vst (C=O). – ^1H NMR (400 MHz): Table 1. Further data: δ 6.36 (d br, 8-H), 6.81 (td, 10-H), 6.97 (ddd, 9-H), 7.35 (d br, 11-H); 7.09 (dd, 4-H), 7.17 (td, 3-H), 7.27 (td, 2-H), 7.39 (d br, 1-H). – ^{13}C NMR (100 MHz, DEPT): Table 3. Further data: δ 52.1, 52.3 (2 OCH_3), 115.0 (C-8), 122.2 (C-10); 125.5, 126.8, 127.18, 127.19, 128.0, 128.3 (6 arom. CH), 134.8 (arom. C_q), 135.2 (2 arom. C_q), 146.8 (C-7a); 171.4, 173.7 (2 C=O). – MS (110 °C); *m/z* (%): 378 (100) [M^+, ^{13}C 24/23], 347 (13) [M^+ - OCH_3; ^{13}C 2.9/3.1], 319 (44) [M^+ - CO_2CH_3; ^{13}C 9.7/9.6], 305 [319 - CH_2; ^{13}C 0.89/0.88], 288 (9) [M^+ - CO_2CH_3 - OCH_3; ^{13}C 2.0/2.4], 246 (9), 234 (100) [M^+ - Dimethyl fumarate, ^{13}C 18/18], 233 (29) [234 - 1, **33**], 217 (17), 205 (15), 189 (6) [M^{++}], 144 (36) [$C_{10}H_{10}N^+$, N-Methylisoquinolinium; ^{13}C 4.0/3.7], 129 (5) [Isoquinoline$^+$]; 113 (6) [$C_5H_5O_3^+$, **34**]. – Anal. for $C_{22}H_{22}N_2O_4$: calcd C 69.82, H 5.86, N 7.40; found C 70.00, H 5.98, N 7.61.

***N*-Acetyl Derivative 28**: (a) **16** (1.00 g, 2.74 mmol), reacted with 7 mL of acetic anhydride at room temp. for 48 h. The excess of the reagent was distilled off at 12 Torr; 970 mg (86%) of colorless **28**, mp 214-215 °C, crystallized from $CHCl_3$/cyclohexane. – IR (KBr): ν 746 cm^{-1}, 752 st (arom. CH out-of-

plane def.), 1164 st (C–O); 1425 st, 1478 m, 1598 w (arom. ring vibr.), 1672 st (amide I), 1738 (C=O, ester). – ^{1}H NMR ($CDCl_3$): The rotamers with respect to the amide bond are responsible for some split signals, the minor not always being resolved. δ 2.30, 2.23 (2 s, 73:27, $NCOCH_3$). – Anal. for $C_{23}H_{22}N_2O_5$: calcd N 6.89; found N 6.98. – (b) [39] The primary adduct **13a** (1.00 g, 2.74 mmol) was refluxed for 10 min in 2 mL of acetyl chloride and 10 mL of benzene. After evaporation, the pale-yellow residue was triturated with methanol and gave 610 mg (55%) of **28** in colorless prisms, identical with the specimen above in mp, mixed mp, and N analysis (found 6.78). Mol. mass by osmometry (benzene, 37 °C): calcd 407.5, found 412.

***N*-Formyl Derivative 29**: 200 mg of **16** was reacted with 2 mL of formic acetic anhydride (1 mL each of formic acid and acetic anhydride) at room temp. for 15 h. Workup with aqueous $NaHCO_3$ and CH_2Cl_2 gave 140 mg of crystalline **29**, mp 204-206 °C. – IR (KBr): $\tilde{\nu}$ 752 cm^{-1}, 790 (arom. CH out-of-plane def.), 1170 (C–O), 1442, 1480 m, 1598, 1608 w (arom. ring vibr.), 1698, 1740 st br (amide I and ester C=O). – ^{1}H NMR ($CDCl_3$, 400 MHz): The double set of signals corresponding to conformations **29A** and **29B** occurred in integral ratios of 77:23; see Table 1. Further data of **29A**: δ 6.40 (d br, 8-H), 6.90 (td, 10-H), 7.04 (td, 9-H); 7.13 - 7.27 (signal overlap, 3-H, 4-H), 7.31 (td, 2-H), 7.42 (d br, 1-H). **29B**: δ 6.38 (d br, 8-H), 6.86 (td, 10-H), 7.02 (td, 9-H); other Ar-H signals overlapping. – ^{13}C NMR (100 MHz, DEPT): The signal heights reflect the ratio of 77:23 for **A/B**; the following assignments are tentative. δ**A**/δ**B** 44.8/43.8 (C-11b), 47.8/48.8 (C-13), 48.4/48.4 (C-12), 52.56/52.65 (OCH_3), 52.67/52.65 (OCH_3), 59.1/55.0 (C-5), 73.4/67.2 (C-6a), 115.9/115.5 (C-8), 123.3/122.8 (C-10); 125.15/125.19, 126.5/125.5, 127.2/127.0, 127.5/127.7, 128.6/128.5, 129.0/129.2 (6 arom. CH); 134.3/134.4, 135.0/135.5, 136.5/136.4 (3 arom. C_q), 145.6/145.8 (C-7a); 159.6/160.5 (C=O, amide), 169.6/169.8, 172.1/172,7 (2 ester C=O). – MS (220 °C); *m/z* (%): 392 (100) [M^+, ^{13}C 27/25], 333 (56) [M^+ - CO_2CH_3; ^{13}C 6.1/6.1], 305 (56) [333 - CO; ^{13}C 13/11], 288 (76) [305 - OH; ^{13}C 14/15], 273 (41) [M^+ - CO_2CH_3 - HCO_2CH_3; ^{13}C 8.3/8.6], 256 (34), 219 (13) [M^+ - CHO - Dimethyl fumarate, **32**], 218 (12) [219 - H, $C_{15}H_{10}N_2^+$], 130 (5) [$C_9H_8N^+$, Isoquinolinium$^+$], 113 (4) [$C_5H_5O_3^+$, **34**], 84 (76) [$HC{\equiv}C\text{-}CO_2CH_3^+$], 77 (3) [$C_6H_5^+$]. – Anal. for $C_{22}H_{20}N_2O_5$: calcd C 67.34, H 5.14, N 7.14; found C 66.97, H 5.22, N 7.21.

Dimethyl 2,3,4,5,6,7-Hexahydro-6-oxo-1*H*-4.7-(*o*-benzeno)-1,5-diazonine-2,3-dicarboxylate (31): (a) **16** (1.65 g, 4.53 mmol) and 2.00 g (9.18 mmol) of chloranil in 20 mL of xylene were refluxed for 5 h. The cold black solution was poured into 300 mL of ether and washed with 0.5 N NaOH, until the washings were colorless. After removal of the solvents, the dark-brown residue was purified by CC (basic Al_2O_3, benzene). Side-products were eluted by benzene, and benzene/ether (3:1) furnished **31**, mp 213-214 °C (CH_2Cl_2/cyclohexane). In subsequent experiments, the CC was dispensable, and the dark residue was triturated with a small amount of ether, seeding crystals being added; the yield of **31** was 30-40%. – IR ($CDCl_3$): $\tilde{\nu}$ 1665 cm^{-1} (amide I), 1735 (C=O, ester), 3380 (N–H). – UV (Ethanol): λ 276 nm sh (3.31), 206 (4.43). – ^{1}H NMR: δ 3.00, 3.18 (2 s, 2 NH ?), 3.68, 3.71 (2 s, 2 OCH_3), 3.98 (dd, J = 11.5, 8.6 Hz, 1 H), 4.73 (s, 1 H), 5.10 (d, J = 3.6 Hz, 1 H). – Anal. for $C_{21}H_{20}N_2O_5$: calcd C 66.30, H 5.30, N 7.40; found C 66.23, H 5.40, N 7.28. – Mol. mass (osmometry in benzene, 37 °C): calcd 380, found 373. Formula **31** is tentative. – (b) *Diacetyl Derivative*: After refluxing of **31** (185 mg) in 5 mL of acetic anhydride for 12 h and evaporating the excess of reagent, 135 mg of colorless needles was obtained from CH_2Cl_2/methanol, mp 225-227 °C. – IR (KBr): $\tilde{\nu}$ 978 cm^{-1}, 1190 br, 1278, 1357, 1424, 1480; 1665 (amide I), 1695 st (C=O, Ar-$COCH_3$?), 1730 st (C=O, ester). – ^{1}H NMR: δ 1.80 (s, CH_3), 2.61 (s, CH_3), 2.83 (dd, J = 12.0, 7.2 Hz, 1 H), 3.73, 3.75 (2 s, 2 OCH_3), 5.09 (s, 1 H), 5.75 (d, J = 12.0 Hz, 1 H),

6.25 (d, J = 7.2 Hz); the CH_3 groups at high field could be N-CO-CH_3 or Ar-CO-CH_3. - Anal. for $C_{25}H_{24}N_2O_7$: calcd C 64.65, H 5.21, N 6.03; found C 64.70, H 5.29, N 5.86.

Dimethyl 6,6a,7,11b-Tetrahydro-5H-5,7-ethanoindolo[2,3-c]isoquinoline-12ß,13ß-dicarboxylate* (36) *and Derivatives

12ß,13ß-Dicarboxylic Ester 36. (a) *From* **16**: 400 mg (1.10 mmol) of **16** was reacted with a solution of 0.40 g of sodium in 40 mL of methanol (dried by the magnesium methoxide procedure) at reflux for 1 h; on cooling, 325 mg (81%) of **36** were obtained. Recrystallization from CH_2Cl_2/cyclohexane furnished colorless needles, mp 206-207 °C. - UV (Ethanol): λ 299 nm (3.30), 254 (3.70). - IR (KBr): $\tilde{\nu}$ 760 cm^{-1} st (arom. CH out-of-plane def.); 1144 m, 1215, 1241 st (C-O, C-N); 1480 st, 1604 w (arom. ring vibr.), 1738 vst (C=O); (nujol): 3367 (N-H free), ~ 3200 sh (NH assoc.); (CCl_4): 3371 (NH). - ^1H NMR (400 MHz): Table 1. Further data: δ 6.86 (dt, 10-H), 6.92 (d br, 8-H), 7.11 (td, 9-H), 7.35 (d br, 11-H); 7.11 (td, 3-H), 7.19 (dd, 4-H), 7.26 (td, 2-H), 7.40 (d br, 1-H). - ^{13}C NMR (100 MHz, DEPT): Table 3. Further data: δ 115.3 (C-8), 122.6 (C-10); 125.6, 125.8, 126.3, 128.0, 128.1, 128.3 (6 arom. CH); 135.3, 135.9, 140.6 (3 arom. C_q), 149.3 (C-7a); 172.0, 172.7 (2 C=O). - MS (100 °C); *m/z* (%): 364 (17) [M^+, HR calcd 364.1418, found .1424; ^{13}C 4.0/3.6], 305 (13) [M^+ - CO_2CH_3], 273 (10) [305 - CH_3OH], 220 (30) [M^+ - Dimethyl fumarate], 219 (17) [220 - H, **32**], 129 (23) [Isoquinoline$^+$], 113 (17) [**34**], 93 (23), 86 (63), 84 (100) [HC≡C-$CO_2CH_3^+$]. Anal. for $C_{21}H_{20}N_2O_4$: calcd C 69.20, H 5.53, N 7.69; found C 69.21, H 5.68, N 7.66.

(b) The *12α,13α-dideuterio derivative* **37** was analogously prepared by treating **16** with $NaOCH_3$ in CH_3OD. - ^1H NMR (400 MHz): The signals at δ 2.73 (13α-H) and 4.38 (12α-H) were reduced to < 1%, and the dd at δ 4.83 (5-H) has become s, slightly broadened by longe-range coupling with 6a-H. - ^{13}C NMR (100 MHz): The CD-signals of C-13 and C-12 appear as small t at 47.8 and 61.3; -0.5 and -0.4 ppm are the H,D isotope effects on δ_C.

(c) *From the cycloadduct* **35** *of dimethyl maleate*: The hydrazo rearrangement of the minor adduct (10%) **35** proceeded in acid-free $CDCl_3$, *i.e.*, in neutral medium, with a half-life of 36 h at 25 °C and quantitative yield. The NMR spectra, recorded after 40 d, did not show any side product.

(d) *From the maleic anhydride adduct of* **12a**: When 108 mg (1.10 mmol) of maleic anhydride was added to the ethereal solution of **12a**, prepared from 301 mg (1.00 mmol) of *N*-anilinoisoquinolinium bromide, the red color of **12a** immediately disappeared. After concentrating the ether solution to ~ 5 mL, pale-yellow crystals of *6,6a,7,11b-tetrahydro-5H-5,7-ethanoindolo[2,3-c]isoquinoline-12ß,13ß-dicarboxylic acid anhydride* (200 mg, 63%), mp 241 °C (dec. with gas evolution) precipitated. Dissolving in much ether and concentrating at room temp. led to colorless crystals, mp 243 °C (dec). - IR (KBr): $\tilde{\nu}$ 1780 cm^{-1} st and 1860 m (C=O of anhydride), 3340 m (N-H). - Anal. for $C_{19}H_{14}N_2O_3$: calcd C 71.69, H 4.43, N 8.80; found C 72.04, H 4.62, N 8.78. - Hydrogen chloride was passed into the solution of the anhydride in methanol at 0 °C. After refluxing for 1 h, workup with CH_2Cl_2 and aqueous sodium carbonate afforded the colorless crystals of the dimethyl ester **36** (mp and mixed mp).

***N*-Methyl Derivative 38**: The *N*-methyl compound **27** was subjected to the same treatment with $NaOCH_3$ in abs. methanol, as described for **16** →**36**. The colorless crystals melted at 167-168 °C. - IR (KBr): $\tilde{\nu}$ 734 cm^{-1} w, 758 st (arom. CH out-of-plane def.); 1043 st; 1109, 1154 st (C-O); 1190, 1212, 1236, 1261 st br; 1435, 1462 m, 1481 st, 1498 m (arom. ring vibr.), 1740 st br (C=O). - ^1H NMR (400 MHz): Table 1. δ(Ar-H): 6.83 (td, 10-H), 6.90 (d br, 8-H), 7.10 (td, 9-H), 7.32 (d br, 11-H); 7.14 (td, 3-H), 7.21

(dd, 4-H), 7.26 (td, 2-H), 7.38 (d, 1-H). – ^{13}C NMR (400 MHz, DEPT): Table 3. Further data: δ 52.0, 52.4 (2 OCH_3), 114.8 (C-8), 122.5 (C-10); 125.7, 126.7, 127.3, 127.5, 128.1, 128.3 (6 arom. CH); 134.8, 135.2, 135.9 (3 arom. C_q), 148.4 (C-7a); 171.8, 171.9 (2 C=O). – Anal. for $C_{22}H_{22}N_2O_4$: calcd C 69.82, H 5.86, N 7.40; found C 69.73, H 5.98, N 7.69.

***N*-Formyl Derivative 39**: (a) **16** (820 mg, 2.25 mmol) was refluxed in 20 mL of formic acid (99%) for 30 h; the excess of acid was distilled off at 10 Torr. Trituration with ether afforded 790 mg (89%) of **39** in colorless granules, mp 178-183 °C. The NMR spectra indicated a still incomplete isomerization: **29/39** = 20:80. After five recrystallizations from CH_2Cl_2, the mp 183-184 °C was still lower than that of the specimen below; the NMR spectra showed some **29**. – (b) **36** was converted by formic acetic anhydride to **39**, mp 188-189 °C. – IR (KBr): $\tilde{\nu}$ 757 cm^{-1} st (arom. CH out-of-plane def.); 1043 st, 1108 m, 1180-1290 br.; 1435, 1480 st, 1581, 1589 m (arom. ring vibr.), 1688 (amide I), 1738 (C=O, ester). – ^{1}H NMR (400 MHz): Table 1. The signals of Ar-H were insufficiently separated except for those at low δ_H: **A/B** (48:52) 6.91/6.94 (td, 10-H), 6.95/6.96 (d br, 8-H). – ^{13}C NMR (100 MHz, DEPT): δ(**39A/39B**) 44.5/43.7, 48.6/45.7, 49.0/51.4, 62.5/62.0, 71.7/64.7 (5 aliph. CH); 53.3/52.5, 53.0/52.4 (2 OCH_3); 115.5/114.9 (C-8), 123.5/123.1 (C-10), 147.9/148.0 (C-7a), 159.3/161.1 (CHO), 170.3/170.8, 170.7/171.8 (2 C=O, ester). – MS (145 °C); *m/z* (%): 392 (100) [M^+, ^{13}C 25/25], 333 (13), 305 (22) [$C_{19}H_{17}N_2O_2^+$; ^{13}C 4.7/4.4], 288 (63), 273 (22), 256 (11), 219 (13) [$C_{15}H_{11}N_2^+$, **32**], 218 (9), 217 (7), 158 (11) [$C_{10}H_8NO^+$, *N*-Formylisoquinolinium$^+$], 130 (8) [$C_9H_8N^+$, Isoquinolinium$^+$]. – Anal. for $C_{22}H_{20}N_2O_5$: calcd C 67.34, H 5.14, N 7.14; found C 67.07, H 5.00, N 7.34. Mol. mass (osmometry in $CHCl_3$, 37 °C): calcd 392, found 391.

Rearrangement of the Cycloadducts of Ethylene and Acrylonitrile

6,6a,7,11b-Tetrahydro-5*H*-5,7-ethanoindolo[2,3-*c*]isoquinoline (44): **40** [17] (200 mg, 0.81 mmol) in 5 mL of acid-free $CHCl_3$ rearrange spontaneously at room temp.; **44** was obtained as a colorless oil (182 mg, 91%). – IR (CCl_4): $\tilde{\nu}$ 1096 cm^{-1}, 1130, 1159 st (C-O, C-N), 1465 m, 1483 st (arom. ring vibr.), 3350 w (N–H). – ^{1}H NMR (100 MHz): Table 2.

13ß-Carbonitrile 45: The oily 1ß-carbonitrile **41** [17] (600 mg, 2.20 mmol) and 550 mg (2.40 mmol) of dry picric acid in 40 mL of methanol were refluxed for 20 min. The scarcely soluble picrate was washed with cold methanol and treated with dilute aqueous ammonia and CH_2Cl_2. The crude oily base **45** (0.56 g) gave 0.51 g (85%) of colorless needles, mp 154-155 °C. – IR (KBr): $\tilde{\nu}$ 724 cm^{-1}, 735 m, 750 st (arom. CH out-of-plane def.), 1464, 1485 st, 1600, 1609 w (arom. ring vibr.), 2235 m (C≡N), 3340 (N–H). – ^{1}H NMR (400 MHz): Table 2. Additional data: δ 2.84 (s, NH; disappears with D_2O). The clarified spectrum of **46** and evaluation of the roof effect provided the assignments of the Ar-H: 6.76 (d br, 8-H), 6.83 (td, 10-H), 7.10 (td, 9-H), 7.37 (dd, 11-H); 7.09 (dd, 4-H), 7.15 (ddd, 3-H), 7.29 (td, 2-H), 7.41 (dd, 1-H). – ^{13}C NMR (100 MHz, DEPT): Table 3. Aromatic C atoms: δ 114.6 (C-8), 122.0 (C-10); 125.3, 125.6, 126.5, 128.1, 128.4, 128.7 (6 arom. CH); 134.8, 135.6, 138.2 (3 arom. C_q), 149.5 (C-7a). – MS (100 °C); *m/z* (%): 273 (88) [M^+; ^{13}C 18/17], 245 (9) [M^+ - HCN - H, $C_{17}H_{13}N_2^+$; ^{13}C 1.8/2.0], 233 (18) [$C_{16}H_{13}N_2^+$; ^{13}C 3.2/3.1], 220 (100) [M^+ - Acrylonitrile; ^{13}C 17/18], 219 (97) [$C_{15}H_{11}N_2^+$, **32**], 218 (17) [219 - H], 204 (11) [$C_{15}H_{10}N^+$], 130 (14) [$C_9H_8N^+$, Isoquinolinium$^+$], 109.6 (12) [219/2, $C_{15}H_{11}N_2^{++}$], 77 (2.8) [$C_6H_5^+$]. – Anal. for $C_{18}H_{15}N_3$: calcd C 79.09, H 5.53, N 15.38; found for **45** (**46**) C 79.09 (79.22), H 5.69 (5.58), N 15.21 (15.15).

13α-Carbonitrile 46: Correspondingly, the crystalline carbonitrile **42** [17] (500 mg, 1.83 mmol) was

reacted with picric acid (500 mg, 2.18 mmol) in 30 mL of methanol; 0.41 g of oily **46** furnished 0.38 g (77%) of fine colorless needles, mp 188-189 °C. – IR (KBr): ν 2230 cm^{-1} (C≡N), 3360 m (N–H). – ^1H NMR (400 MHz): Tables 2 and 4. Further data: δ 2.52 (s br, NH). – ^{13}C NMR (100 MHz, DEPT): Tables 3 and 4. Further data: δ 132.1, 136.9, 137.6 (3 arom. C_q), 153.0 (C-7a).

13ß-Chloro-13α-carbonitrile 47: The same procedure with picric acid (1.00 g, 4.37 mmol) converted the cycloadduct **43** [17] (1.00 g, 3.25 mmol) to 850 mg (85%) of oily base **47** which crystallized slowly from $CHCl_3$/ether at -10 °C; mp 125-127 °C. – IR (KBr): $\tilde{\nu}$ 698 cm^{-1} br (C–Cl), 741, 752 st (arom. CH out-of-plane def.), 1464, 1481 st, 1600, 1608 m (arom. ring vibr.), 2225 w (C≡N), 3350 (N–H). – ^1H NMR (400 MHz): Table 2. The comparison with the δ_H of **46** provides the substituent effect of *trans-vic*-Cl on the 12α-H ($\Delta\delta$ = +0.79 ppm); those of *cis-vic*-Cl on 12ß-H (+0.09 ppm) and 5-H (+0.03 ppm) are marginal. A similar divergence of the increments, *trans-vic*-Cl > *cis-vic*-Cl, was reported for the precursor pair.[17] Further data: δ 3.28 (s br, NH), 6.89 (dt, 8-H), 6.95 (td, 10-H), 7.14 (td, 9-H), 7.22 (tt, 3-H), 7.29 (dd, 4-H), 7.35 (td, 2-H), 7.46 (dd, 1-H), 7.49 (td, 11-H). – ^{13}C NMR (100 MHz, DEPT): Table 3. Further data: 115.4 (C-8), 117.5 (CN), 123.3 (C-10); 125.4, 126.5, 128.1, 128.7, 128.8, 129.8 (6 arom. CH); 131.9, 135.4, 136.2 (3 arom. C_q), 150.3 (C-7a). – Anal. for $C_{18}H_{14}ClN_3$: calcd C 70.24, H 4.59, N 13.65; found C 70.32, H 4.80, N 13.46.

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REFERENCES AND NOTES

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