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PYRROLOTETRAZOLES AND RING-FUSED DERIVATIVES

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Abstract – The preparative chemistry of seven types of pyrrolotetrazoles (formally: pyrrolo[1,2-*d*]tetrazoles) **A**–**G** including five ring-fused derivatives such as **B'**, **B''**, **C'**, **C''**, and **E'** is surveyed in this article. Theoretical work on annular tautomerism and pyrrolotetrazole–azidopyrrole isomerism is dealt with complementarily.

INTRODUCTION

Among the plethora of tetraazapentalenes the title systems are unique for the extremely unsymmetrical distribution of their nitrogen atoms: all are gathered in one of the two half-rings (Figure 1). A specific review of the field has not been produced so far, but certain parts have been surveyed in a wider context. Thus, two overviews appeared in the series of 'Comprehensive Heterocyclic Chemistry', the first treating the systems **A**, **B**, and **E** with literature coverage till the mid 1990s,[1] the second (an update) dealing with the types **A**, **B**, **B'**, **D**, **E**, **E'**, and **F** while considering work till the mid 2000s.[2] Moreover, a twenty-year-old review on (benzo-)fused systems **B'** and **E'** and their triazole analogues is available.[3] The proper aim of this report is to illustrate the preparative chemistry as it developed from a few starts in the 1930s to the present. The material will be organized in eleven Sections, as outlined overleaf.

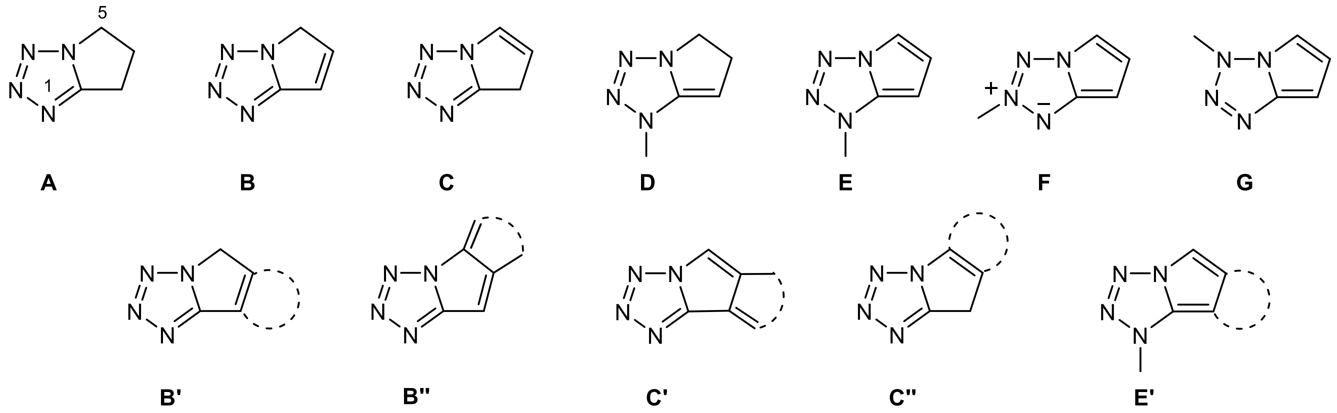


Figure 1. Title systems **A – G** including ring-fused derivatives **B', B'', C', C''**, and **E'**

1) 6,7-Dihydro-5*H*-pyrrolotetrazoles (A)

a) Synthesis: (i) Intramolecular cyclization of 4-azidoalkanenitriles; (ii) Conversion of pyrrolidine derivatives; (iii) Miscellaneous

b) Reactions: (i) *C*-Alkylation and quaternization; (ii) Ring opening; (iii) Coordination with iodine

2) 5*H*-Pyrrolotetrazoles (B)

a) Synthesis: (i) Intramolecular cyclization of 4-azidoalk-2-enenitriles; (ii) Ring closure of 2-functionalized pyrroles; (iii) Intramolecular Wittig reaction

b) Reactions: Quaternization and acylation

3) Ring-fused derivatives B' and B'' of 5*H*-pyrrolotetrazoles (B)

a) Synthesis: (i) Intramolecular azido/cyano cycloaddition; (ii) From hydrazinopyrrole derivatives; (iii) From diazidobenzoquinones

b) Reactions: (i) *C*-Alkylation; (ii) Degradation of tetrazole ring

4) 7*H*-Pyrrolotetrazoles (C) and ring-fused derivatives C' and C''

Synthesis (not specified)

5) Pyrrolotetrazole–azidopyrrole isomerism of the classes A–C

6) 5,6-Dihydro-1*H*-pyrrolotetrazoles (D)

Synthesis (not specified)

7) 1*H*-Pyrrolotetrazoles (E)

a) Synthesis: (i) Cyclization of 1-substituted 4-(2-acylalkyl)-5-(acylmethyl)tetrazolium salts; (ii) Cyclization of 1-substituted 4,5-bis(acylmethyl)tetrazolium salts with carboxylic acid derivatives; (iii) *N*-Substitution of 5*H*-pyrrolotetrazoles (**B**)

b) Reactions: (i) Protonation, S_E-reactions, and additions to activated multiple bonds; (ii) Pyrrole ring opening of 5-nitroso- and 5-phenylazo derivatives

8) Ring-fused 1*H*-pyrrolotetrazoles: 1*H*-tetrazoloisoindoles (E')

a) Synthesis (not specified)

b) Reactions: (i) S_E-Reactions and additions to heteroallenes; (ii) Tetrazole ring opening

9) 2*H*-Pyrrolotetrazoles (F)

a) Synthesis: (i) Cyclization of 2-substituted 4-(2-acylalkyl)-5-(acylmethyl)tetrazolium salts; (ii) Cyclization of 2-substituted 4,5-bis(acylmethyl)tetrazolium salts with carboxylic acid derivatives

b) Reactions: (i) Protonation and S_E-reactions; (ii) Addition to DMAD; (iii) Pyrrole ring opening of 5-nitroso- and 5-phenylazo derivatives

10) 3*H*-Pyrrolotetrazoles (G)

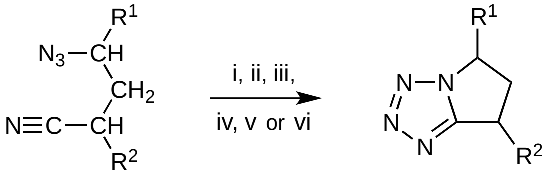
11) Experimental structural methods (i) X-Ray diffraction; (ii) Spectroscopic methods

1) 6,7-DIHYDRO-5*H*-PYRROLOTETRAZOLES (A)

a) Synthesis

(i) Intramolecular cyclization of 4-azidoalkanenitriles:

This entry is known as one of the classical routes to **A**, it proceeds readily when catalyzed by Brønsted and Lewis acids or, in certain cases, by heating the substrate in an aprotic polar solvent. The parent **Aa** and its congener **Ac** have first been prepared using Brønsted acids (Scheme 1).[4a,5] Later, in conjunction with studies on the behaviour of complex salts like nitrosyl tetrafluoroborate as well as hexafluoroantimonate towards 4-azidobutanenitrile (**1a**), it became apparent that also Lewis acids work well: thus, addition of boron trifluoride or antimony pentafluoride to the said nitrosyl salts improved the yield of **Aa** considerably (62 *vs.* 28 and 100 *vs.* 62%, respectively) and, moreover, separate experiments demonstrated that Lewis acids *alone* were capable to induce ring closure very rapidly.[6] This finding seems to have been overlooked by workers who, decades later, discovered boron trifluoride to be a powerful means for 'facile' cyclization such as to promote the processes (**1a** → **Aa**) and (**1b** → **Ab**).[7]



1a-c **Aa-c**

i: $ClSO_3H$, $CHCl_3$, 20−40 °C ii: conc. H_2SO_4, CCl_4, 30 °C iii: $NO[BF_4]$, $CHCl_3$, 25 °C
iv: $NO[SbF_6]$, $CHCl_3$, 25 °C v: $BF_3 \cdot OEt_2$, $MeNO_2$, 0 °C to rt vi: fuming H_2SO_4, $CHCl_3$, 30 °C

1, A	R^1	R^2	method	yield (%)	mp (°C)	ref.
a [a]	H	H	i or ii	~ 100	110	4a
			i	74	110	5
			iii [b]	28	[c]	6
			iv [d]	68	[c]	6
			v	99	[c]	7
b [e]	H	OMe	v	95	[c]	7
c	Et	Me	vi	92	[f]	4a

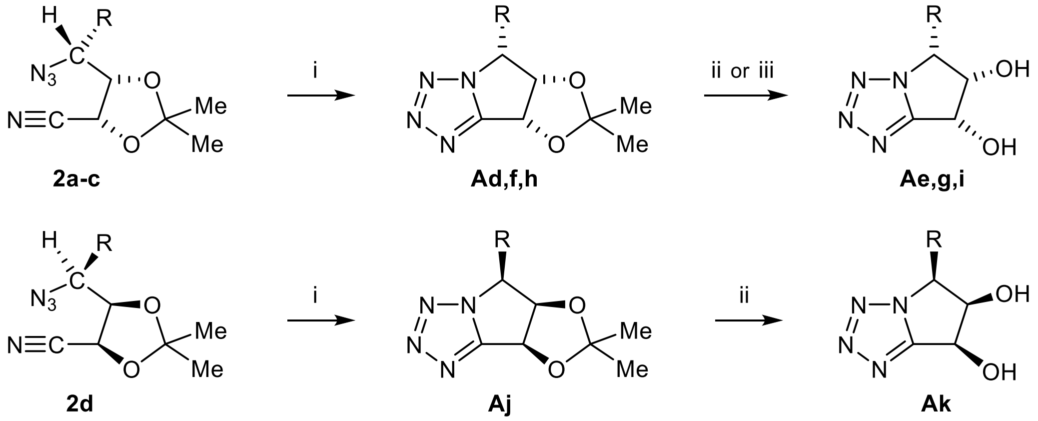
[a] For an X-ray analysis of **Aa**, see ref. 4b. [b] Besides 26−37% fluorobutanenitriles and 4–5% butenenitriles. [c] Unreported. [d] Besides 4–10% fluorobutanenitriles and 8–10% butenenitriles. [e] **1b**: Generated *in situ* from 3,3-dimethoxypropyl azide and $Me_3SiCN/BF_3 \cdot OEt_2$. [f] Oil, bp_1 160 °C.

Scheme 1

The cyclization reaction (**1** → **A**) has also been studied by DFT/B3LYP calculations including substrates having R^1 = H, R^2 = Me or OMe (≡ **1b**, **Ab**) as well as R^1/R^2 = CH_2OCH_2.[8]

The above synthetic principle has been extended to make tetrazole analogues of hexoses in the furanose form (Scheme 2): The azidonitrile **2a** (obtained from D-mannose), on being heated in DMSO, slowly cyclized to compound **Ad** which on hydrolysis gave the 'D-mannotetrazole' **Ae** in good yield. Similarly, the substrates **2c**,**d** led – *via* the acetonides **Ah**,**j** – to the 'D- and L-rhamnotetrazoles' **Ai** and **Ak**.[9a,b] Also a diastereomer of **Ae**, *i.e.* compound **Ag**, has been prepared in this way.[10]

The sugar mimics **Ae**,**i**,**k** have been shown to act as glycosidase inhibitors: the derivatives **Ae**,**i** inhibit β-mannosidase in human liver (α-mannosidase being unaffected),[11a] whereas **Ak** affects α-rhamnosidase in *P. decumbens*.[11a,b]



i: DMSO, 110 °C, 160 h (with **2a**), 110 − 120 °C, 115 h (with **2c**) or 186 h (with **2d**)

ii: CF_3CO_2H/H_2O (1/1), rt, 28 h (with **Ad**), 23 h (with **Ah**) or 22 h (with **Aj**) iii: acid (no details) (with **Af**)

2	A	R	method	yield (%)	mp (°C)	ref.
a	**d**	(*R*)-1,2-dihydroxyethyl	i	92	153 − 154	9a,b
	e	(*R*)-1,2-dihydroxyethyl	ii	75	110	9a,b
b [a]	**f**	(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl	[b]	89	126.5 − 127.5	10
	g	(*S*)-1,2-dihydroxyethyl	iii	[c]	[c]	10
c	**h**	(*R*)-1-hydroxyethyl	i	87	147 − 152	9a,b
	i	(*R*)-1-hydroxyethyl	ii	85	161 − 163.5	9a,b
d	**j**	(*S*)-1-hydroxyethyl	i	90	150.5 − 152	9a,b
	k	(*S*)-1-hydroxyethyl	ii	82	162.5 − 164	9a,b

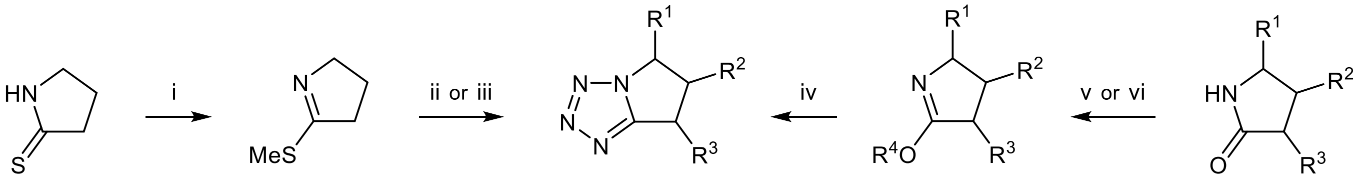
[a] Intermediate, generated *in situ* from the diastereomeric mesylate and sodium azide.
[b] Details unreported. [c] Unreported.

Scheme 2

(ii) Conversion of pyrrolidine derivatives:

This principle was first realized in the late 1950s, namely as a two-step procedure consisting in methylation of pyrrolidine-2-thione (**3**) to give the thioimidate **4** (30%) followed by action of hydrogen azide to afford the target compound **Aa** (20%) (Scheme 3).[12] The low yield of the latter was improved later by modifying the handling of **4**.[13], [14a] This easy entry to class **A** is also possible with pyrrolidinones

6, as exemplified by the sequences (**6a** → **5a** → **Aa**),[15] (**5b** → **Al**),[16] (**6b** → **5c** → **Am**),[17] and (**6c** → **5d** → **Ao**).[18] Hydrolysis of **Am** gave the free acid **An** as the target proper. The latter material, like further carboxy-substituted bicyclic hetero systems, served as a building block for a hydroxymethyl pyrrolidine as β3 adrenergic receptor agonist,[17] whereas compound **Ao** – along with close analogues – was converted to the corresponding urea (R^3 = 4-$FC_6H_4NHCONH$) having a formyl peptide receptor-like 1 agonist effect.[18]



3 **4** **Aa,l-o** **5a-d** **6a-c**

i: MeI, C_6H_6, rt, 4 h ii: HN_3, $CHCl_3$, rt, 44 h, then reflux, 2.5 h iii: HN_3, Et_2O, 40 °C, 8 h, then reflux, 5 h iv: NaN_3, AcOH, 60−70 °C, 6 h (with **5a**) or 60 °C, 48 h/5 h (with **5b**,**c**/**5d**) v: $(MeO)_2SO_2$, C_6H_6, 60−70 °C, then reflux, 3 h (with **6a**; no details with **6b**) vi: $Et_3O[PF_6]$, CH_2Cl_2, rt, 20 h (with **6c**)

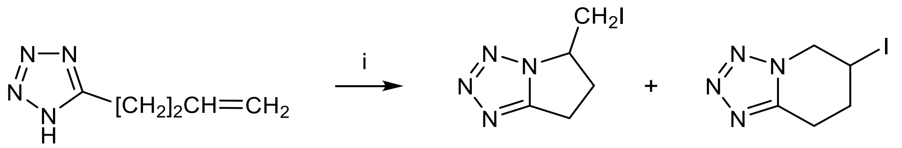
A	from	5	6	R^1	R^2	R^3	R^4	**A**: yield (%)	mp (°C)	ref.
a	**4** [a]			H	H	H		20	110	12
a	**4** [b]			H	H	H		56	109−110	13, 14a
a	**5a** [c]	**a**	**a**	H	H	H	Me	30	110	15
l	**5b**	**b**		H	Ph	H	Et	58	70	16
m	**5c**	**c** [d]	**b**	CO_2Me	H	H	Me	31	[e]	17
n [f]	**Am**			CO_2H	H	H		[e]	[e]	17
o [g]	**5d**	**d** [g]	**c** [g]	H	4-$MeOC_6H_4$	$PhCH_2OCONH$	Et	50	oil	18

[a] Method ii; yield based on **3** (yield of **4**: 30%). [b] Method iii; yield based on **4** (obtained quantitatively from **3**). [c] Yield of **5a** 63%. [d] From **6b** after the procedure decribed for **5a** by A. E. Wick, P. A. Bartlett, and D. Dolphin, *Helv. Chim. Acta*, 1971, **54**, 5139. [e] Unreported. [f] Crude product, prepared: LiOH, THF/H_2O/MeOH, 60 °C, 16 h. [g] R^2, R^3 *trans* configured.

Scheme 3

(iii) Miscellaneous:

Studying the effect of iodine on *N*-unsubstituted tetrazoles having a C(5)-substituent with an ω-unsaturation, 5-(but-3-enyl)tetrazole (**7**) was reported to undergo iodocyclization to afford a 72% yield of a 1 : 1 mixture of the (iodomethyl)pyrrolotetrazole **Ap** and the ring-enlarged product **8** (Scheme 4).[19]

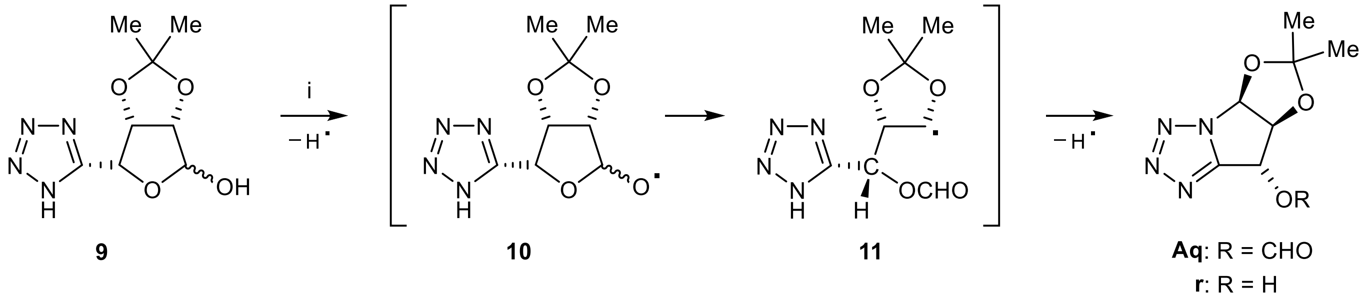


7 **Ap** **8**

i: I_2, $NaHCO_3$, MeCN, 0 °C, 3 h

Scheme 4

In conjunction with the synthesis of tetrazole-fused glycosides through a tandem fragmentation–cyclization process it was found that the hemiacetal **9**, on treatment with iodosobenzene/iodine and photoirradiation, gave the product **Aq** (Scheme 5). The reaction started by generating the radical **10** which in turn led to **11** as precursor of **Aq**. Compound **Ar** resulted from hydrolysis of the formate group during work-up.[20]

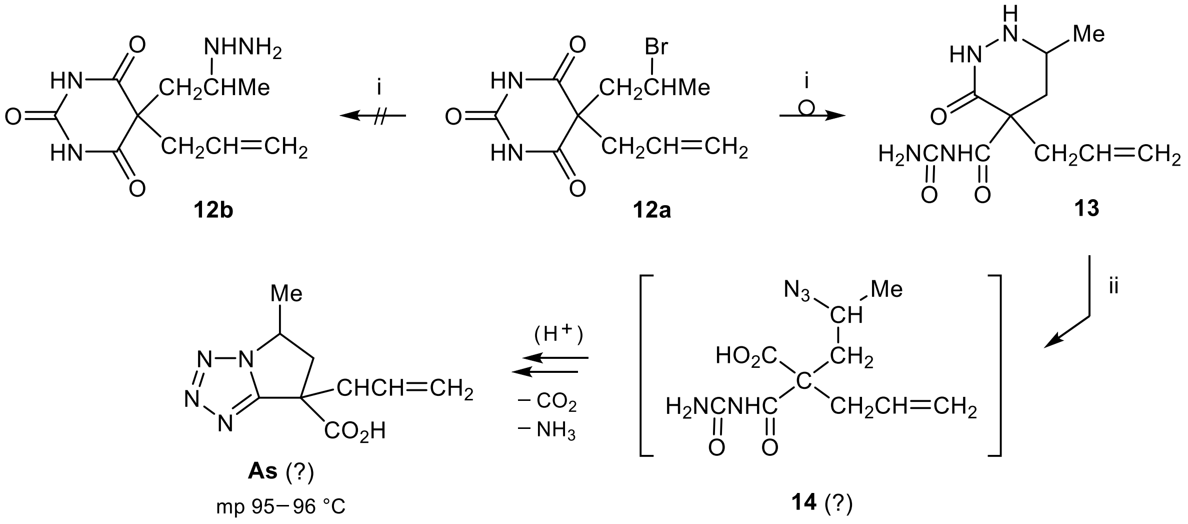


i: PhIO/I_2, AcOEt, hν, reflux, 1 h

A	yield (%)	mp (°C)	ref.
q	56	oil	20
r	9	145.4−147.1	20

Scheme 5

In an attempt to convert the barbituric acid **12a** into the hydrazine congener **12b** the perhydropyridazine derivative **13** was obtained instead (Scheme 6). In order to establish its structure, the material was treated with nitrous acid to give, *inter alia*, a compound that was viewed as the pyrrolotetrazole **As**. Its formation was proposed as proceeding through the azide **14**.[21] A reinvestigation of this work seems desirable.



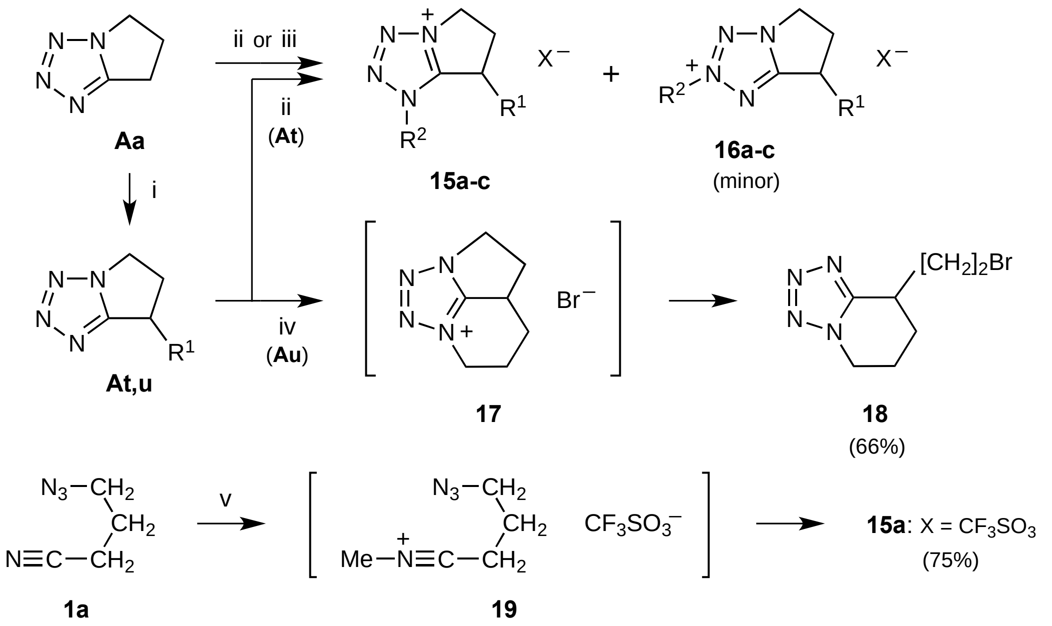
i: $NH_2NH_2 \cdot H_2O$ (90%), EtOH, reflux, 3.5 h ii: $NaNO_2$/HCl, 0 °C, 45 min

Scheme 6

b) Reactions

(i) *C*-Alkylation and quaternization:

Formally representing 1,5-dialkyltetrazoles, compounds **A** are susceptible to deprotonation at C(7) and quaternization (Scheme 7). The former mode allowed the conversion into 7-alkyl derivatives such as **At**,**u**.[22a] The second reaction has been reported as early as 1963 when **Aa** was treated with dialkyl sulfates to give the salts **15a**,**c**.[23] Most likely, the isomers **16a**,**c** had formed too, but at that time the ambident behaviour of 1(,5)-(di)substituted tetrazoles had not been recognized yet. Only in later experiments, performed with **Aa**,**t**, those side products, *i.e.* **16a**,**b**, were observed indeed.[22a] A route that circumvents the formation of **16** consists in the intramolecular cyclization of γ-azidonitrilium salts like **19**; the procedure requires rigorous exclusion of traces of acids and moisture.[22a] Another intramolecular process, however, failed: the anticipated quaternary salt **17** isomerized to the tetrazolopyridine derivative **18**, obviously due to ring strain.[22a] – The above mentioned compounds **15** served as starting materials for class **D** [see Section (6)].



i: BuLi, THF, −78 °C; then MeI (for **At**) or $Br[CH_2]_3Br$ (for **Au**), overnight to rt
ii: $(MeO)_2SO_2$ (neat), 120 °C, 1 h (ref. 22a) or 100−110 °C, 15 min (ref. 23) iii: $(EtO)_2SO_2$ (neat), 130 °C, 1 h
iv: 1,2-$Cl_2C_6H_4$, 175 °C v: CF_3SO_2OMe, $Cl[CH_2]_2Cl$, 2,6-di-*tert*-butylpyridine, reflux, 4 h

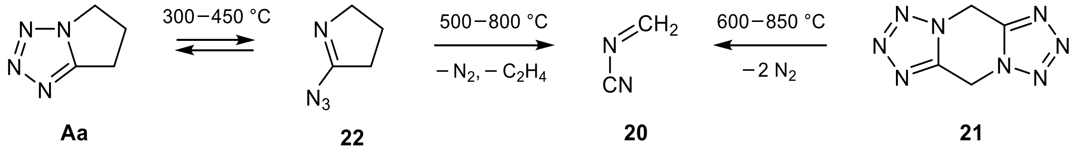
A	R^1	yield (%)	mp (°C)	ref.	**15** [a], **16** [b]	R^1	R^2	X	ref.
t	Me	73	52−53	22a	**a**	H	Me	$MeOSO_3$	22a, 23
u	$[CH_2]_3Br$	53	oil	22a	**b**	Me	Me	$MeOSO_3$	22a
					c	H	Et	$EtOSO_3$	23

[a] **15a** isolated as PF_6 salt (60%)[22a] or used as such (no yield),[23] **15b** isolated as PF_6 salt (56%),[22a] **15c** used as such (no yield).[23] [b] **16a,c** not mentioned in ref. 23.

Scheme 7

(ii) Ring opening:

Submitted to flash vacuum pyrolysis at ≥ 500 °C, compound **Aa** extruded molecular nitrogen and ethylene to give *N*-cyanoformaldimine (**20**) (Scheme 8).[13,14a–c] This material could be trapped at 77 K, it was found stable in the gas phase up to ~800 °C at low pressure and short contact times (in the solid state it polymerized above –100 °C).[14a] Under the same conditions also the ditetrazolopyrazine **21** gave **20**. By contrast, gentle pyrolysis of **Aa** (< 500 °C) allowed the observation of the open-chain isomer **22** [IR band at ~2130 cm^{-1} (77 K)], but on being warmed to room temperature it reverted to **Aa**. This demonstrates that under normal conditions the equilibrium (**Aa** ⇄ **20**), first addressed in 1959,[12] lies on the tetrazole side [*cf.* Section (5), Table 2, series (***1***)]. Above 500 °C also the azide **22** disappeared in favour of **20**.[14a]



Scheme 8

(iii) Coordination with iodine:

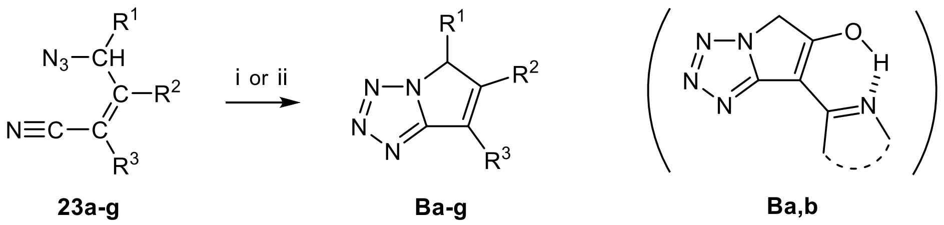
The donor ability of **Aa** in the iodine charge-transfer complex was studied in 1,2-dichloroethane, showing formation constants K_f, M^{-1} (°C) such as 2.10 ± 0.03 (5), 1.63 ± 0.04 (15), 1.42 ± 0.09 (25), 1.16 ± 0.06 (35). Higher homologues of **Aa** gave somewhat greater values, but the donor properties are altogether quite weak.[5]

2) 5*H*-PYRROLOTETRAZOLES (B)

a) Synthesis

(i) Intramolecular cyclization of 4-azidoalk-2-enenitriles:

Adopting the method suitable for class **A** [see Section (1. a)], treatment of 4-azidoalk-2-enenitriles like **23** with Brønsted acids resulted in smooth ring closure (Scheme 9). Thus, substrates such as **23a**,**b**, made from 4-chloro-2-(2-hetaryl)-3-oxobutanenitriles (stabilized as enols owing to the adjacent heterocycle), gave the first type **B** derivatives in excellent yield: the compounds **Ba**,**b** as high melting solids.[24] Later authors synthesized a range of alkyl derivatives like **Bc-e** and, apparently unaware of the preceding work, envisaged them as a new class of fused-ring heterocycle.[25] The stereo form of **23**, made from chlorobutenenitriles, turned out to be crucial: only the *Z* isomer reacted. So the parent compound **Bf** and the 5-methyl congener **Bg** could not be obtained, apparently because of an unfavourable stereochemistry (for another fruitless approach to **Bf**, attempted by an intramolecular Wittig reaction, *cf.* Scheme 12). – Extensive computational studies of the process (**23** → **B**) have been performed at the B3LYP/311++G(3df,3dp) level of theory.[26]



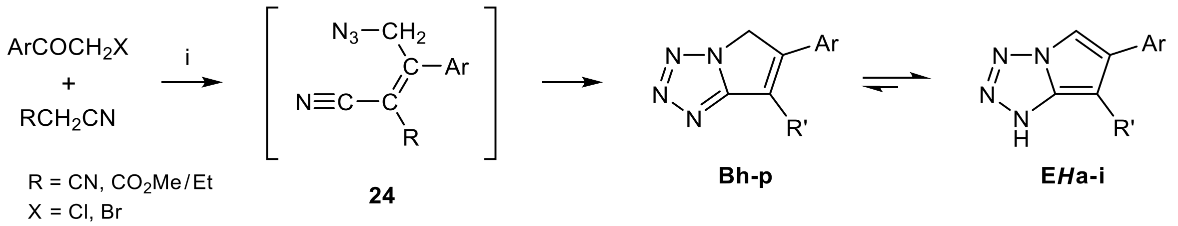
i: CF_3CO_2H, −15 °C ii: $ClSO_3H$, $CHCl_3$, rt, 0.5 h

23, B	R^1	R^2	R^3	method	yield (%)	mp (°C)	ref.
a	H	OH	Het^1 [a]	i	93	233 [b]	24
b	H	OH	Het^2 [a]	i	89	> 320	24
c	H	H	Me	ii	57	113	25
d	H	Me	H	ii	25	104	25
e	H	Me	Me	ii	73	93	25
f [c]	H	H	H	ii	0		25
g [d]	Me	H	H	ii	0		25

[a] Het^1 = 2-pyridyl, Het^2 = benzimidazol-2-yl. [b] Decomp. [c] **23f**: mixture *E*:*Z* = 7:3. [d] **23g**: *E* isomer only.

Scheme 9

More recently, derivatives such as **Bh-p** have been claimed to arise in a one-pot reaction performed with malononitrile (or alkyl cyanoacetate), phenacyl halide, and sodium azide in a basic alcoholic medium at reflux temperature (the immediate candidates for ring closure **24** eluding isolation) (Scheme 10).[27] The products **B** were not obtained as such but, according to the spectroscopic data (no ring methylene group), as the tautomers **E*H***, *i.e.* as *N*-unsubstituted derivatives of class **E**. This would match earlier HF/6-31(d,p)



i: NaN_3 (2 equiv. for **Bh-l**, 1 equiv. for **Bm-p**), K_2CO_3 (10 mol%), EtOH, reflux, 5 h

B	E*H*	R' [a]	yield (%) [b]	mp (°C)	Ar	B	E*H*	R'	yield (%) [b]	mp (°C)	ref.
h	**a**	T	48	110−111	Ph	**m**	**f**	CO_2Et	30	130−132	27
i	**b**	T	52; 48 [c]	134−136	4-ClC_6H_4	**n**	**g**	CO_2Me	31	139−141	27
j	**c**	T	47; 46 [c]	152−155	4-BrC_6H_4	**o**	**h**	CO_2Me	33	163−164	27
					4-BrC_6H_4	**p**	**i**	CO_2Et	30; 29 [c]	137−139	27
k	**d**	T	45	131−132	4-$MeOC_6H_4$						27
l	**e**	T	50	128−130	4-PhC_6H_4						27

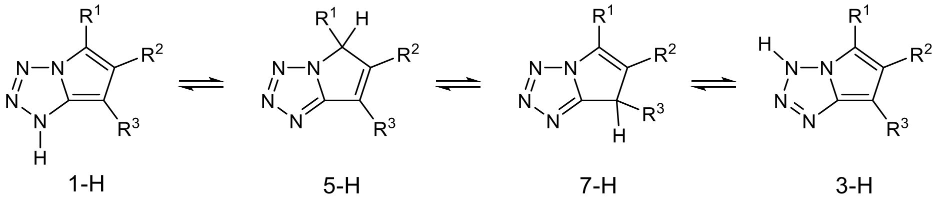
[a] T = tetrazol-5-yl. [b] Yield figures refer to reactions using $ArCOCH_2Br$ (unless otherwise stated). [c] Using $ArCOCH_2Cl$.

Scheme 10

calculations, showing that acceptor groups attached to the pyrrole half-ring shift the equilibrium from the usually favoured 5-H form towards the 1-H form [see Table 1: series (***1***–***5***) *vs.* (***6***–***11***)].[28] Considering the complementary B3LYP/6-31G(d,p) computations,[29a,b] this trend appears even more pronounced. As for the effect of the 7-ethoxycarbonyl and 7-(1*H*-tetrazol-5-yl) substituents present in the products of Scheme 10 [*cf.* series (***14***) and (***17***)], the former group favours the 1-H form more than does the latter [at least at the B3LYP/6-31G(d,p) level]. The same applies to the 'full' structures [series (***18***) and (***19***)].

In general, the 3-H forms are the least favoured tautomers. This is owing to the two adjacent azane-type nitrogens, with a non-planar (!) hydrogen at N(3). Even so, the higher energies of the species (***1***/3-H) and (***5***/3-H) compared to (***1***/5-H) and (***5***/5-H), recently determined at the B3LYP/6-311++G(3df,3pd) level to show Δ*E* 14.5 and 19.8 kcal mol^{-1}, have been commented on as 'surprising'.[26]

Table 1. Relative energies (Δ*E*, kcal mol^{-1})
of tautomeric forms of selected *N*-unsubstituted pyrrolotetrazoles [a]

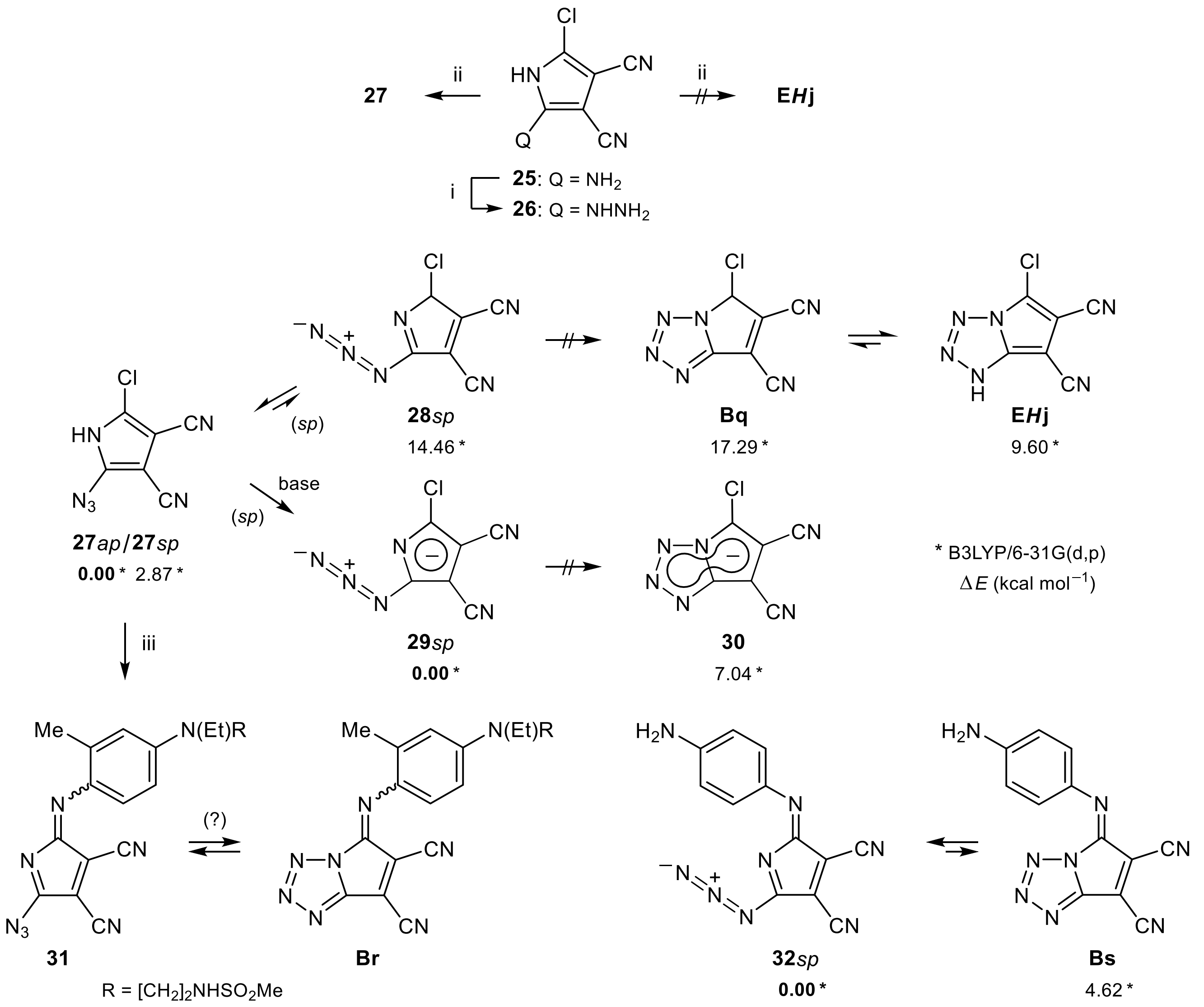


series	R^1	R^2	R^3	HF/6-31G(d,p)				B3LYP/6-31G(d,p)			
				1-H	5-H	7-H	3-H	1-H	5-H	7-H	3-H
1	H	H	H	11.27	**0.00**	2.48	24.96	4.34	**0.00**	1.71	15.91
2	Me	H	H	11.62	1.01	**0.00**	24.93	5.25	2.25	**0.00**	16.45
3 [b]	H	Me	H	13.25	**0.00**	3.11	27.45	6.43	**0.00**	2.08	18.20
4 [c]	H	H	Me	15.36	**0.00**	6.39	27.79	8.03	**0.00**	6.31	18.59
5 [d]	H	Me	Me	16.11	**0.00**	6.04	28.99	9.11	**0.00**	5.91	19.81
6	CN	H	H	0.70	0.77	**0.00**	14.80	**0.00**	8.92	4.63	11.55
7	H	CN	H	6.08	**0.00**	1.33	19.97	0.75	**0.00**	1.25	12.93
8	H	H	CN	1.10	**0.00**	6.71	18.26	**0.00**	3.98	12.09	14.24
9	CN	CN	H	**0.00**	3.14	2.45	14.04	**0.00**	11.11	6.66	11.89
10	H	CN	CN	**0.00**	3.62	8.15	17.29	**0.00**	6.42	14.01	14.56
11 [e]	Cl	CN	CN	**0.00**	3.86	7.71	16.10	**0.00**	7.69	12.80	13.46
12	E [f]	H	H	2.91	**0.00**	0.06	12.18	**0.00**	4.80	2.57	6.26
13	H	E [f]	H	9.34	**0.00**	1.62	22.41	3.27	**0.00**	1.51	14.77
14	H	H	E [f]	0.15	**0.00**	6.87	20.55	**0.00**	4.83	11.65	17.06
15	T [g]	H	H	5.04	2.42	**0.00**	17.41	**0.00**	6.45	0.40	9.59
16	H	T [g]	H	8.45	**0.00**	2.90	21.66	2.89	**0.00**	2.48	14.23
17	H	H	T [g]	5.34	**0.00**	8.61	22.77	0.27	**0.00**	9.96	14.36
18 [h]	H	Ph	E [f]	0.46	**0.00**	3.85	21.77	**0.00**	3.58	7.42	17.65
19 [i]	H	Ph	T [g]	3.93	**0.00**	9.71	25.55	1.60	**0.00**	12.17	18.71
20	[CH=CH]$_2$		H	16.33	□	**0.00**	32.23	10.22	□	**0.00**	24.05
21 [j]	H	[CH=CH]$_2$		31.01	**0.00**	□	42.03	19.75	**0.00**	□	28.29

[a] Gas phase. Values unpublished,[29a,b] save the HF/6-31(d,p) data of series (***1***–***11***).[28] [b] ***3***/5-H ≡ **Bc** of Scheme 9. [c] ***4***/5-H ≡ **Bd** of Scheme 9. [d] ***5***/5-H ≡ **Be** of Scheme 9. [e] ***11***/1-H ≡ **EHj** of Scheme 11, ***11***/5-H ≡ **Bq** of Scheme 11. [f] E = CO_2Et. [g] T = 1*H*-tetrazol-5-yl. [h] ***18***/1-H ≡ **EH*f*** of Scheme 10. [i] ***19***/1-H ≡ **EH*a*** of Scheme 10. [j] ***21***/5-H ≡ **B'x** of Scheme 28.

(ii) Ring closure of 2-functionalized pyrroles:

According to a patent claim treatment of the 2-hydrazinopyrrole **26** with sodium azide gave rise to the *N*-unsubstituted 1*H*-pyrrolotetrazole **E*H*j**; the precursor **26** had been made from the amine **25** and the latter from pyrrole-3,4-dicarbonitrile (Scheme 11).[30] However, a reinvestigation has revealed that, instead of **E*H*j**, its open-chain isomer **27** had been formed.[28] Indeed, theoretical calculations showed this species to be energetically favoured over **E*H*j**. This excludes the occurrence of the process (**27** → **28***sp* → **Bq** → **E*H*j**) as an alternative entry (the lower energy of **E*H*j** *vs.* **Bq** [*cf.* Table 1, series (***11***)] being meaningless here). Since, formally, *N*-unsubstituted 2-azido-1*H*-pyrroles can ring-close as anions, **27** was treated with base, but again no cyclization occurred.[29a] This is consistent with the energy data calculated for the species **29***sp* and **30**.



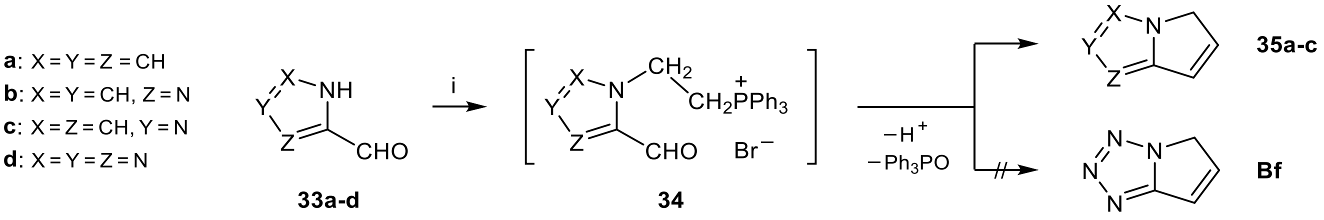
i: $NaNO_2$/HCl, 0 to 5 °C, 30 min; then $SnCl_2$/HCl, > 10 °C ii: $NaNO_2$, 0 to 5 °C
iii: 2-Me-4-[N(Et)R]$C_6H_3NH_2$, oxidant

Scheme 11

Yet, regardless of the nature of the product isolated from the reaction of **26** with nitrous acid, the material served as building block for the azomethine dye **Br** used in photography.[30] Starting from **27**, the synthesis gives the 2*H*-pyrrole **31** that may equilibrate with **Br**. But considering the Δ*E* data of appropriate models like **32***sp*, **Bs**, and those of series (***12***) in Table 2 [Section (5)], the bicycle **Br** is not necessarily present.

(iii) Intramolecular Wittig reaction:

It is well known that certain *N*-unsubstituted azolecarbaldehydes having their functional group adjacent to the pyrrole type nitrogen like **33a-c** add to triphenylvinylphosphonium bromide to form intermediates **34** that in turn undergo an intramolecular Wittig reaction to afford the pyrroloazoles **35a-c** (Scheme 12).[32,33] However, an attempt to extend this synthetic principle to tetrazolecarbaldehyde (**33d**) to get **Bf** failed.[34]



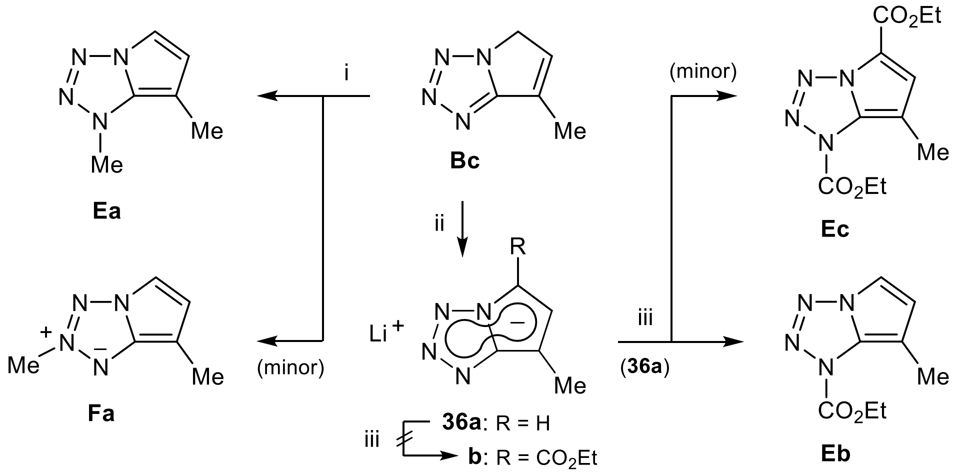
i: [CH_2=$CHPPh_3$]Br, NaH, THF or Et_2O, rt

Scheme 12

b) Reactions

Quaternization and acylation:

Just as the substrate **Aa** (*cf.* Scheme 7), the congener **Bc** was quaternized at N(1) and N(2) (Scheme 13). On addition of alkali carbonate, the acidic pyrrolotetrazolium salts were readily converted to derivatives of the



	yield (%)	mp (°C)	ref.
Ea	20	55−56	35
Eb	40	71−73	35
Ec	~ 5	76−78	35
Fa	trace	[a]	35

[a] Material unisolable.

i: $(MeO)_2SO_2$ (neat), rt, 24 h; then aq. Na_2CO_3, rt
ii: MeLi, THF, − 60 to − 20 °C, 45 min
iii: $ClCO_2Et$, − 60 to − 20 °C, 2 h

Scheme 13

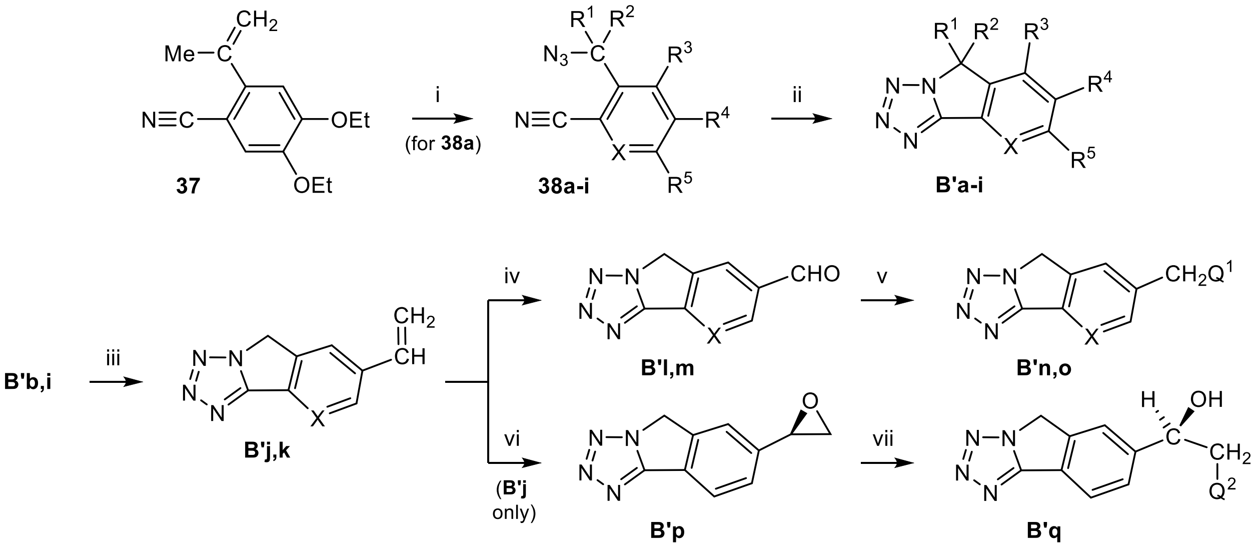
series **E** and **F**.[35] Using the stronger base methyllithium, **Bc** was deprotonated directly to generate the species **36a** which on treatment with ethyl chloroformate underwent acylation. The site attacked was originally thought to be C(5) (→ **36b**),[25] but a later study revealed that *N*-acylation occurred to give compound **Eb** besides a small quantity of the diacyl derivative **Ec**.[35] An attempt to convert **Eb** into **Ec** by treating the former with ethyl chloroformate showed that the reaction did not proceed without prior lithiation.[34, 35]

3) RING-FUSED DERIVATIVES B' AND B'' OF 5*H*-PYRROLOTETRAZOLES (B)

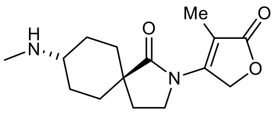
a) Synthesis

(i) Intramolecular azido/cyano cycloaddition:

The early route to 5*H*-tetrazoloisoindole (**B'**: R^{1-5} = H, X = CH)[3] was followed to give derivatives **B'a-h** by cyclizing the substrates **38a-h**; of these, **38a** reacted *in situ* when formed from **37** (Scheme 14).[36, 37a,b] The



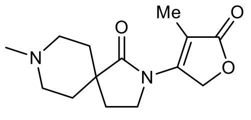
i: NaN_3, TFA, rt, 12 h ii: TFA, rt, 2 h (with **38b,c,e-h**) or rt, 3 d (with **38i**) or 140 °C/MW, 0.5 h (with **38d**) iii: $K[BF_3(CH{=}CH_2)]$, $[Pd(dppf)]Cl_2$, Et_3N, EtOH, reflux, 6 h (with **B'b**) or 80 °C, 7 h (with **B'i**) iv: $NaIO_4$, OsO_4, $MeOH/H_2O$, rt, 3 h v: Q^1H, $Ti(\textit{i}\text{-}PrO)_4$, $MeOH/CH_2Cl_2$, rt, 2 h; then $Na[BH(CN)_3]$, 0.5 h vi: $3\text{-}ClC_6H_4CO_2OH$, $CHCl_3$, 5 to 25 °C, 6 h; then CHIRALPAC AY column vii: Q^2H, Et_3N, EtOH, 90 °C, 1 h



Q^1

38, B'	R^1	R^2	R^3	R^4	R^5	X	ref.	**B'**	X	ref.
a [a]	Me	Me	H	OEt	OEt	CH	36	**j**	CH	37a
b	H	H	H	Br	H	CH	37a,b	**k**	N	37a,b
c	H	H	F	Br	H	CH	37a	**l**	CH	37a
d	H	H	Cl	Br	H	CH	37b	**m**	N	37a
e	H	H	Me	Br	H	CH	37a,b	**n**	CH	37b
f	H	H	H	Br	Me	CH	37a	**o**	N	37b
g	Me	H	H	Br	H	CH	37a,b			
h	H	H	H	H	Br	CH	37a			
i	H	H	H	Br	H	N	37a			

[a] **B'a**: Yield 87%, mp 125−126 °C; **B'b-o**: yield and mp unreported.

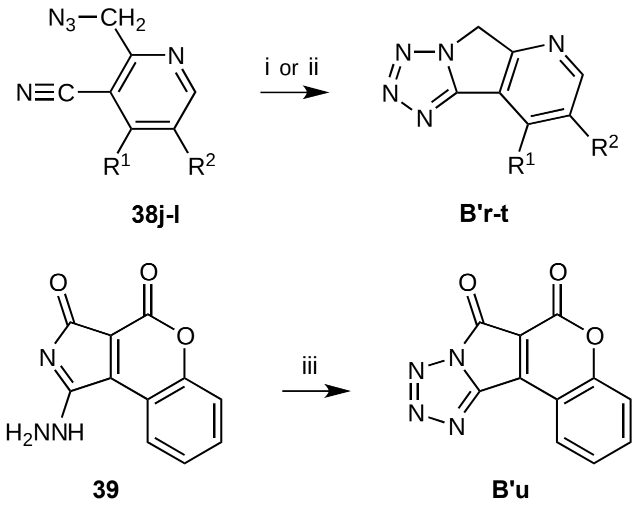


Q^2

Scheme 14

method was also feasible for the pyridine congener **B'i**.[37a] The compounds **B'b-i** served as building blocks for the stepwise synthesis of inhibitors of the renal outer medullary potassium channel, *inter alia* **B'n**,**o**,**q**. For the latter materials the bromo-functionalized derivatives **B'b**,**i** acted as key intermediates.[37a,b]

Further pyridine analogues of **B'**, such as **B'r-t**, were available by cyclizing **38j-l**, but here ring closure was achieved *via* heating – a process that was appreciably accelerated by sonication (Scheme 15).[38, 39]



i: PhMe, 130 –140 °C, 90 h (ref.38) ii: PhMe, 130−140 °C, MW, 2−4 h (ref.39)
iii: $NaNO_2$, HCl/AcOH (1:1), 0 °C to rt, 2 h

38	**B'**	R^1	R^2	yield (%)	mp (°C)	ref.
j	**r** [a]	t-Bu	H			38, 39
k	**s**	Ph	H	83 [b]	208−210 [c]	38, 39
l	**t**	$-[CH_2]_4-$				38, 39
	u			85	165−167	40

[a] For X-ray data,[38] *cf.* Section (11), Table 4. [b] By method (i);[38] otherwise only yield *ranges*: **B'r-t**, method (i) 36−83%;[38] **B'r,t**, method (ii) 80−99%.[39] [c] Decomp.

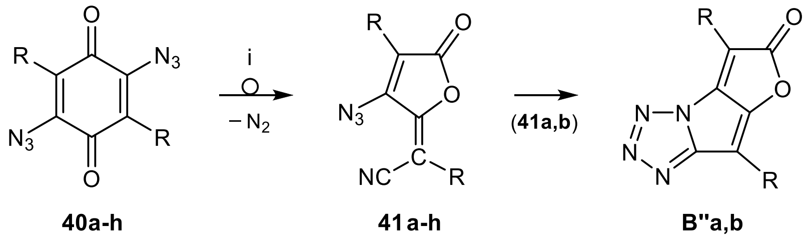
Scheme 15

(ii) From hydrazinopyrrole derivatives:

Following the route that once led to the parent 5*H*-tetrazoloisoindole,[3] treatment of the hydrazine **39** with nitrous acid afforded the derivative **B'u** (Scheme 15). This material has been prepared for cytotoxic studies which were performed together with a greater number of tetracyclic compounds of related structure.[40]

(iii) From diazidobenzoquinones:

Derivatives of class **B''** resulted in a two-step manner from 2,5-diazidobenzo-1,4-quinones **39a**,**b** having bulky ligands at C(3) and C(6) (Scheme 16): Acid catalysis generated the butenolides **40a**,**b** which in turn cyclized to give **B''a**,**b**. By contrast, when reacting **39c-h** the process stopped at the stage of **40c-h**.[41]



i: conc. H$_2$SO$_4$, 0−10 °C, 1 h

40, 41, B"	R [a]	yield (%) [b]	mp (°C)	ref.
a	*t*-Bu	76	134−136	41
b	CMe$_2$Et	80	85−90	41

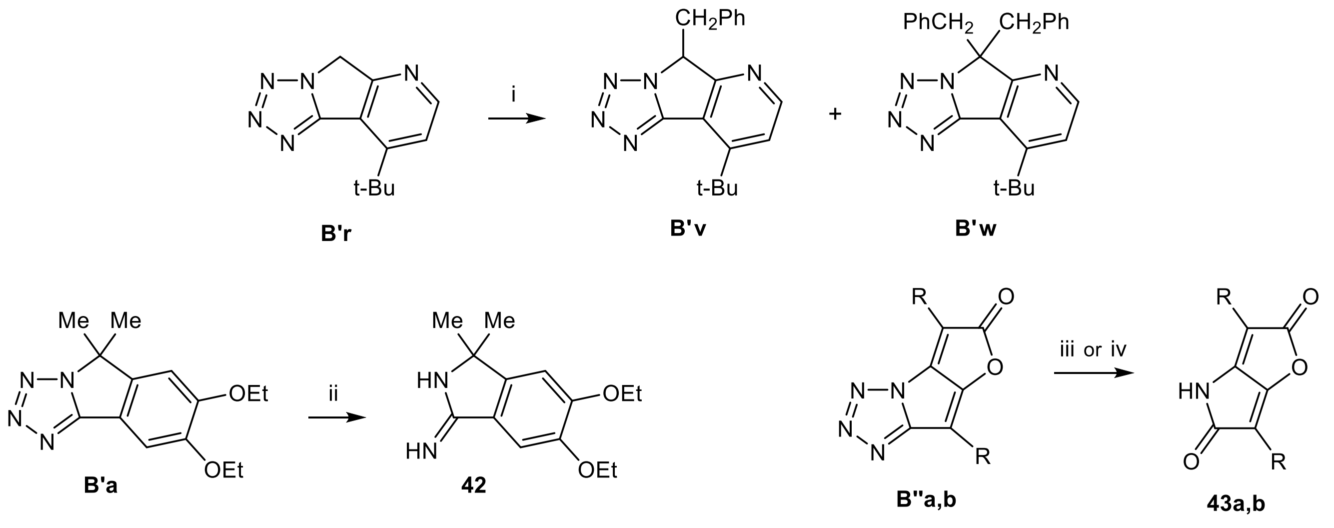
[a] **40c-h, 41c-h**: R/R = H/H (**c**), Me/Me (**d**), *i*-Pr/*i*-Pr (**e**), H/Ph (**f**), Me/*i*-Pr (**g**), *i*-Pr/Me (**h**). [b] **41c-h**: yield 28−95%.

Scheme 16

b) Reactions

(i) *C*-Alkylation:

In the presence of a strong base such as potassium *tert*-butoxide the pyridine analogue of tetrazoloisoindole **B'r** was deprotonated at C(5) (*cf.* the behaviour of **Bc** in Scheme 13) and, on addition of the alkylating agent, mono and double benzylation occurred to give a separable mixture of **B'v** and **B'w** (Scheme 17).[39]



i: t-BuOK, THF, PhCH$_2$Br, −10 °C, 3.5 h ii: Ni−Al, aq. NaOH, 0 to 70 °C, > 30 min iii: EtOH (95%), reflux, 5 min; then rt, 12 h; then briefly heated to 60 °C (with **B"a**) iv: EtOH (80%), conc. H$_2$SO$_4$ (trace), reflux, 15 min; then rt, 12 h (with **B"b**)

B'	yield (%)	mp (°C)	ref.		yield (%)	mp (°C)	ref.	**B", 43**	R	yield (%)	mp (°C)	ref.
v	33	113−114	39	**42**	81	85−87	36	**a**	*t*-Bu	76	192−193	41
w	25	195−197	39					**b**	CMe$_2$Et	53	180−181	41

Scheme 17

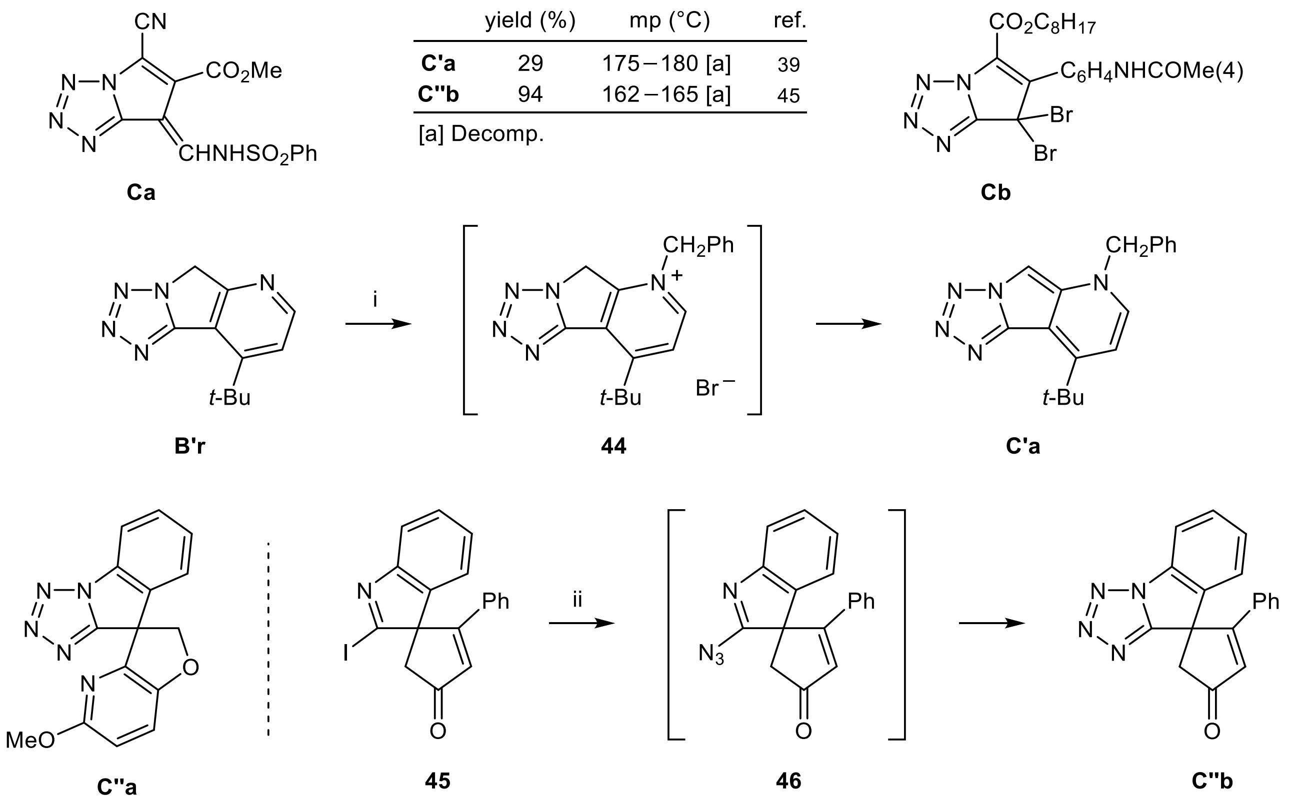
(ii) Degradation of tetrazole ring:

Treatment of the derivative **B'a** with Raney-Ni led to the amidine **42** as building block for a PAR-1 antagonist (Scheme 17).[36] The derivatives **B''a**,**b** were found sensitive towards protic media: aqueous ethanol (first at reflux, then at room temperature) converted **B''a** to the lactam **43a**; the analogue **B''b** underwent the same process (→ **41b**), but because of the bulkier substituent acid was needed in addition.[41]

4) 7*H*-PYRROLOTETRAZOLES (C) AND RING-FUSED DERIVATIVES C' AND C''

Synthesis

Alongside congeners of type **B** certain derivatives of class **C**, such as **Ca**[42] and **Cb**,[43] were presented in the patent literature on photosensitive materials; yet, preparative details were not disclosed (Scheme 18). Treatment of the derivative **B'r** with benzyl bromide in the absence of a strong base did not affect C(5), as shown in Scheme 17, but actually the pyridine nitrogen (the tetrazole ring being less nucleophilic). The resultant quaternary salt **44**, because of an enhanced acidity of the methylene group, underwent proton loss to afford the product **C'a**.[39] – Examples of class **C''** are limited to spiro derivatives of 9*H*-tetrazoloindole, *inter alia* to **C''a**[44a] and **C''b**.[45] Tetrazole formation occurred on azidation of a 2-halo-3*H*-indole precursor, in the second case by treatment of compound **45**.[45] Here the product was shown erroneously as the azide **46**,



	yield (%)	mp (°C)	ref.
C'a	29	175 – 180 [a]	39
C''b	94	162 – 165 [a]	45

[a] Decomp.

i: $PhCH_2Br$, Me_2CO, 65 °C, 80 h

ii: NaN_3, DMF, 60 °C, 1.5 h

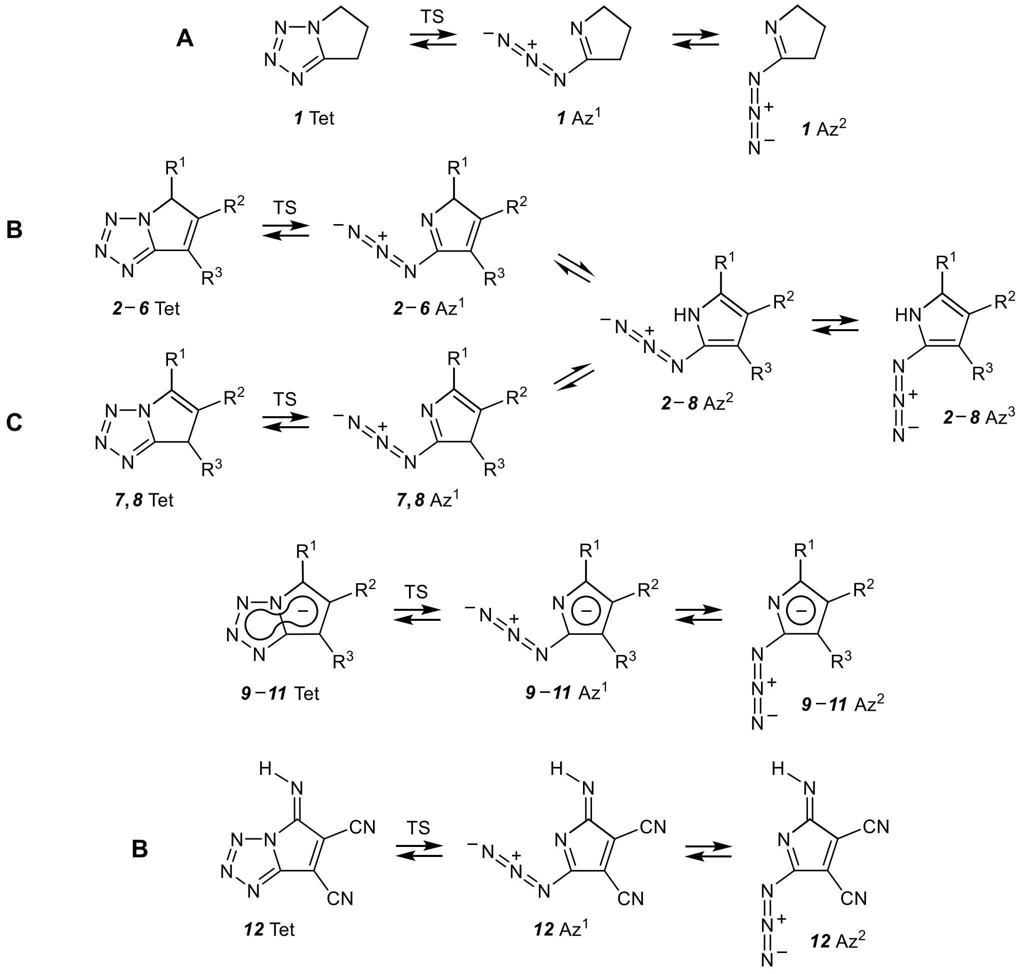
Scheme 18

although published spectroscopic data clearly point to **C''b**: IR, no azide band; ^{13}C NMR, tetrazole signal at δ 164.2 ppm[45] [*cf.* derivatives **A** and **B**: Section (11), Table 6]. Further support for the cyclic isomer came from the calculated energies (Δ*E* data) of appropriate models [see Section (5), Table 2, series (***8***)].[29a,b]

5) PYRROLOTETRAZOLE–AZIDOPYRROLE ISOMERISM OF THE CLASSES A–C

This important phenomenon is limited to the *N*-unsubstituted pyrrolotetrazoles **A**–**C**. In contrast to bicycles whose tetrazole moiety is fused to an azole in the proper sense, *i.e.* to a ring having at least one pyridine-type nitrogen atom, the present system has scarcely been looked at till now.[46] As apparent from recently calculated energy data of the involved species (Table 2),[29a,b] the equilibrium depends on both the ring system and substituents. Thus, with the series (***1***), (***3***), (***6***), (***8***), and (***9***) the bicyclic structure is favoured, whereas the opposite is true of the series (***4***), (***5***), (***11***), and (***12***), irrespective of the computational level.

Table 2. Relative energies (Δ*E*, kcal mol^{-1}) of selected pyrrolotetrazoles **A**–**C**, isomeric azidopyrroles, and transition states [a] [29a,b]



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[**Table 2** (continued)]

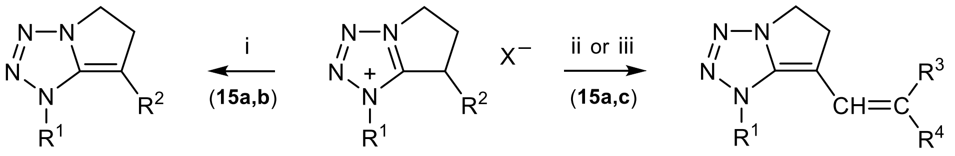
series	R^{1}	R^{2}	R^{3}	HF/6-31G(d,p) Tet	TS	Az^{1}	Az^{2}	Az^{3}	B3LYP/6-31G(d,p) Tet	TS	Az^{1}	Az^{2}	Az^{3}
1 [b]				**0.00**	38.35	10.55	16.96	□	**0.00**	26.59	9.18	12.07	□
2 [c]	H	H	H	**0.00**	35.24	6.02	7.96	4.32	2.99	26.96	7.79	2.24	**0.00**
3 [d]	H	H	Me	**0.00**	35.89	7.08	10.81	9.35	**0.00**	24.34	5.63	1.71	1.26
4	H	CN	CN	11.75	43.40	10.77	4.66	**0.00**	14.15	35.10	13.32	2.96	**0.00**
5 [e]	Cl	CN	CN	14.39	43.89	10.35	4.71	**0.00**	17.29	36.53	14.46	2.87	**0.00**
6 [f]	H	[CH=CH]$_2$		**0.00**	36.73	8.06	28.74	26.45	**0.00**	25.18	6.63	15.47	13.65
7	H	H	H	**0.00**	34.70	5.47	5.49	1.84	4.69	28.07	9.54	2.24	**0.00**
8	[CH=CH]$_2$		H	**0.00**	34.66	5.35	12.31	8.59	**0.00**	23.24	4.66	4.17	2.08
9	H	H	H	**0.00**	35.61	8.99	11.73	□	**0.00**	24.84	6.27	7.89	□
10	H	CN	CN	**0.00**	29.71	0.04	4.91	□	0.92	20.87	**0.00**	3.30	□
11 [g]	Cl	CN	CN	7.05	32.22	**0.00**	4.72	□	7.04	23.34	**0.00**	3.19	□
12 [h]				5.96	33.71	**0.00**	8.71	□	4.56	21.83	**0.00**	4.64	□

[a] Gas phase. [b] ***1*** Tet ≡ **Aa** of Scheme 1, ***1*** Az$^{1/2}$ ≡ **22** of Scheme 8. [c] ***2*** Tet ≡ **Bf** of Scheme 9. [d] ***3*** Tet ≡ **Bc** of Scheme 9. [e] ***5*** Tet ≡ **Bq** of Scheme 11, ***5*** Az^{1} ≡ **28***sp* of Scheme 11, ***5*** Az$^{2/3}$ ≡ **27***ap*/*sp* of Scheme 11. [f] ***6*** Tet ≡ **B'x** of Scheme 28. [g] ***11*** Tet ≡ **30** of Scheme 11, ***11*** Az^{1} ≡ **29***sp* of Scheme 11. [h] All *E* isomers (not shown) are higher in energy.

6) 5,6-DIHYDRO-1*H*-PYRROLOTETRAZOLES (D)

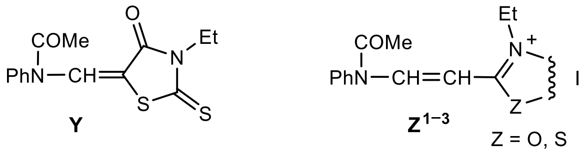
Synthesis

Deprotonation of the salts **15a**,**b** (X = PF_6) in an aprotic medium at low temperature led to the derivatives **Da**,**b**, representing elusive materials that could be observed only spectroscopically (Scheme 19).[22b] Further



Da,b **15a-c** **Dc-f**

i: KH, 18-crown-6, THF-d_8, −78 to −45 or −50°C ii: **Y** or **Z**^{1}, Et_3N, abs. EtOH, reflux, 1−4 h; then KI (with **15c**)
iii: **Z**^{2} or **Z**^{3}, Ac_2O, Et_3N, Δ, 10−15 min; then KI (with **15a** or **15c**)



Y **Z$^{1-3}$** Z = O, S

Z^{1}: Het = 3-ethylbenzoxazolium
Z^{2}: Het = 3-ethyl-4,5-dihydrothiazolium
Z^{3}: Het = 3-ethylbenzothiazolium

15	D	R^{1}	R^{2}	X	R^{3}	R^{4}	**D**: yield (%)	mp (°C)	ref.
a	**a**	Me	H	$MeOSO_3$ [a]			unisolable	oil [b]	22b
b	**b**	Me	Me	$MeOSO_3$ [a]			unisolabe	oil [b]	22b
c	**c**	Et	H	$EtOSO_3$	- - - Het of **Y** - - -		[c]	270 [d]	23
	d	Et			H	Het of **Z^{1}**	[c]	260	23
	e	Me			H	Het of **Z^{2}**	[c]	~ 130	23
	f	Et			H	Het of **Z^{3}**	[c]	250 [d]	23

[a] For generation of **Da,b**: X = PF_6. [b] Extremely unstable. [c] Unreported. [d] Decomp.

Scheme 19

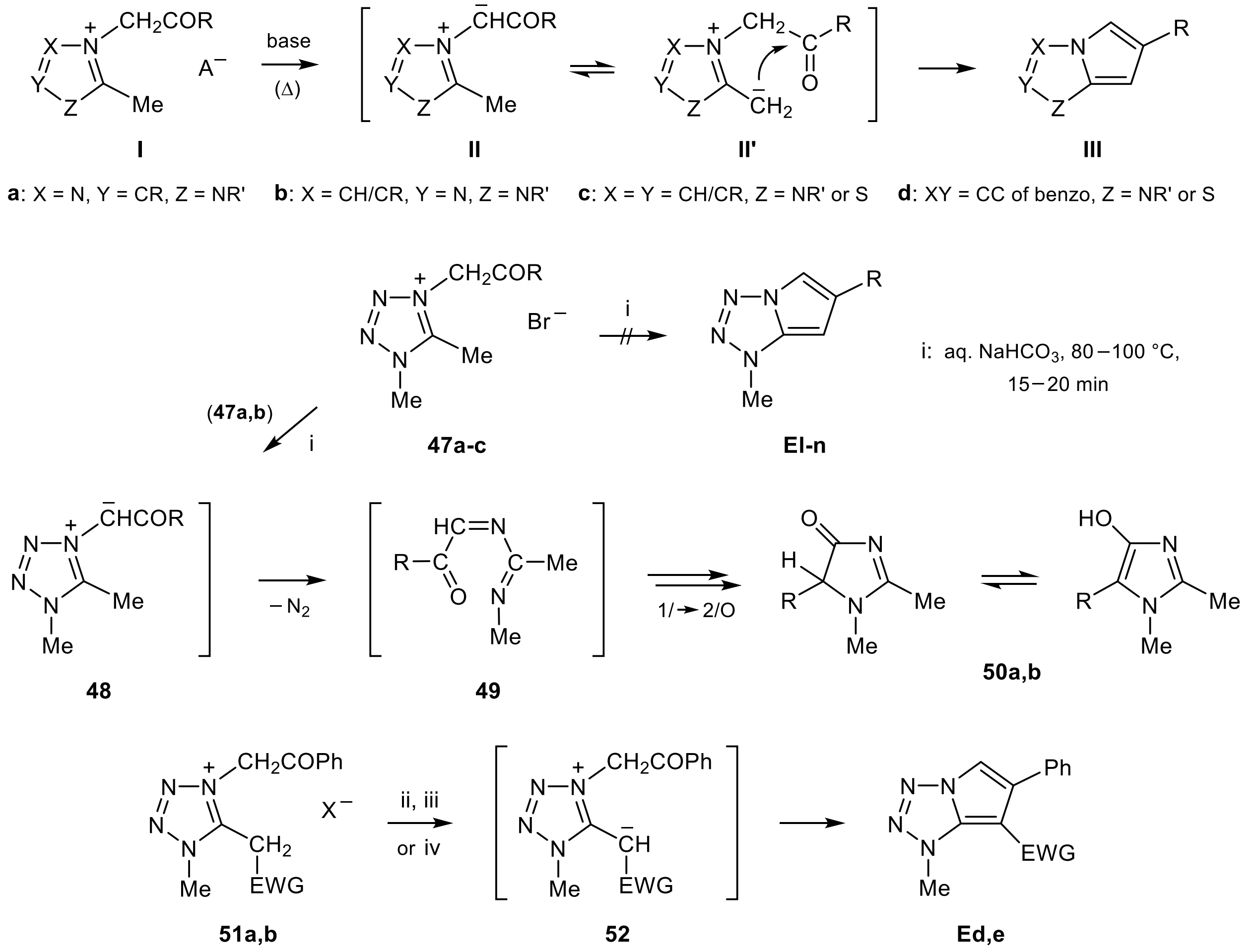
members of **D** resulted on reacting the 7-unsubstituted salts **15a,c** with the enamides **Y** and **Z**$^{1-3}$ in the presence of base and (partly) acetic anhydride, giving stable dyes like **Dc-f** for use in photography.[23, 47a]

7) 1*H*-PYRROLOTETRAZOLES (E)

a) Synthesis

(i) Cyclization of 1-substituted 4-(2-acylalkyl)-5-(acylmethyl)tetrazolium salts:

The Chichibabin-type sequence (**I** → **II** → **II'** → **III**) that allows the preparation of a wide variety of pyrroloazoles **IIIa-d**,[48] failed in the tetrazole series (Scheme 20): Being treated in the traditional manner,



a: X = N, Y = CR, Z = NR' **b**: X = CH/CR, Y = N, Z = NR' **c**: X = Y = CH/CR, Z = NR' or S **d**: XY = CC of benzo, Z = NR' or S

i: aq. $NaHCO_3$, 80−100 °C, 15−20 min

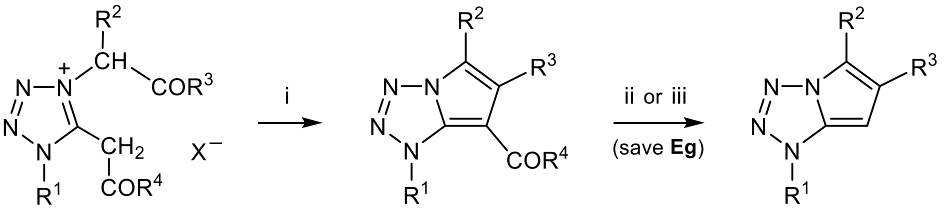
ii: aq. $NaHCO_3$, 80−100 °C, reflux, 1 h iii: aq. $NaHCO_3$, 70 °C, 2 h iv: NaOAc/AcOH, 100−110 °C, 1 h

47	E [a]	50	R	yield (%)	ref.	51	E	EWG	X	method	yield (%)	mp (°C)	ref.
a	**m**	**a**	Ph	48	49	**a**	**d**	COMe	BF_4	ii/iv	2/56; 66	93−97/92−94	29a/53; 54
b	**n**	**b**	4-BrC_6H_4	49	49	**b**	**e**	4-$NO_2C_6H_4$	$SbCl_6$	iii/iv	6/71	174	34
c	**l**		Me	see text	49								

[a] For successful synthesis of **El-n**, see Scheme 21.

Scheme 20

the quaternary salts **47a-c** did not afford the expected products **El-n**: While the substrate **47c** lost its CH_2COR group, **47a**,**b** were converted to the imidazolones **50a**,**b**.[49] Apparently the elusive *N*-ylide **48**,[50] prior to forming a '*C*-ylide' corresponding to **II'**, expelled dinitrogen to generate the transient amidine **49** which in turn stabilized by rearrangement to **50**.[51] However, more promising candidates appeared to be tetrazolium salts that have an electronegative group at the 5-methyl ligand, such as **51a**,**b**, since here the crucial '*C*-ylide' **52** arises directly.[52] Indeed, the desired pyrrolotetrazoles **Ed**,**e** could be isolated, albeit in low yield. This led to experiments under various conditions,[34] showing that only working in an acetate buffer was capable of raising the yields considerably.[53,54] This medium not only enables deprotonation of the salts **51** to give **52** but, still more important, activates the carbonyl group for intramolecular attack.



51c-h **Ef-k** **El-p**

i: NaOAc/AcOH, 100−110 °C, 1 h ii: 6−12 M HCl (EtOH), reflux, 1−4 h (with **Ef,j,k**)
iii: KOH (EtOH), reflux, 20 h; then 12 M HCl, reflux, 0.5 h (with **Eh,i**)

51	E	R^1	R^2	R^3	R^4	X	**E**: yield (%)	mp (°C)	ref.
c	**f**	Me	H	Me	Me	BF_4	86	152−154	53, 54
d	**g**	Me	H	Me	OMe	$MeOSO_3$	57 [a]	105−108	54
e	**h**	Me	H	Ph	OMe	$MeOSO_3$	82 [b]	128−129	53, 54
f	**i**	Me	H	4-BrC_6H_4	OMe	$MeOSO_3$	64 [c]	117−118	53, 54
g	**j**	Me	Me	Ph	OMe	$MeOSO_3$	52 [d]	123−125	54
h	**k**	Ph	H	Ph	Me	BF_4	82 [e]	95−96	53, 54
i	**l**	Me	H	Me			66	oil [f]	53, 54
j	**m**	Me	H	Ph			66 [g], 76 [h]	140−142	53, 54
k	**n**	Me	H	4-BrC_6H_4			58	201−203	53, 54
l	**o**	Me	Me	Ph			85	86−88	54
m	**p**	Ph	H	Ph			81	127−129	53, 54

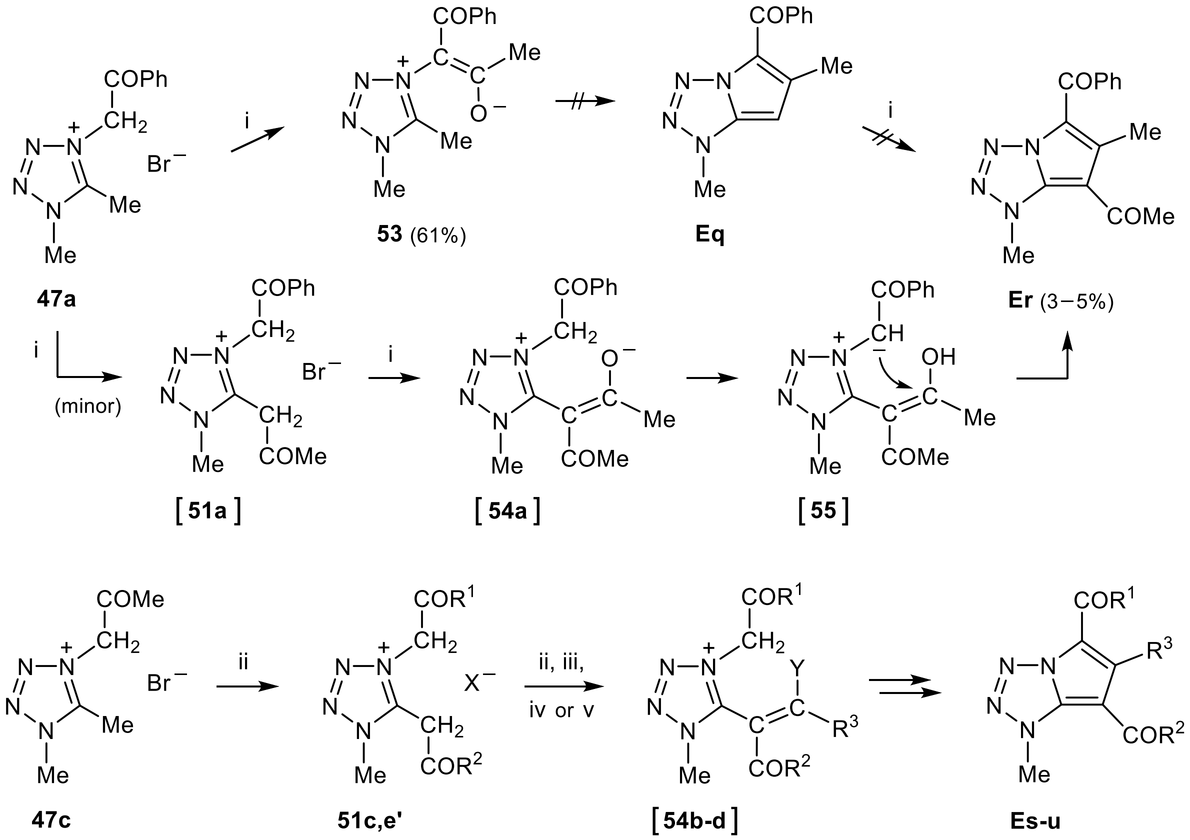
[a] Based on 6:4 mixture of **51d** and isomeric **72b** (X = $MeOSO_3$) (see Scheme 32). [b] Based on 7:3 mixture of **51e** and isomeric **72d** (X = $MeOSO_3$). [c] Based on 6:4 mixture of **51f** and isomeric **72e** (X = $MeOSO_3$). [d] Based on 7:3 mixture of **51g** and isomeric **72f** (X = $MeOSO_3$). [e] Based on 1:1 mixture of **51h** and isomeric 5-acetonyl-3-phenacyl-1-phenyltetrazolium tetrafluoroborate. [f] Mp < 0 °C; picrate: mp 102−104 °C.[54] [g] From **Ed** (see Scheme 20). [h] From **Eh**.

Scheme 21

In the above manner further pyrrolotetrazoles such as **Ef-k** were obtained very readily (Scheme 21).[53, 54] Of paramount importance was the finding that the COR^4 group in **Ed**,**f-k** can be removed very easily so as to provide derivatives like **El-p** that proved inaccessible from the salts **47**. Usually these 'auxiliary' groups were split off using hydrochloric acid, but the ester functions of **Eh**,**i** had first to be hydrolyzed with alkali.

(ii) Cyclization of 1-substituted 4,5-bis(acylmethyl)tetrazolium salts with carboxylic acid derivatives:

It is this variant of cyclizing tetrazolium salts that led to the first representative of class **E** to be isolated: the derivative **Er** (Scheme 22).[50, 55] The material occurred in low yield as byproduct of the *N*-ylide **53** which



51	R^1	R^2	X	54	Y	R^1	R^2	R^3	E
c	Me	Me	BF_4	**b**	O^-	Me	Me	Me	**s**
e' [a]	Ph	OMe	Br	**c** [b]	OEt	Me	Me	H	**t**
				d [b]	NMe_2	Ph	MeO	H	**u**

[a] From crude **51e**.[56] [b] Anion of **54c,d** (BF_4, Br) omitted.

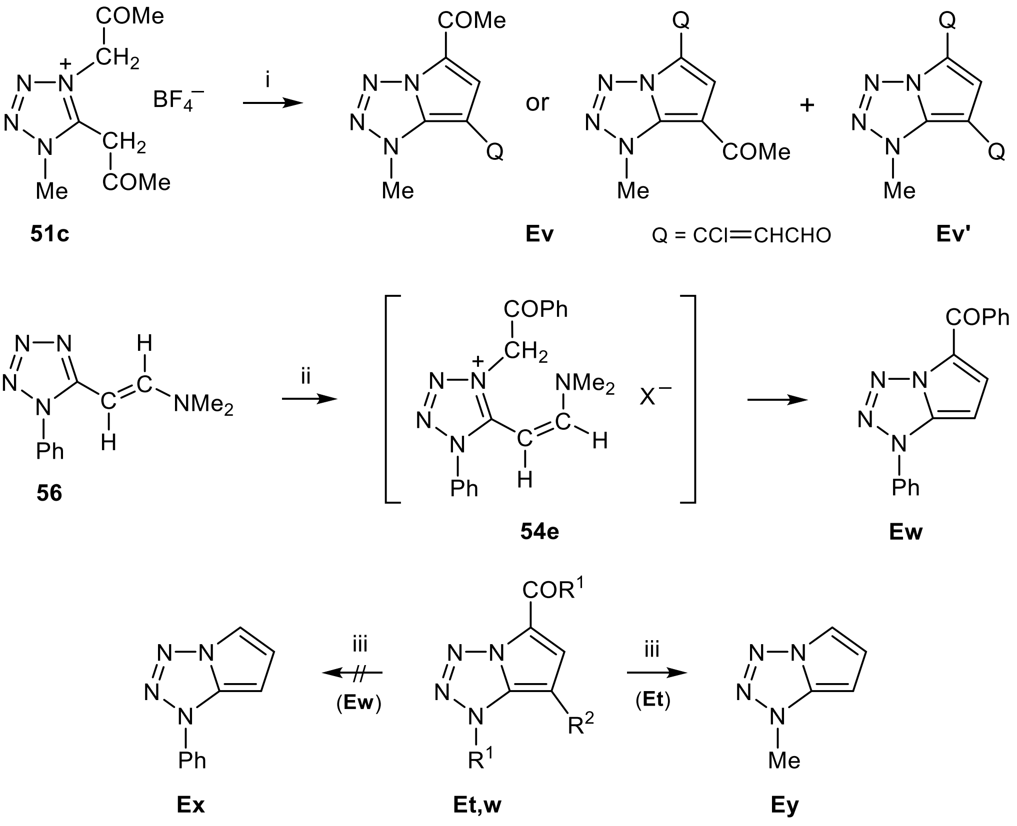
i: Ac_2O/Et_3N, rt, 48 h ii: Ac_2O/Et_3N, 90–110 °C, 1–2 h
iii: Ac_2O/Et_3N, 110 °C, 20 min; then 130 °C, 40 min
iv: $CH(OEt)_3$, EtOH, reflux, 5 h; then pyridine/piperidine (10/1), reflux, 1 h
v: $DMF/POCl_3$, 0 °C to rt, 1 h; then 15–30 min, 90 °C

E	from	method	yield (%)	mp (°C)	ref.
r	**47a** / **51a**	ii / iii	2 / 14 [a]	210	34 / 50
r	**54a** [b]	ii	8 [c]		54
s	**47c**	ii	6	130–131	50
t	**51c**	iv	41	178–180	54
u	**51e'**	v	4–14 [d]	144–147	34

[a] Besides traces of **Es**. [b] Prepared from **51a** and Ac_2O/Et_3N; 20 °C, 4 h: yield 45%, mp 134–137 °C.[54] [c] Besides 16% **Es**. [d] Yield erratic; besides traces of **Eh** (Scheme 21).

Scheme 22

was made from the salt **47a** using acetic anhydride and base at room temperature. Regarding the mechanism, **Er** did not arise *via* compound **Eq** followed by electrophilic substitution; rather, according to a known pattern,[48] stepwise acetylation of the methyl group of **47a** generated the '*C*-ylide' **54a** which, *via* **55**, gave the final product **Er**.[54] Working at higher temperature had no effect on **Er**,[34] but starting from separately prepared **54a**, the yield increased.[54] With all experiments a benzoyl–acetyl exchange took place (presumedly at the stage of **54a** or **55**) such as to give variable amounts of the 5-acetyl congener **Es**.[50,54] Expectedly, **Es** was obtained as the sole product from the 5-methyl salt **45c**, albeit in modest yield.[50]
6-Unsubstituted members **Et**,**u** were prepared from pure **49c**,**e'** and certain formic acid derivatives;[34,54] *N*,*N*-dimethylformamide diethyl acetal was unsuitable for **Eu**, as this reagent did not generate **54d** but acted as dehydrating agent to afford compound **Eh** of Scheme 21.[54] In addition, acetyl groups in **51** were found



i: DMF/POCl$_3$, 0 °C to rt, 1 h; then 15−30 min, 90 °C
ii: PhCOCH$_2$Br, MeNO$_2$, 50−55 °C, 3 h; then NaOAc/AcOH, 100−110 °C, 1 h
iii: 6−12 M HCl, 100 °C, 2.5−4 h

E	R^1	R^2	yield (%)	mp (°C)	ref.
t	Me	COMe			
v,v'			total 4		34
w	Ph	H	6	171−172	54
y			7	33−34	54

Scheme 23

sensitive towards Vilsmeier reagent: the said functions were transformed into 1-chloro-2-formylvinyl groups. This trouble was encountered in the course of the above synthesis of **Et** from **51c**: unless using triethyl orthoformate as formylating agent, a mixture of the derivatives **Ev,v'** resulted (Scheme 23).[34]

A synthetic variant resembling the route to **Eu** in Scheme 22 consists in phenacylation of the enamine **56** followed by ring closure of the intermediary salt **54e** to give, in low yield, the bicycle **Ew**. Attempts to remove the benzoyl group from the latter to obtain compound **Ex** met with failure.[34] By contrast, defunctionalization of the diacetyl congener **Et** proceeded quite readily; the low yield of **Ey** reflects the anticipated[48] instability of this compound.[54]

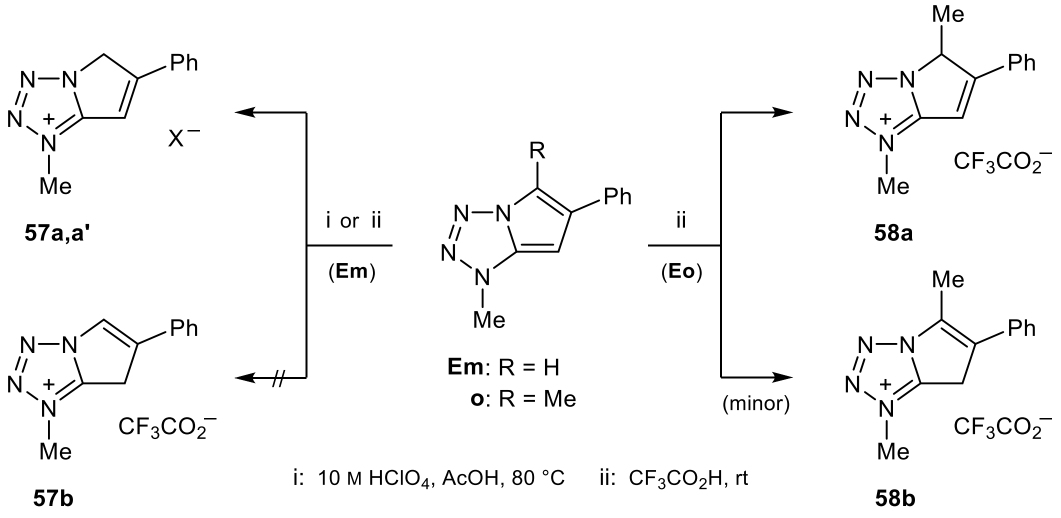
(iii) *N*-Substitution of 5*H*-pyrrolotetrazoles (**B**):

This access has been dealt with in conjunction with the reactivity of class **B** [see Section (2. b)].

b) Reactions

(i) Protonation, S_E-reactions, and additions to activated multiple bonds:

Compounds **E** are capable of forming stable salts with strong acids, as exemplified by the picrate of **El**[54] and the perchlorate **57a'** of **Em**[57] (Scheme 24). The preferred site of protonation is C(5). This was borne out by studying the substrates **Em,o** in trifluoroacetic acid: **Em** was attacked exclusively at C(5) (→ **57a**),

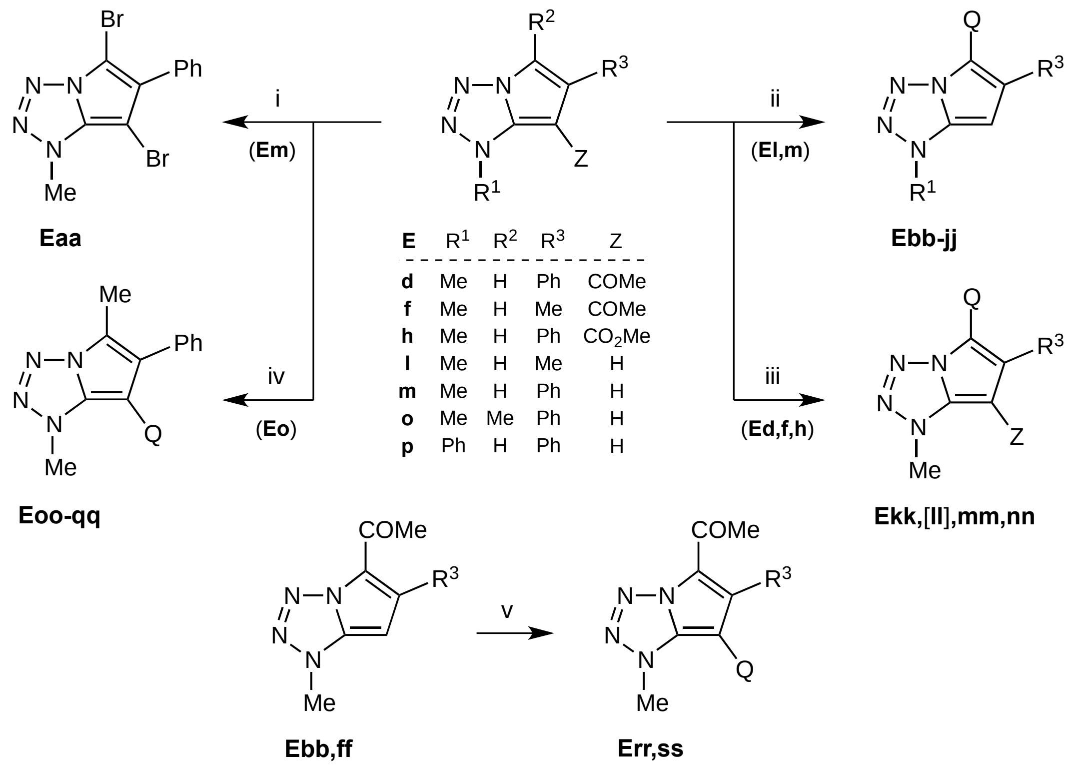


i: 10 M $HClO_4$, AcOH, 80 °C ii: CF_3CO_2H, rt

	X	ratio **a** / **b** [b]	ref.	ΔE, kcal mol^{-1} [c]		ref.
57a' [a]	ClO_4		57	[d]	[e]	
57a/**b**	CF_3CO_2	100/0	57	0.00/7.77	0.00/4.62	29a,b
58a/**b**		67/33	57	0.00/4.72	0.00/0.16	29a,b

[a] Yield 87%, mp 206−209 °C. [b] By ^{1}H NMR. [c] Calculations of cations (gas phase). [d] B3LYP/6-31G(d,p). [e] B3LYP/6-311+G(d,p) (for 6-*unsub*stituted analogues).

Scheme 24



E	R^1	R^2	R^3	Z
d	Me	H	Ph	COMe
f	Me	H	Me	COMe
h	Me	H	Ph	CO_2Me
l	Me	H	Me	H
m	Me	H	Ph	H
o	Me	Me	Ph	H
p	Ph	H	Ph	H

i: Br_2, $CHCl_3$, 0 °C, 30 min ii: Ac_2O (neat), 20 °C, 24 h (for **Ebb**) or 7 d (for **Eff**); $(PhCO)_2O$, Et_2O, rt, 12 h (for **Ecc**); $[PhN_2]Cl$, AcOH, 0 °C to rt, 15 min (for **Edd,ii,jj**); DMF/$POCl_3$, 0 °C, 45 min (for **Eee**); PhNCO, CH_2Cl_2, rt, 2 d (for **Egg**); DMAD, MeOH, rt, 1 h [for (*E*)-**Ehh**] iii: Ac_2O (neat), NaOAc, 100 – 110 °C, 2 d (for **Ekk,ll**); DMAD, MeOH, reflux, 3 h [for (*E*)-**Emm**]; $[PhN_2]Cl$, AcOH, 0 °C to rt, 1 h (for **Enn**) iv: Ac_2O (neat), 20 °C, 3 h (for **Eoo**); $[PhN_2]Cl$, AcOH, 0 °C, 15 min (for **Epp**); $NaNO_2$, AcOH, 0 °C to rt, 30 min (for **Eqq**) v: Ac_2O (neat), NaOAc, 140 °C, 2 d (for **Err**); $NaNO_2$, AcOH, 0 °C to rt, 30 min (for **Ess**)

E	R^1	R^3	Z	Q	from	yield (%)	mp (°C)	ref.
aa					**Em**	46	112 – 114	57
bb	Me	Me		COMe	**El**	67	121 – 122	57
cc [a]	Me	Me		COPh	**El**	33	170 – 171	57
dd	Me	Me		N=NPh	**El**	71	128 – 131	34
ee	Me	Ph		CHO	**Em**	68	128 – 129	57
ff	Me	Ph		COMe	**Em**	77	119 – 121	57
gg	Me	Ph		CONHPh	**Em**	38	156 – 158	57
(*E*)-**hh** [b]	Me	Ph		CE=CHE [c]	**Em**	38	131 – 133	57
ii	Me	Ph		N=NPh	**Em**	81	169 – 171 [d,e]	53, 57
jj	Ph	Ph		N=NPh	**Ep**	77	195 – 199	34
kk [f]		Me	COMe	COMe	**Ef**	23 [g]	130 – 131	57
ll		Ph	COMe	COMe	**Ed**	0		57
(*E*)-**mm** [b]		Ph	CO_2Me	CE=CHE [c]	**Eh**	40	147 – 149	57
nn		Ph	CO_2Me	N=NPh	**Eh**	64	240 – 242 [e]	53, 57
oo				COMe	**Eo**	71	67 – 69	57
pp				N=NPh	**Eo**	62	148 – 150	57
qq				NO	**Eo**	66	167 – 170	34
rr [f]		Me		COMe	**Ebb**	[h]		34
ss		Ph		NO	**Eff**	50	186 – 189 [e]	34

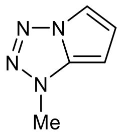
[a] Corresponds to **Eq** of Scheme 22. [b] *Z* Isomer not observed. [c] E = CO_2Me. [d] Ref. 53 mp 168 – 170 °C. [e] Decomp. [f] Corresponds to **Es** of Scheme 22. [g] Yield only 1% when working without NaOAc.[34] [h] Rate of conversion 55% (^1H NMR); compound not isolated.[34]

Scheme 25

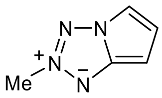
the isomer **57b** being unobserved. By contrast, the 5-methyl derivative **Eo** was protonated also at C(7) (→ **58b**), albeit to a minor extent.[57] This finding is reflected by computed energies of the respective cations, showing $E_{\mathbf{58a-58b}} < E_{\mathbf{57a-57b}}$.[29a,b]

The reactivity towards electrophiles is well documented (Scheme 25).[34, 53, 57] As a rule, monosubstitution was observed (bromination accepted) if both positions 5 and 7 are free, the preferred site of attack being C(5) to afford products such as **Ebb-jj**. This is consistent with the data of Scheme 24 and the atomic charges of the parent **Ey** [Table 3; for a comment on **Fv**, *cf.* Section (9. b)]. The electron-releasing 6-methyl group may exert an accelerating effect, as observed with acetylation (and also benzoylation[34]) of the substrate **El** compared to **Em**. Substitution at C(7) occurred only if position 5 was occupied, as evidenced by the conversions (**Eo** → **Eoo-qq**). Substrates having an acceptor ligand at C(7), such as **Ef**,**h**, proved sufficiently reactive to afford products like **Ekk**,**mm**,**nn**; however, a phenyl substituent at C(6), as present in the derivative (**Ed**), deactivates the system to such an extent as to vitiate the formation of compound **Ell**. On the other hand, a 6-phenyl substituent adjacent to an acceptor group at C(5) did not exclude an S$_E$-reaction, as shown by the conversion of **Eff** to **Ess**. Finally, attempts of nitration, *e.g.* of **Em**, remained unrewarded.[34]

Table 3. Calculated atomic charges for the parents **Ey** and **Fv** [a,b]



Ey



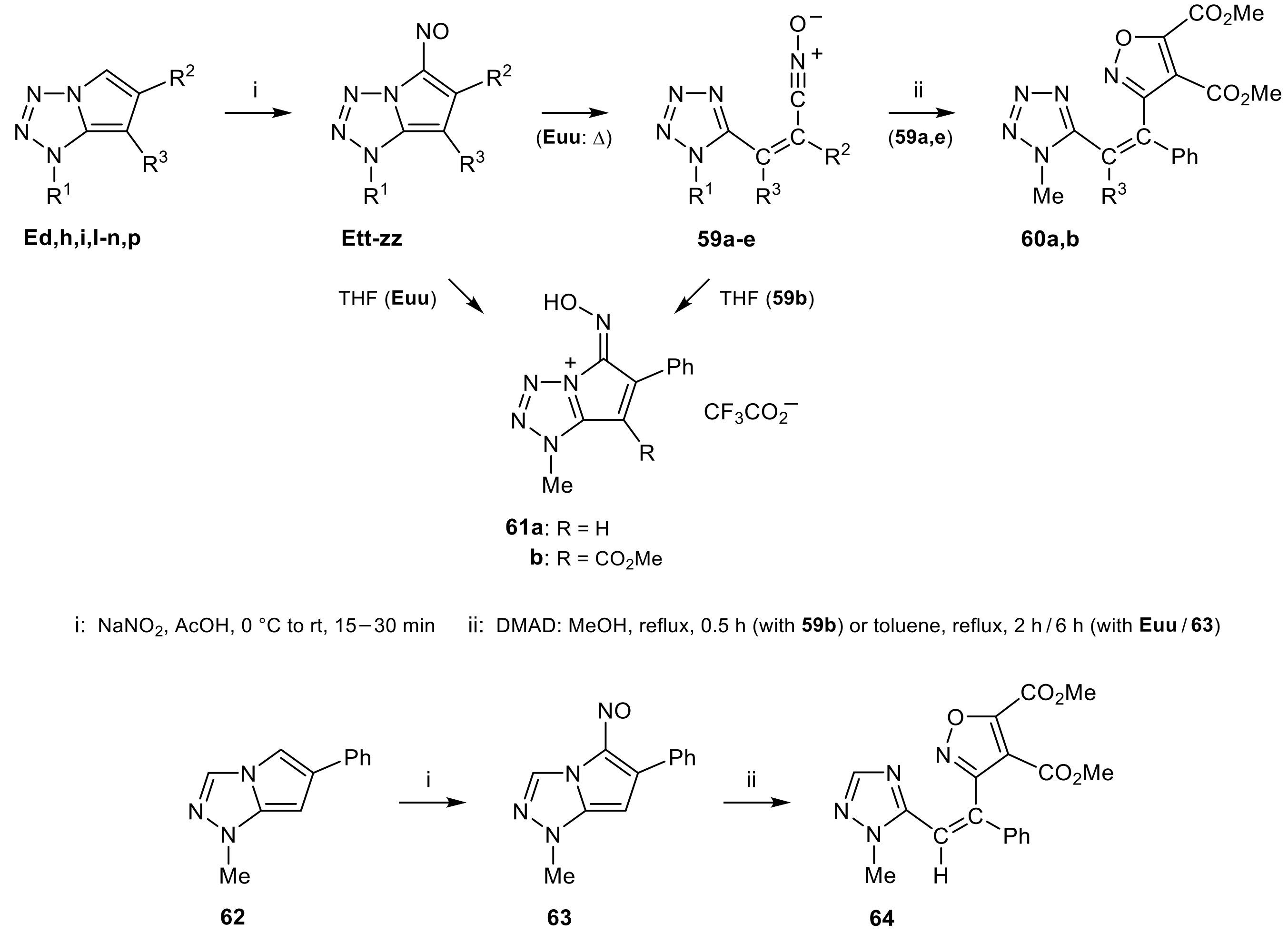
Fv

AM1		B3LYP/6-311+G(d,p)			AM1		B3LYP/6-311+G(d,p)	
total	π	total	π		total	π	total	π
–0.199	1.669	–0.070	1.515	N(1)	–0.061	1.269	–0.212	1.208
0.017	1.126	–0.035	1.158	N(2)	–0.067	1.444	0.069	1.430
0.020	1.175	–0.077	1.187	N(3)	–0.046	1.362	0.124	1.288
–0.135	1.543	0.100	1.441	N(4)	–0.048	1.417	–0.016	1.401
–0.099	1.124	–0.120	1.161	C(5)	–0.181	1.220	–0.170	1.189
–0.159	1.065	–0.258	1.034	C(6)	–0.119	1.022	–0.224	1.018
–0.197	1.166	0.161	1.162	C(7)	–0.199	1.165	0.014	1.146
–0.024	1.110	–0.389	1.114	C(7a)	–0.079	1.105	–0.296	1.104

[a] Gas phase. [b] AM1 data obtained using HyperChem, version 4.5,[57,58] B3LYP/6-311+G(d,p) data obtained using Gaussian 98.[29a,b,59]

(ii) Pyrrole ring opening of 5-nitroso- and 5-phenylazo derivatives:

Most surprising were the results of nitrosation at C(5) (Scheme 26).[53, 57] While substrates having an acceptor group at C(7) gave the expected nitroso derivatives **Ett-vv**, those with a free 7-position, *i.e.* **Eww-zz**, once formed immediately ring-opened to afford the valence-isomeric nitrile oxides **59a-d**; with DMAD they were convertible to isoxazoles, *e.g.* **59a** → **60a**. However, also the 'stable' derivatives **Ett-vv** were found susceptible to that ring opening: on being heated with DMAD, the reaction (**Euu** → [**59e**] → **60b**) occurred.



i: NaNO$_2$, AcOH, 0 °C to rt, 15−30 min ii: DMAD: MeOH, reflux, 0.5 h (with **59b**) or toluene, reflux, 2 h / 6 h (with **Euu** / **63**)

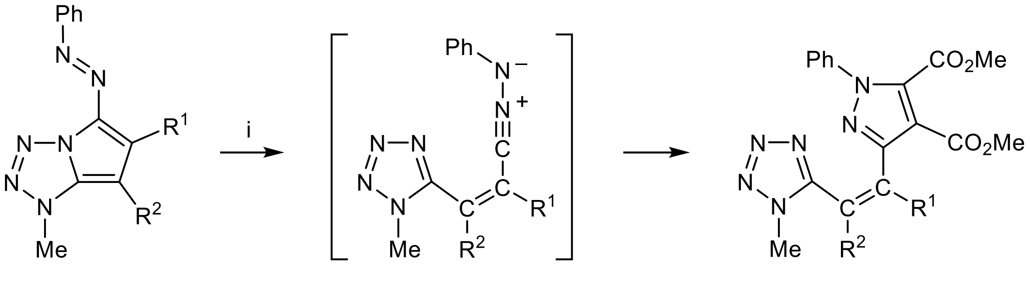
E [a]	**59**	**60**	from	R^1	R^2	R^3	yield (%)	mp (°C)	ref.
tt			**Ed**	Me	Ph	COMe	71	141−143 [c]	53
uu	**e** [b]		**Eh**	Me	Ph	CO$_2$Me	78	138−140	53
vv			**Ei**	Me	4-BrC$_6$H$_4$	CO$_2$Me	62	128−130 [c]	53
ww	**a**		**El**	Me	Me	H	33	114−115	53
xx	**b**		**Em**	Me	Ph	H	51	138−139 [c]	53, 57
yy	**c**		**En**	Me	4-BrC$_6$H$_4$	H	34	154−155 [c]	53
zz	**d**		**Ep**	Ph	Ph	H	67	144−146 [c]	53, 57
		a	**59b**			H	92	161−162	53, 57
		b	**Euu**			CO$_2$Me	47	129−131	53, 57
			62 [d]				35	153−157	34, 53
			63				87	203−210 [c]	53
			64				9	126−129	53

[a] **Eww-zz** isolated as **59a-d**. [b] Intermediate only. [c] Decomp. [d] From 1,5-dimethyl-4-phenacyl-1,2,4-triazolium bromide (mp 209−211 °C).[34]

Scheme 26

On addition of TFA the nitrile oxides **59a-d** adopted a bicyclic structure, as demonstrated by the process (**59b** → **61a**); the same type of product, *i.e.* the oxime **61b**, resulted on protonation of **Euu**.[34] Regarding the occurrence of that valence isomerism outside the series **E**, the new nitrosopyrrolo[2,1-*c*]triazole **63** was found to be a stable compound (in contrast to **Exx**); when it was heated with DMAD for a prolonged period of time, only a small quantity of the isoxazole **64** was obtained.[53] On extending this treatment to long known substrates such as 2-methyl-5-nitroso-1,6-diphenylpyrrolo[1,2-*b*][1,2,4]triazole and 5-nitroso-6-phenylpyrrolo[2,1-*b*]thiazole, the respective isoxazole derivatives could not be detected at all.[34]

In contrast to the elusive 5-nitroso compounds **Eww-zz**, analogous azo derivatives are isolable materials; they were viewed as potential nitrile imines **65** (Scheme 27). Indeed, when **Edd**,**ii** were heated with DMAD, the pyrazoles **66a**,**b** arose, but pyrrole ring opening occurred less readily than with **Euu**. In line with this, the acceptor-substituted substrate **Enn** proved entirely unreactive (as did the 1-phenyl derivative **Ejj**[34]).



Edd,ii,nn **65a-c** **66a-c**

i: DMAD, toluene, reflux, 24 h

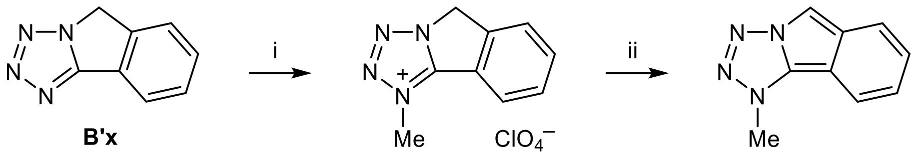
E	65, 66	R^1	R^2	yield (%)	mp (°C)	ref.
dd	**a**	Me	H	36	139 − 141	34
ii	**b**	Ph	H	76	174 − 176	53, 57
nn	**c**	Ph	CO_2Me	0		57

Scheme 27

8) RING-FUSED 1*H*-PYRROLOTETRAZOLES E: 1*H*-TETRAZOLOISOINDOLES (E')

a) Synthesis

Quaternization of compound **B'x** followed by deprotonation of the salt **67** continues to be the sole route to the parent **E'a** (Scheme 28).[60–62] By type, this entry matches the preparation of **Ea** from **Bc** [*cf.* Section (2. b), Scheme 13].[63] The product **E'a** is extremely unstable,[65] only recently it has been isolated pure.[61]



B'x **67** **E'a**

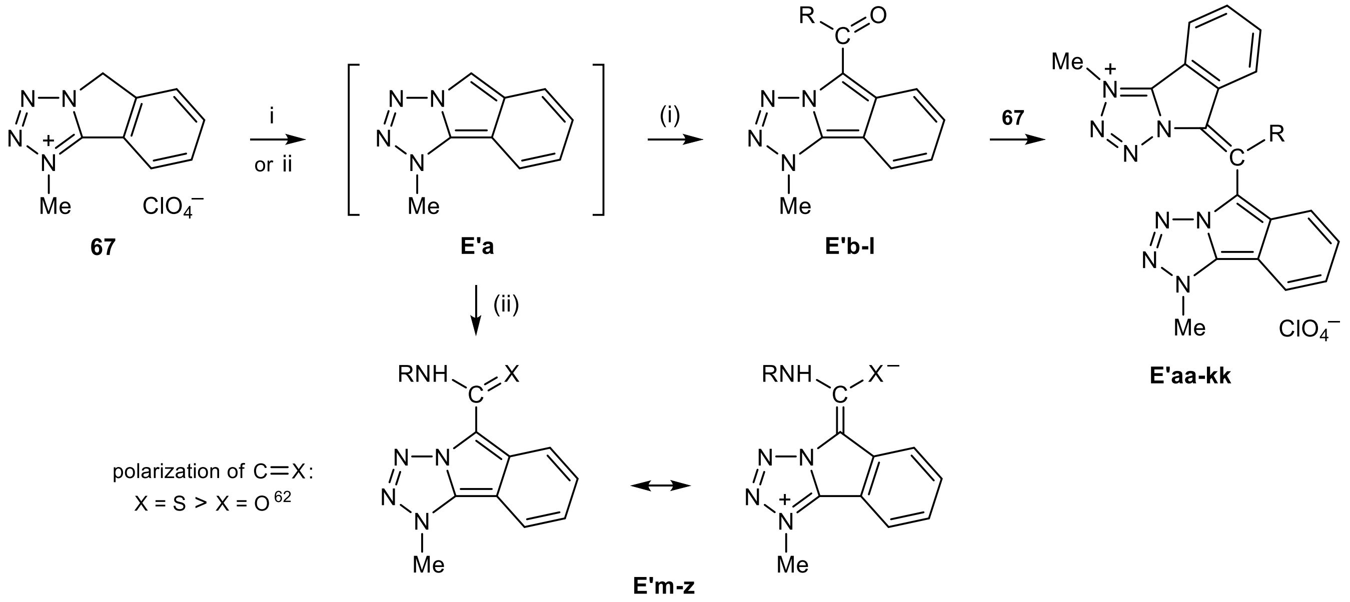
i: $(MeO)_2SO_2$ (neat), Δ; then aq. $NaClO_4$ ii: Et_3N (?); then sublimation at 10^{-5} Torr

Scheme 28

b) Reactions

(i) S_E-Reactions and additions to heteroallenes:

Not unlike substrates **E** having a free 5-position,[57] compound **E'a** – generated from **67** – reacted *in situ* with acid chlorides straightforwardly to afford 5-acyl derivatives such as **E'b-l** (Scheme 29).[61] Of these products,



i: RCOCl, Et_3N (2 equiv.), dioxane, 100 °C, 1 h ii: RNCX, Et_3N, DMF, rt, 1 h

E'	yield (%)	mp (°C)	R	E'	yield (%)	mp (°C)	ref. [a]
b	8	199	Me	**aa**	61	166	60, 61
c	0		Bu	**bb**	62	195	61
d	0		$[CH_2]_3Cl$	**cc**	64	158	61
e	42	187	Ph	**dd**	51	197	60, 61
f	0		$2\text{-}ClC_6H_4$	**ee**	2	151	61
g	40	177	$4\text{-}MeC_6H_4$	**ff**	53	187	61
h	81	182	$4\text{-}NO_2C_6H_4$	**gg**	< 1	[c]	60, 61
i	27	183	$2,4\text{-}(MeO)_2C_6H_3$	**hh**	34	181	60, 61
j	59	161	2-thienyl	**ii**	30	185	60, 61
k	47	156	5-bromo-2-furyl	**jj**	36	176	61
l	79	172	[b]	**kk**	2	[c]	61

[a] For yields and mp.s of **E'aa,dd,gg-ii**, see ref.[61]; for yields of **E'b,e,h-j**, see ref.[60] as well.
[b] R = 3-(2-Chlorophenyl)-5-methylisoxazol-4-yl. [c] Unreported.

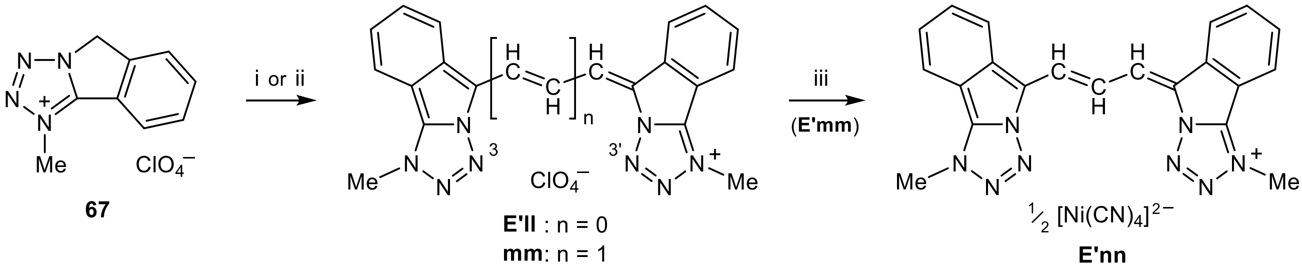
E'	X	R	yield (%)	mp (°C)	E'	X	R	yield (%)	mp (°C)	ref.
m	O	*c*-C_6H_{11}	68	181	**t**	S	*c*-C_6H_{11}	83	203	62
n	O	2-thienylmethyl	76	174	**u**	S	CH_2Ph	84	202	62
o	O	$CH_2C_6H_4F(4)$	73	170	**v**	S	Ph	84	211	62
p	O	$3\text{-}MeOC_6H_4$	68	179	**w**	S	$3\text{-}CF_3C_6H_4$	84	207	62
q	O	$3,5\text{-}(MeO)_2C_6H_3$	71	182	**x**	S	$4\text{-}CF_3C_6H_4$	93	205	62
r	S	Me	81	175	**y**	S	$4\text{-}EtOC_6H_4$	83	208	62
s	S	*t*-Bu	82	185	**z**	S	$4\text{-}NO_2C_6H_4$	84	183	62

Scheme 29

E'b,**e** had previously been prepared using acetic and benzoic anhydrides.[3] All of these compounds are stable materials (in marked contrast to **E'a**) but were found capable to react with unconsumed **67**/**E'a** giving cyanine dyes like **E'aa-kk**. Here the best results were obtained when the salt **67**, the acid chloride, and the base were reacted in a 1 : 1 : 2 ratio. Agents with R = Alk gave the highest yields, while electronegative or sterically demanding R groups proved detrimental, as demonstrated by the products **E'ee**,**gg**,**kk**. The structure of this class of compound has been confirmed by an X-ray diffraction analysis of **E'dd**.[61]

Likewise smoothly did proceed the addition to heteroallenes: Isocyanates and isothiocyanates gave good yields of the amides **E'm-q** and thioamides **E'r-z**, respectively.[62] A comparative study of the structures of both series, performed theoretically and by X-ray diffraction of **E'n** and **E'x**, showed a markedly stronger polarization of the C=X bond for X = S.[62]

Longer known cyanine dyes are the derivatives **E'll**,**mm** (Scheme 30).[3, 64b] Later, **E'll** has been studied theoretically (to include models **E'a** with 5-Me, 5-CH$_2^+$ instead of 5-H) and by X-ray diffraction. The latter data showed a twisted structure of the cation due to the repulsion between N(3) and N(3') [see, in addition, Section (11), Table 4].[66] Anion exchange with hexacyanoferrate(III) and tetracyanonickelate(II) gave salts whose UV/Vis spectra were studied.[3, 67] Of these salts, **E'nn** has also been submitted to an X-ray analysis.[68]

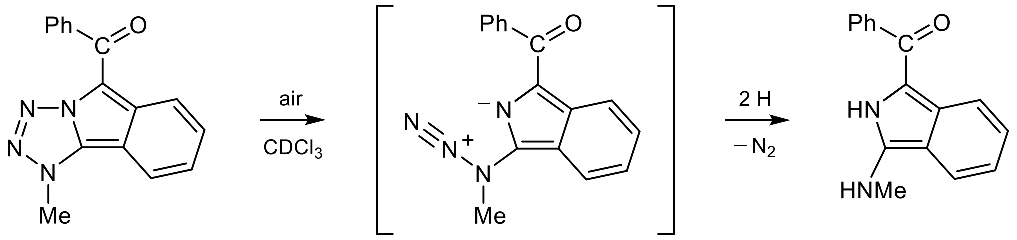


i: CH(OR)$_3$, pyridine, reflux, 10 min (for **E'll**) ii: EtOCH=CH—CH(OEt)$_2$, pyridine, reflux, 5 min (for **E'mm**)
iii: K$_2$[Ni(CN)$_4$], MeCN/*i*-PrOH/H$_2$O, reflux, 10 min

Scheme 30

(ii) Tetrazole ring opening:

During an IR spectroscopic study of the compounds **E'b**,**e**,**h**,**i**,**l** in CDCl$_3$ it was observed that in air exposed solutions degradation occurred, as detailed for **E'e** (Scheme 31).[60] The arising material was envisaged as having structure **69** (the respective C*H* tautomer being less likely). Its formation was thought to proceed, *inter alia*, *via* the species **68** which was stabilized by extrusion of dinitrogen with uptake of two hydrogen atoms. To accommodate that ring opening, the authors drew on the azido–tetrazole isomerism described for certain *N*-unsubstituted ring-fused pyrrolotetrazoles.[46,69] However, the cited examples do not seem to be directly relevant: Mechanistically, those systems can ring-open only after a proton shift or as anion (*cf.* ref.[28]), in other words: species of the type **68** (H instead of Me) do not occur.



E'e **68** **69**

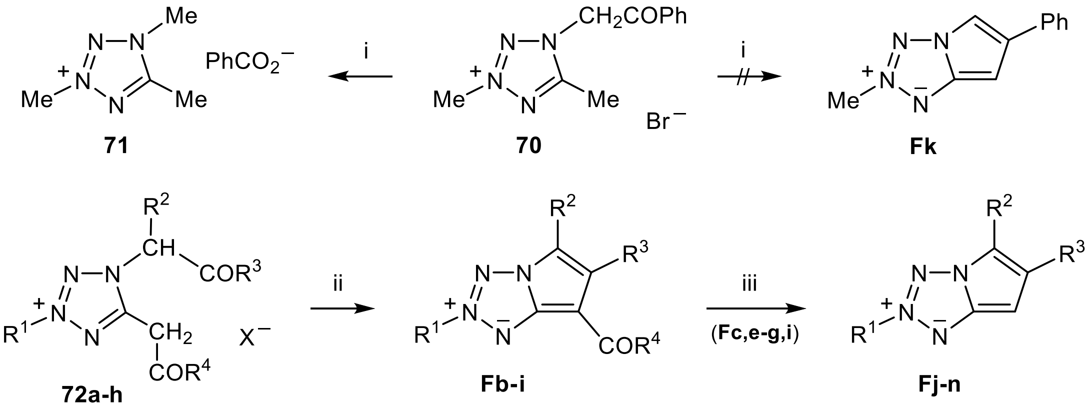
Scheme 31

9) 2*H*-PYRROLOTETRAZOLES (F)

a) Synthesis

(i) Cyclization of 2-substituted 4-(2-acylalkyl)-5-(acylmethyl)tetrazolium salts:

Access to class **F**, which belongs to the family of type C heteropentalene mesomeric betaines,[70] resembles the entry to the isomers **E** (Scheme 32). Whereas the 5-methyl group of the salt **70** is inactive and treatment



71 **70** **Fk** **72a-h** **Fb-i** **Fj-n**

i: aq. NaHCO$_3$, reflux, 2 h ii: NaOAc/AcOH, 100−110 °C, 1 h (with **72c** 2 h) iii: 12 M HCl, reflux, 1−2 h

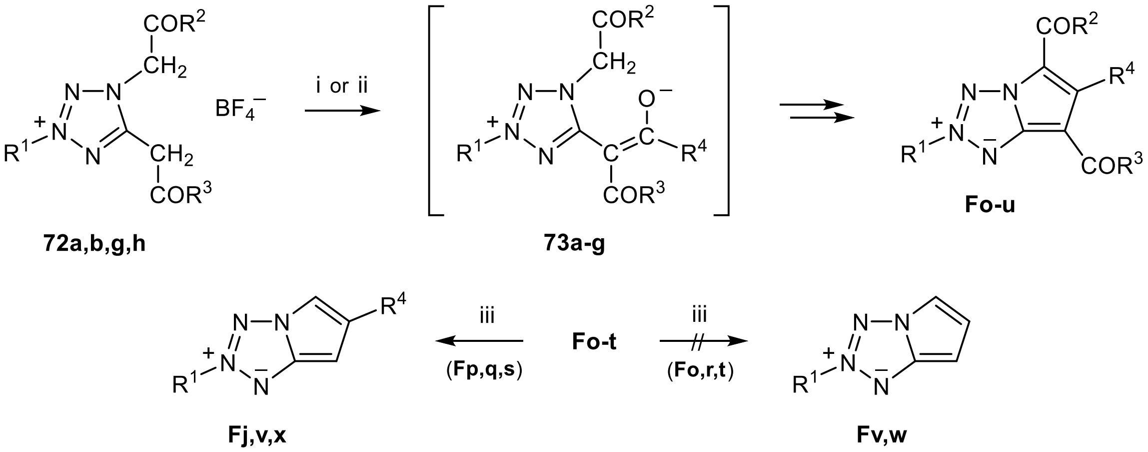
72	F	R^1	R^2	R^3	R^4	X	**F**: yield (%)	mp (°C)	ref.
a	**b**	Me	H	Me	Me	BF$_4$	0		54
b	**c**	Me	H	Me	OMe	BF$_4$	33	104−105	54
c	**d**	Me	H	Ph	Me	BF$_4$	10	167−169	54
d	**e**	Me	H	Ph	OMe	BF$_4$	60	145−146	54
e	**f**	Me	H	4-BrC$_6$H$_4$	OMe	BF$_4$	60	174	54
f	**g**	Me	Me	Ph	OMe	MeOSO$_3$	20 [a]	177−179	54
g	**h**	Ph	H	Me	Me	BF$_4$	17	149−150	54
h	**i**	Ph	H	Ph	Me	BF$_4$	80	161−163	54
	j	Me	H	Me			73	39−40	54
	k	Me	H	Ph			98	129−131	54
	l	Me	H	4-BrC$_6$H$_4$			99	212−214	54
	m	Me	Me	Ph			80	90−91	54
	n	Ph	H	Ph			98	198−199	54

[a] Based on 3:7 mixture of **72f** and isomer **51g** (see Scheme 21).

Scheme 32

with base caused Kröhnke's so-called acid splitting[71] to produce 2,4,5-trimethyltetrazolium benzoate (**71**),[51] cyclization succeeded smoothly with the substrates **72** in an acetate buffer. Apart from **72a**, all of the salts **72b-h** gave the expected target compounds **Fc-i**. Defunctionalization with hot mineral acid occurred readily (as it did in the isomeric **E** series) to afford high yields of the 7-unsubstituted derivatives **Fj-n**.[54]

(ii) Cyclization of 2-substituted 4,5-bis(acylmethyl)tetrazolium salts with carboxylic acid derivatives: After the pattern described for class **E** [see Section (7. a), part (ii)] the salts **72** reacted readily to give 5,7-diacyl substituted bicycles such as **Fo-u** (Scheme 33).[54] Using the mixed acetic formic anhydride, the 6-unsubstituted derivatives **Fo**,**p**,**r**,**t** arose, the corresponding 6-methyl congeners **Fq**,**s**,**u** which are conceivable side products being unobserved. But the synthesis of the latter succeeded with acetic anhydride. Defunctionalization could be achieved with **Fp**,**q**,**s** only, giving the derivatives **Fj**,**v**,**x**. As observed with **Fp** and **Fs**, the reaction proceeds stepwise, with the group attached at C(5) being removed first.



i: AcOCHO/Et$_3$N, 60–65 °C, 2 h ii: Ac$_2$O/Et$_3$N, 90–100 °C, 2 h iii: 12 M HCl, reflux, 1–5.5 h

72	73	F	R^1	R^2	R^3	R^4	F: yield (%)	mp (°C)	ref.
a	a	o	Me	Me	Me	H	39	233 234	54
b	b	p	Me	Me	OMe	H	32	186–188	54
	c	q	Me	Me	OMe	Me	66	212–213	54
g	d	r	Ph	Me	Me	H	29	211–212	54
	e	s	Ph	Me	Me	Me	58	259	54
h	f	t	Ph	Ph	Me	H	96	220–221	54
	g	u	Ph	Ph	Me	Me	14 [a]	236	54
		v	Me			H	0/15 [b]	36–38	54
		j	Me			Me	99 [c]	39–40	54
		w	Ph			H	0/0 [d]		54
		x	Ph			Me	98 [e]	86–88	54

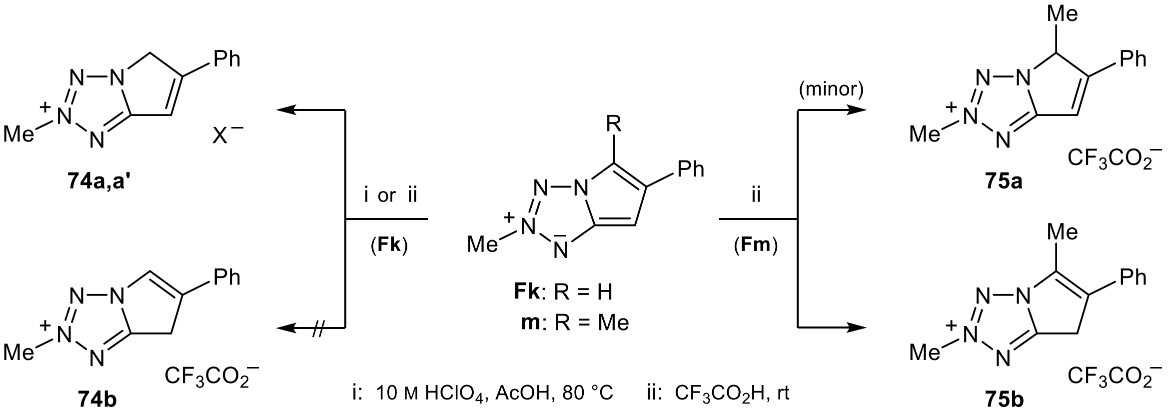
[a] Besides 17% **Fs** through benzoyl–acetyl exchange with **73g** (*cf.* Scheme 22: **54a** → **54b**). [b] From **Fo**/**Fp**. [c] 73% from **Fc** (*cf.* Scheme 32). [d] From **Fr**/**Ft**. [e] From **Fs**.

Scheme 33

b) Reactions

(i) Protonation and S_E-reactions:

Not unlike their congeners **E**, the compounds **F** are capable of forming stable salts with strong acids, as illustrated by the perchlorate **74a'** of **Fk** (Scheme 34).[57] With position 5 being unsubstituted, the preferred site of protonation is C(5). This was further evidenced by studying **Fk** in trifluoroacetic acid which gave the salt **74a**, the isomer **74b** being unobserved (*cf.* Scheme 24). But contrasting with the foregoing, the 5-methyl derivative **Fm** was protonated predominantly at C(7) (→ **75b**).[57] Calculations of the respective cations at the B3LYP/6-31G(d,p) level showed **74a** energetically favoured over **74b** (though not to the same extent as found for **57a** against **57b**; *cf.* Scheme 24). But while the cations **75a**,**b** scarcely differed at that level, the higher B3LYP/6-311+G(d,p) level gave a distinctly lower energy for the 6-unsubstituted analogue of **75b**, quite in contrast to the finding made in the **E** series.[29a,b]



74a,a'

74b

Fk: R = H
m: R = Me

75a

75b

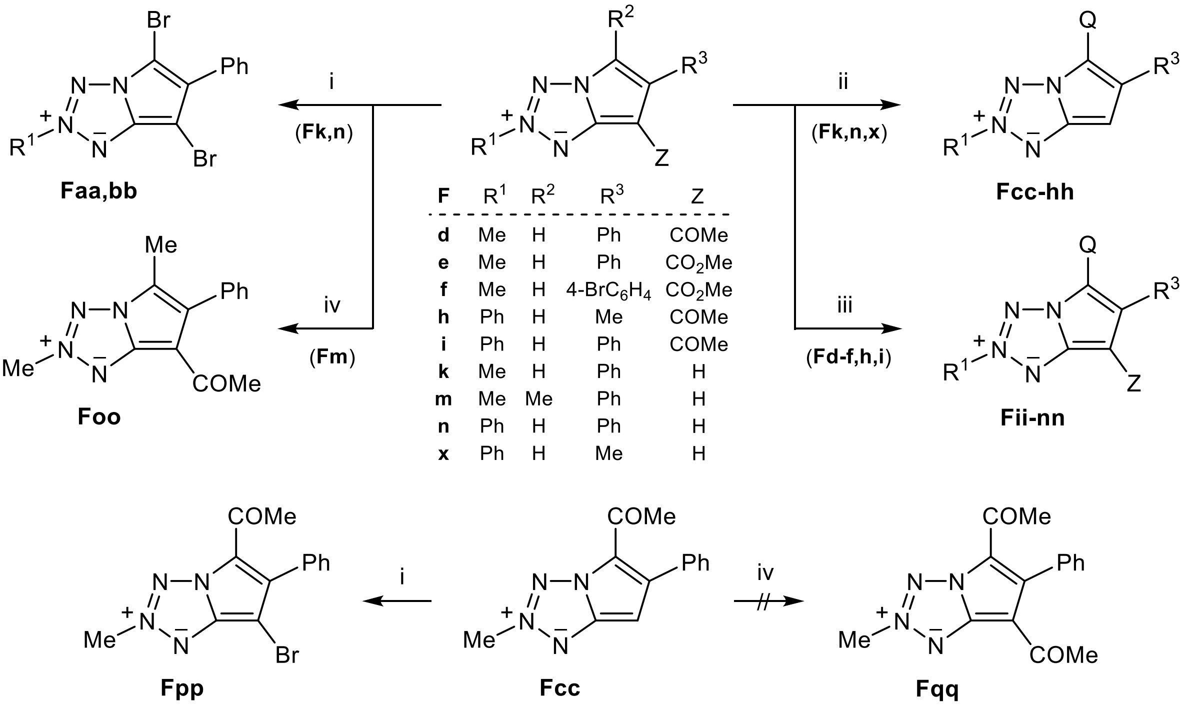
i: 10 M $HClO_4$, AcOH, 80 °C ii: CF_3CO_2H, rt

	X	ratio **a**/**b** [b]	ref.	Δ*E*, kcal mol^{-1} [c]		ref.
74a' [a]	ClO_4		57	[d]	[e]	
74a / **b**	CF_3CO_2	100/0	57	0.00/2.92	0.00/2.25	29a,b
75a / **b**		20/80	57	0.00/0.51	1.91/0.00	29a,b

[a] Yield 60%, mp 256 °C. [b] By ^{1}H NMR. [c] Calculations of cations (gas phase). [d] B3LYP/6-31G(d,p). [e] B3LYP/6-311+G(d,p) (for 6-*unsubstituted* analogues).

Scheme 34

A plethora of S_E-reactions of the substrates **F** have been reported (Scheme 35).[57, 58] In principle, the results correspond to those obtained in the isomeric class **E**. This concerns: (i) exclusive monosubstitution [at C(5)] by electrophiles other than bromine (→ **Fcc-hh**), (ii) substitution at C(7) only in case position 5 is occupied (→ **Foo,pp**), (iii) facile substitution at C(5) of substrates having an acceptor group at C(7) (→ **Fii-nn**). Notwithstanding these parallels, there is a noticeable difference: substrates **F** show an enhanced reactivity. As a conspicuous example, the acetylation of **Fk** may be cited: The formation of **Fcc** occurred in one day only, whereas the analogous reaction in the **E** series required one week. This is consistent with the markedly higher electron density at C(5), calculated for the parent (**Fv**) [*cf.* Section (7. b), part (i), Table 3].



F	R^1	R^2	R^3	Z
d	Me	H	Ph	COMe
e	Me	H	Ph	CO_2Me
f	Me	H	4-BrC_6H_4	CO_2Me
h	Ph	H	Me	COMe
i	Ph	H	Ph	COMe
k	Me	H	Ph	H
m	Me	Me	Ph	H
n	Ph	H	Ph	H
x	Ph	H	Me	H

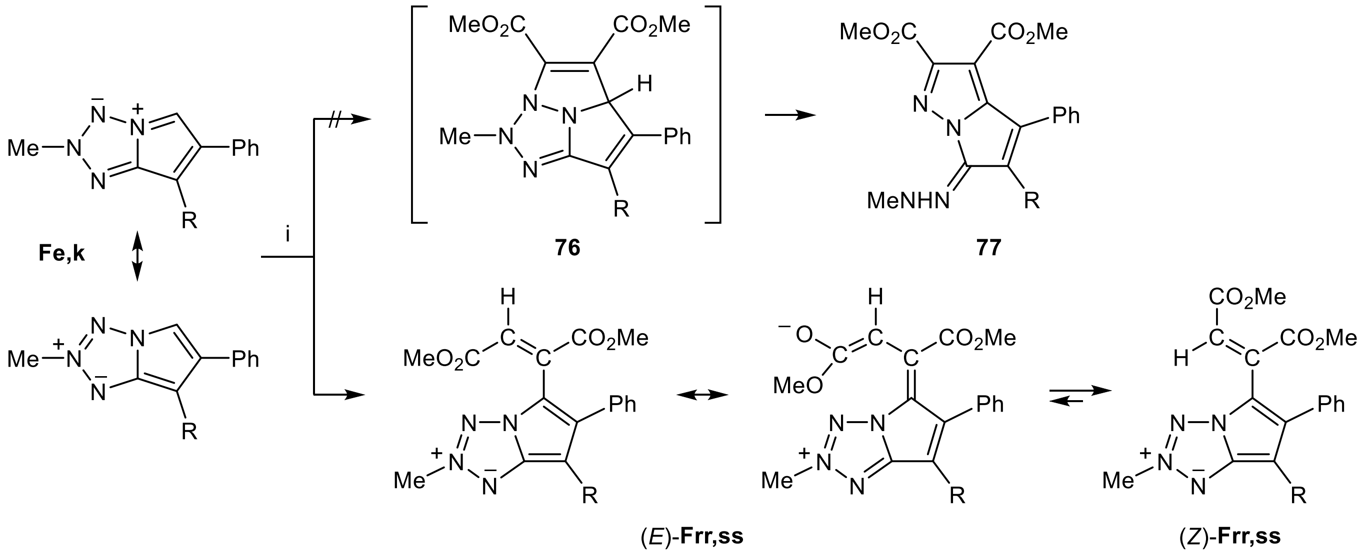
i: Br_2, $CHCl_3$, 0 °C, 30 min ii: Ac_2O (neat), 20 °C, 24 h (for **Fcc**) or 120 °C, 2.5 h/1 h (for **Fff**/**Fgg**); DMF/$POCl_3$, 0 °C, 45 min (for **Fdd**); $[PhN_2]Cl$, AcOH, 0 °C to rt, 15 min (for **Fee**); AcOCHO (neat), 80 °C, 30 min (for **Fhh**) iii: Br_2, $CHCl_3$, 0 °C, 30 min (for **Fii-kk,nn**); $[PhN_2]Cl$, AcOH, 0 °C to rt, 1 h (for **Fll**); Ac_2O (neat), 120 °C, 8 h (for **Fmm**) iv: Ac_2O (neat), 20 °C, 24 h

F	R^1	R^3	Z	Q	from	yield (%)	mp (°C)	ref.
aa	Me				**Fk**	67	143−144	57
bb	Ph				**Fn**	62	165−166	58
cc	Me	Ph		COMe	**Fk**	62	96−97	57
dd	Me	Ph		CHO	**Fk**	57	144−146	57
ee	Me	Ph		N=NPh	**Fk**	78	142−144	57
ff	Ph	Me		COMe	**Fx**	81	139−141	57
gg	Ph	Ph		COMe	**Fn**	66	148−150	58
hh	Ph	Ph		CHO	**Fn**	69	166−167	58
ii	Me	Ph	COMe	Br	**Fd**	67	168−169	58
jj	Me	Ph	CO_2Me	Br	**Fe**	90	225	57
kk	Me	4-BrC_6H_4	CO_2Me	Br	**Ff**	80	195	58
ll	Me	Ph	CO_2Me	N=NPh	**Fe**	69	238−240	57
mm	Ph	Me	COMe	COMe	**Fh**	50	259	57
nn	Ph	Ph	COMe	Br	**Fi**	52	161−163	58
oo						62	163−164	57
pp						88	156−157	58

Scheme 35

(ii) Addition to DMAD:

As type C heteropentalene mesomeric betaines,[70] the compounds **F** are 1,3-dipoles (potential azomethine imines) which might give rise to a cyclazine such as **76** (Scheme 36). This species, because of three adjacent azane-type nitrogen atoms, should immediately ring-open to afford the 6*H*-pyrrolo[1,2-*b*]pyrazole **77**. Yet,



i: DMAD, MeOH, rt, 1h (with **Fe**) or reflux, 1 h (with **Fk**)

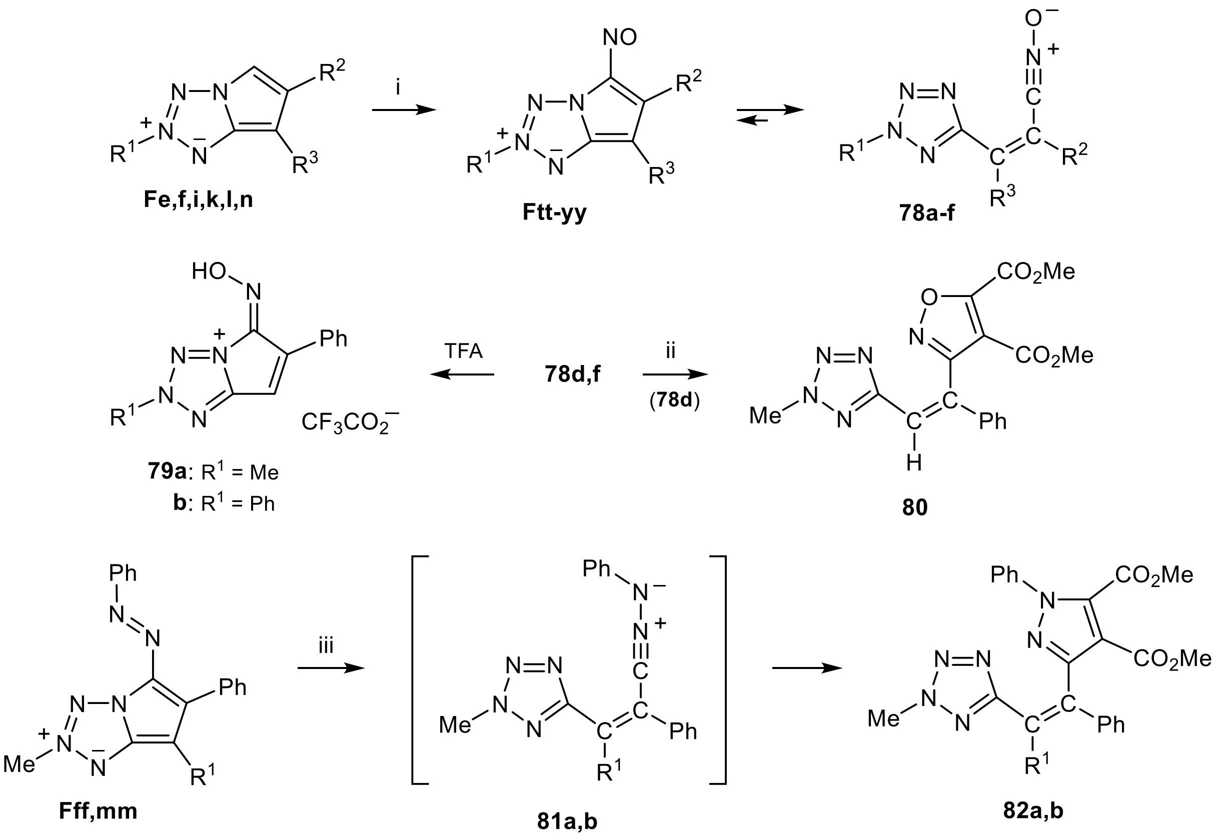
F	from	R	yield (%)	mp (°C)	ref.
(*E*)-**rr**	**Fe**	H	53	171−172	57
(*Z*)-**rr**	**Fe**	H		138−139	57
(*E*)-**ss**	**Fk**	CO_2Me	80	145−147	57
(*Z*)-**ss**	**Fk**	CO_2Me		234−235	57

Scheme 36

there were no indications of the occurrence of such a process, only linear addition was observed, as it took place in the **E** series (*cf.* Scheme 25).[57] But in contrast to the sterically stable fumarates (*E*)-**Ehh**,**mm**, their analogues (*E*)-**Frr**,**ss** tended to isomerize into the corresponding maleates [the derivative (*E*)-**Frr** remarkably rapidly]. This was understood as a consequence of the enhanced electron density at C(5) which facilitates polarization of the olefinic double bond; an acceptor group at C(7), as present with (*E*)-**Fss**, has an adverse influence so as to slow down isomerization.

(iii) Pyrrole ring opening of 5-nitroso- and 5-phenylazo derivatives:

Nitrosation of compounds **F** led to results observed with class **E**, *i.e.* the products were found prone to ring opening (Scheme 37).[57,58] Yet, a major difference concerns the stability of nitroso derivatives obtained from substrates having an acceptor group at C(7). While such products of the **E** series are isolable materials and ring-open only under forcing conditions (*cf.* Scheme 26), the congeners **Ftt-vv** exist predominantly as the nitrile oxides **78a-c**. To rationalize this, it has been argued that the 'stabilizing' effect of the acceptor group is offset by the less nucleophilic N(4) atom of a (monocyclic) 2*H*-tetrazole. This ring opening, not surprisingly, occurred also with nitrosated 2*H*-imidazo[1,2-*d*]tetrazoles.[72] The conversions (**78d**,**f** → **79a**,**b**) and (**78d** → **80**) correspond to those performed with nitrile oxides **59** obtained from substrates **E**.



i: $NaNO_2$, AcOH, 0 °C to rt, 15 min   ii: DMAD: MeOH, reflux, 0.5 h   iii: DMAD, toluene, 80 / 120 °C, 2.5 / 24 h (for **81a**/**81b**)

F [a]	78	81, 82	from	R^1	R^2	R^3	yield (%)	mp (°C)	ref.
tt	**a**		**Fe**	Me	Ph	CO_2Me	54	112 − 113	57
uu	**b**		**Ff**	Me	4-BrC_6H_4	CO_2Me	84	87 − 89	58
vv	**c**		**Fi**	Ph	Ph	COMe	48	110 − 111	57
ww	**d**		**Fk**	Me	Ph	H	92	97 − 99	57
xx	**e**		**Fl**	Me	4-BrC_6H_4	H	73	135	58
yy	**f**		**Fn**	Ph	Ph	H	78	132 − 133	57
	80		**75d**				39	78 − 79	57
		a	**Fff**	H			74	98 − 101	57
		b	**Fmm**	CO_2Me			0		57

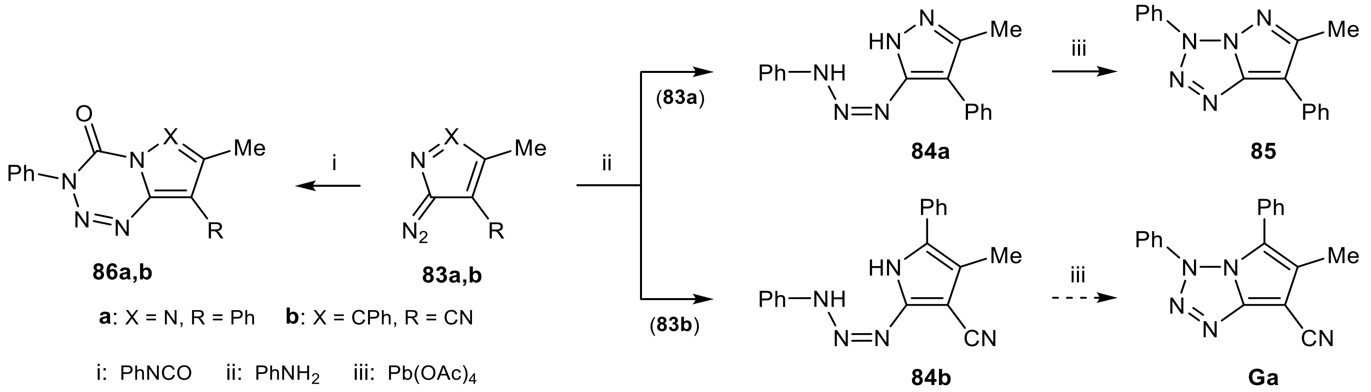
[a] **Ftt-vv**: minor components (%) besides **78a-c**, *e.g.* (i) **Ftt**: 5.4 (24 °C, $CDCl_3$),[58] 5.76 (26 °C, CD_2Cl_2; 5.4[57] error);[58] 9.4 (−30 °C, CD_2Cl_2);[57] 18.6 (*ca.* 25 °C, DMSO-d_6);[58] (ii) **Fuu**: 7 (*ca.* 25 °C, $CDCl_3$).[58]

Scheme 37

In contrast to the elusive nitroso compounds, the analogous azo derivatives **Fff**,**mm** are isolable materials. When **Fff** was heated with DMAD, the transient nitrile imine **81a** was intercepted by the alkyne to give the pyrazole derivative **82a**. In line with the enhanced proclivity of **Ftt-vv** for ring cleavage, the reaction proceeded considerably faster than the corresponding process in the **E** series (*cf.* Scheme 27). But also here attempts at converting a 7-acceptor substituted phenylazo substrate, such as **Fmm**, to the corresponding pyrazole **82b** met with failure.

10) 3*H*-PYRROLOTETRAZOLES (G)

Members of this class have not been prepared as yet, although a promising precursor is at hand (Scheme 38): Considering the straightforward ring closure of the triazenopyrazole **84a** to the pyrazolotetrazole **85** by intramolecular dehydrogenation,[73a] the analogous process should be feasible with the congener **84b**. This substrate was recently provided by coupling the diazopyrrole **83b** with aniline,[74] in extension of the earlier conversion (**83a** → **84a**). However, the authors' interest was not directed to the pyrrolotetrazole **Ga**, their proper aim was the pyrrolotetrazinone **86b**: a potential antitumor agent which resulted from the reaction of **83b** with phenyl isocyanate,[74] *i.e.* in parallel to the formation of the pyrazolo congener **86a** from **83a**.[73a]



Scheme 38

11) EXPERIMENTAL STRUCTURAL METHODS

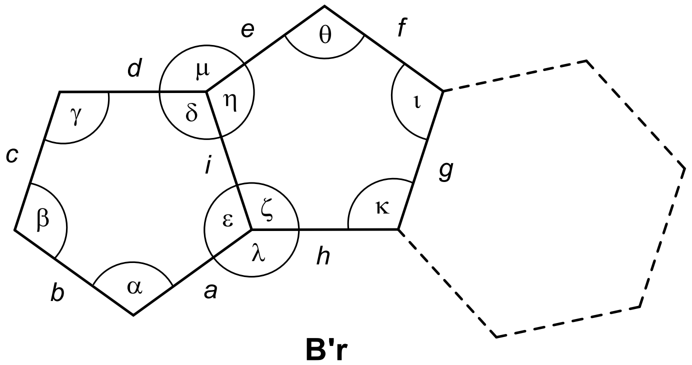
(i) X-Ray diffraction:

Only a limited number of compounds dealt with in the preceding Sections have been submitted to an X-ray diffraction analysis. Apart from the derivative **Aa** (Scheme 1),[4b] the compounds investigated represent *ring-fused* pyrrolotetrazoles such as **B'q** (Scheme 15, 17, 18),[38] **E'n,x** (Scheme 29),[62] **E'dd** (Scheme 29),[61] **E'll** (Scheme 30),[66] and **E'nn** (Scheme 30).[68] Selected data of **B'q** and **E'll** are gathered in Table 4.

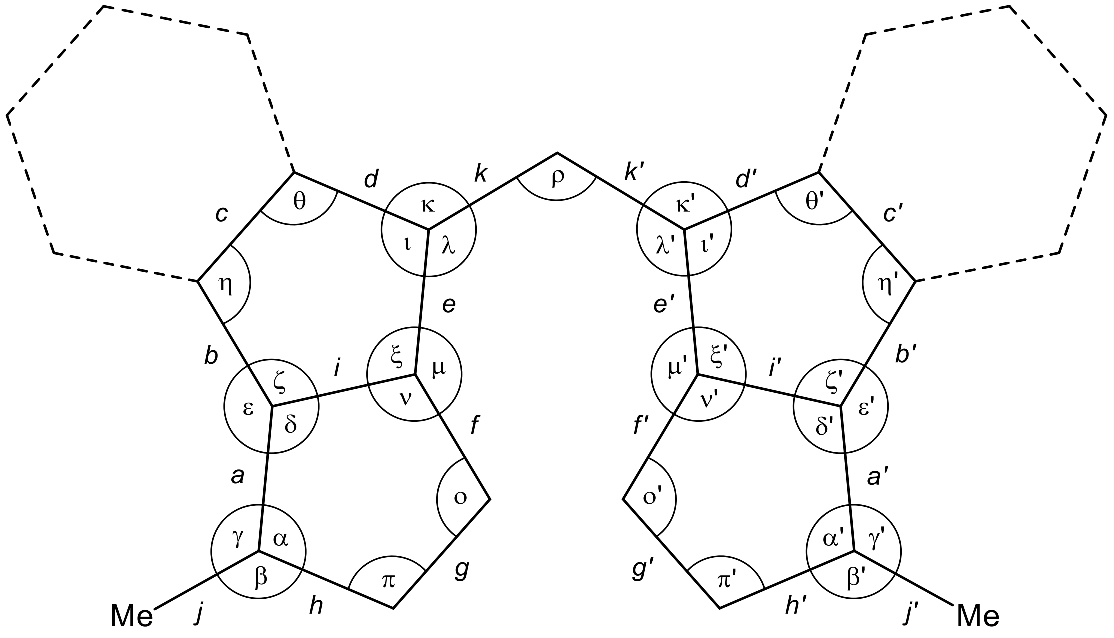
(ii) Spectroscopic methods:

Nearly all of the derivatives **A**, **B**, **D**–**F**, and **B'**–**E'** have been characterized by IR, UV/Vis, NMR, and/or MS spectra. While the majority of the spectra were taken routinely, specific studies are rare; they include the IR bands of acyl derivatives **E'**,[60] the ^{14}N NMR signals [75] and the He(I)PE spectrum of **Aa**,[14c] and the MS fragmentation of **Aa**.[13, 76] – Selected data are provided by Tables 5–7; some comments are given below: (a) Table 5: Regarding IR bands, the ketonic (and ester) derivatives of the classes **E**, **E'**, and **F** exhibit, as known from monocyclic pyrroles, low-frequency carbonyl absorptions; the conspicuous parallelism in the properties of **E**, **F**, and **E'** has been overlooked in discussing the spectra of **E'**.[60]

Table 4. Selected bond distances (Å) and angles (°) of **B'r**[38] and **E'll**[66] from X-ray diffraction



B'r



E'll

B'r [a]

a	*b*	*c*	*d*	*e*	*f*	*g*	*h*	*i*
1.307	1.368	1.303	1.329	1.432	1.509	1.418	1.452	1.344

α	β	γ	δ	ε	ζ	η	θ	ι	κ	λ	μ
104.8	111.8	105.0	109.7	108.7	108.2	115.1	100.3	110.6	105.8	143.1	135.2

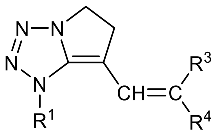
E'll [b]

a	*b*	*c*	*d*	*e*	*f*	*g*	*h*	*i*	*j*	*k*
a'	*b'*	*c'*	*d'*	*e'*	*f'*	*g'*	*h'*	*i'*	*j'*	*k'*
1.344	1.424	1.425	1.440	1.407	1.355	1.298	1.345	1.351	1.449	1.379
1.341	1.413	1.415	1.458	1.410	1.351	1.292	1.365	1.340	1.448	1.366

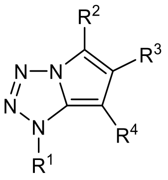
α	β	γ	δ	ε	ζ	η	θ	ι	κ	λ	μ	ν	ξ	ο	π	ρ
α'	β'	γ'	δ'	ε'	ζ'	η'	θ'	ι'	κ'	λ'	μ'	ν'	ξ'	ο'	π'	
108.8	121.9	129.2	104.8	145.5	109.6	104.0	111.2	102.8	130.0	126.5	137.1	110.2	112.3	106.4	109.7	132.7
108.1	122.1	129.8	105.2	143.7	110.9	104.3	110.4	102.9	128.8	128.3	137.0	110.6	111.5	106.6	109.4	

[a] For full structure, see Scheme 15, 17 or 18. [b] For full structure, see Scheme 30.

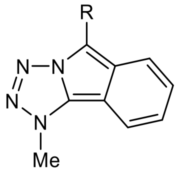
Table 5. IR and/or UV/Vis data of selected compounds **D**, **E**, **E'**, and **F**



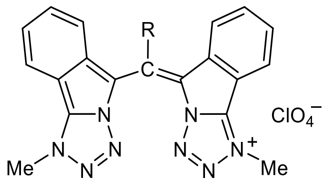
Dc-f



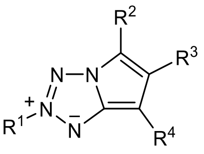
Ed,h,m,p,ff



E'a,b,e



E'aa,dd



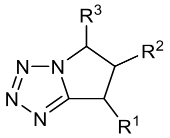
Fd,e,k,m,cc

compd	R^1	R^2	R^3	R^4	$\tilde{\nu}$ (cm^{-1}) [a]	solvent	ref.	compd	R	$\tilde{\nu}$ (cm^{-1}) [a]	solvent	ref.
Ed/**Fd**	Me	H	Ph	COMe	1640/1630	KBr	54	**E'b**	COMe	1633 [b]	CDCl$_3$	60
Eh/**Fe**	Me	H	Ph	CO$_2$Me	1705/1693	KBr	53/54	**E'd**	COPh	1633 [b] [c]	CDCl$_3$	60
Eff/**Fcc**	Me	COMe	Ph	H	1625/1616	KBr	57					
					λ$_{max}$ (nm) [d]					λ$_{max}$ (nm) [d]		
Dc	Et		for R^3/R^4, see Scheme 19		488 (4.95)	[e]	23	**E'a**	H	362 (3.89)	EtOH	61
Dd	Me				442 (4.90)	[e]	23	**E'b**	COMe	338 (3.70)	MeCN	61
De	Et				426 (4.78)	[e]	23	**E'd**	COPh	402sh (3.80)	MeCN	61
Df	Et				476 (4.99)	[e]	23					
Ed/**Fd**	Me	H	Ph	COMe	310/357 [f]	MeOH	54	**E'aa**	Me	552 (5.31)	MeCN	61
Em/**Fk**	Me	H	Ph	H	324/377 [g]	MeOH	54	**E'dd**	Ph	561 (5.82)	MeCN	61
Ep/**Fm**	Ph	H	Ph	H	342/426 [h]	MeOH	54					

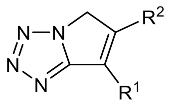
[a] C=O bond. [b] Relevant part of spectrum illustrated. [c] KBr: 1630 cm^{-1}, full spectrum illustrated. [d] Longest wavelength maximum; in parentheses: log ε. [e] Unreported. [f] log ε: 3.97/3.90. [g] log ε: 3.45/3.57. [h] log ε: 3.68/3.74.

Table 6. ^{1}H and ^{13}C NMR data of selected compounds **A**, **B**, and **D–F** [a]

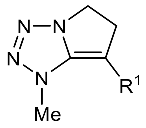
A



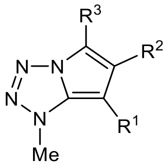
B



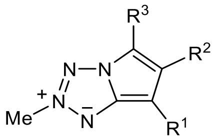
D



E



F



Compd. (ref.)	R^1	R^2	R^3	^{1}H 5-H	^{1}H 6-H	^{1}H 7-H	^{1}H NMe	^{13}C C(5)	^{13}C C(6)	^{13}C C(7)	^{13}C C(7a)	^{13}C NMe	Solvent
Aa (22a) [b]	H	H	H	[c]	[d]			44.7	27.8	18.9	162.9		CDCl$_3$
Ar (20)	OH	OCMe$_2$O		6.56	5.39	5.35		94.3	87.6	67.0	162.2		[e]
At (22a)	Me	H	H	[f]	[g]	[h]		44.1	36.9	27.1	165.7		CDCl$_3$
Bc (25)	Me	H		4.78	6.65			50.3	135.0	127.9	164.0		CDCl$_3$
Bd (25)	H	Me		4.73		6.50		53.5	154.7	112.5	164.2		CDCl$_3$
Da (22b)	H			3.43	2.90	3.73	3.28	51.8	35.2	59.7	151.3	35.2	THF-d_8 [i]
Db (22b)	Me			3.61	2.73		3.35	50.7	39.6	72.6	144.5	34.5	THF-d_8 [i]
Ed (54)	Ac	Ph	H	7.11			4.54	102.5	134.8	97.6	136.4	37.4	CDCl$_3$
El (54)	H	Me	H	6.99		5.33	3.94	99.7	125.9	74.0	132.9	34.4	CDCl$_3$
Es (54)	Ac	H	Ac		7.67		4.57	118.6	125.9	99.8	137.6	37.5	CDCl$_3$
Ey (54)	H	H	H	7.17	6.70	5.49	4.00	99.2	119.4	83.1	129.6	34.4	CDCl$_3$
Fd (54)	Ac	Ph	H	7.15			4.41	101.1	138.8	96.5	149.8	41.9	CDCl$_3$
Fj (54)	H	Me	H	6.96		5.69	4.28	96.1	133.0	78.9	146.4	41.0	CDCl$_3$
Fo (54)	Ac	H	Ac		7.94		4.62	117.5	127.4	102.1	149.6	42.5	CDCl$_3$
Fv (54)	H	H	H	7.14	6.94	5.88	4.33	96.9	120.6	78.2	146.6	41.3	CDCl$_3$

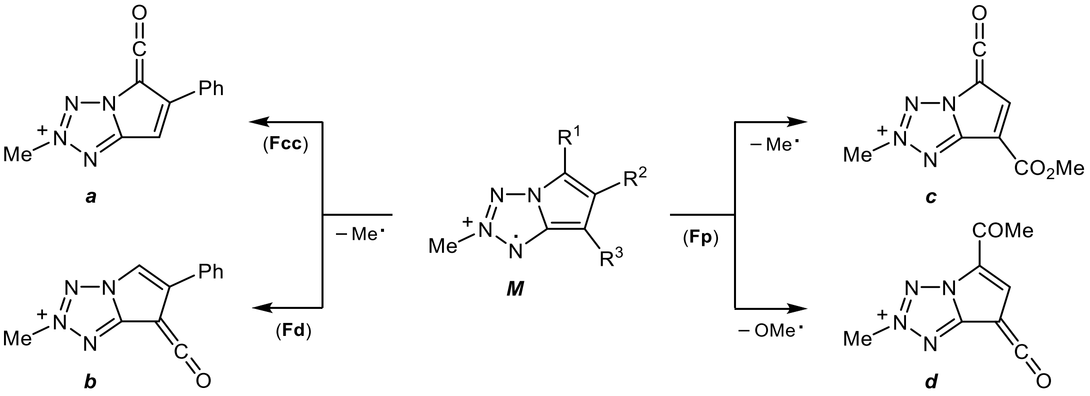
[a] Shift values: δ (ppm) relative to SiMe$_4$. [b] Ref. 14a: values of C(6) and C(7) must be exchanged. [c] 4.34–4.40. [d] 2.94–3.11 (4 H). [e] ^{1}H: CDCl$_3$; ^{13}C: (CD$_3$)$_2$CO; both spectra illustrated in: Supporting Information to ref.[20] [f] 4.26–4.33. [g] 2.53–2.62. [h] 3.39–3.49. [i] Measured at –40 °C.

(b) Table 5: Comparing the UV/Vis data of the derivatives **E** and **F**, those of the latter are characterized by a pronounced bathochromic shift of the longest wavelength maximum. The extreme shift observed with **Fm** reflects the unhindered conjugative interaction between the phenyl group and the heterocycle, which is not possible to that extent with the isomer **Ep**.

(c) Table 6: An analytically important ^{13}C NMR signal constitutes the absorption of C(7a). As apparent from the list of data, it is a reliable criterion not only for recognizing derivatives devoid of an *N*-substituent such as **A** and **B**, but also for discerning the isomers **E** from **F**.

(d) Table 7: A salient MS feature of the ketonic and ester derivatives of **F** constitutes an intense [M–15] and [M–31] peak, respectively; these signals were assigned to the ketenic species ***a*–*d***. The corresponding isomers **E** did not produce fragments of that kind, because here loss of dinitrogen predominates.

Table 7. MS fragmentation of the ketones **Fcc,dd** and the ester **Fp** [a] [54]



M	R^1	R^2	R^3	*M*	*a*	*b*	*c*	*d*
Fcc	COMe	Ph	H	240 (100)	225 (78)			
Fd	H	Ph	COMe	240 (60)		225 (100)		
Fp	COMe	H	CO_2Me	222 (100)			207 (84)	191 (80)

[a] 70 eV, *m/z* (%).

CONCLUSION

The material reviewed in the preceding Sections illustrates that studies in the vast field of the title classes seem well advanced, despite major differences between the single systems: While extensive knowledge on the 10π-aromatic types **E** and **F** has been accumulated and also the classes **A** and **B** have been studied to a considerable extent, other areas, in particular **C** and **G**, wait for being developed. A further desideratum remains an increase of experimental efforts towards the pyrrolotetrazole–azidopyrrole isomerism.

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