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SYNTHESIS AND NITROGEN ELIMINATION OF THE LINEARLY FUSED TETRAZOLO(1,5-b)ISOQUINOLINIUM SALTS[1,2]

Formation of a new tetracycle: Indazolo(2,3-b)isoquinoline

A. MESSMER*, GY. HAJÓS, A. GELLÉRI and L. RADICS

Central Research Institute for Chemistry,
Hungarian Academy of Sciences, H-1525 Budapest, Hungary

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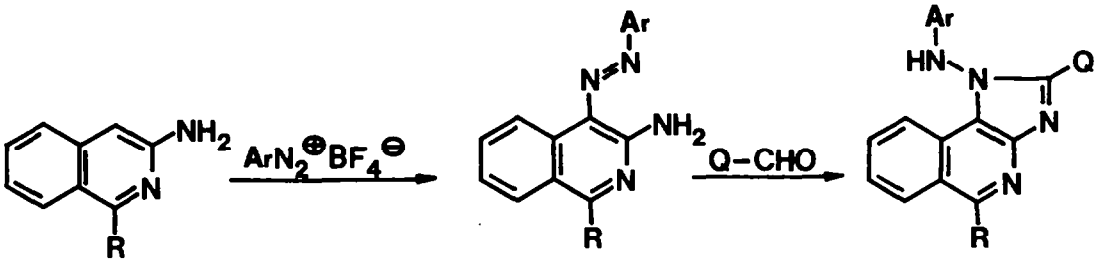
Abstract - Treatment of 3-aminoisoquinoline (1) with aryldiazonium salts gave 2-amino-4-arylazoisoquinolines (2) which reacted with aromatic aldehyde to yield imidazo(4,5-c)isoquinolines. With 3-amino-4-methylisoquinoline (4), however, the same reaction led to 3-isoquinolyltriazenes (5), and these could then be cyclized by the use of "TBB" to give tetrazolo(1,5-b)-isoquinolinium salts (6). The latter azolium salt (6) showed ambident reactivity in the presence of hydroxide ion manifested by simultaneous formation of tolualdehyde derivative 10 and indazolo(3,2-b)isoquinoline system (8). This ambidency as well as the difference in behaviour between the new linearly fused system (6) and its formerly studied angularly fused isomers ("annelation effect") is interpreted in terms of the frontier molecular orbital theory.

As reported in our previous publication[2], cyclization of α-pyridyl triazenes to tetrazolo(1,5-a)pyridinium salts was successfully extended to the synthesis of angularly fused tricyclic tetrazolium salts. No attempt had, however, been made for the synthesis of the third possible benzenologue of tetrazolo(1,5-a)pyridinium system: the linearly fused tetrazolo(1,5-b)isoquinolinium ring[3].

In a similar manner to our earlier cases[2], 3-aminoisoquinoline (1a) when treated

Q = p-CH_3O-C_6H_4-



1 2 3

	R
a	H
b	Br

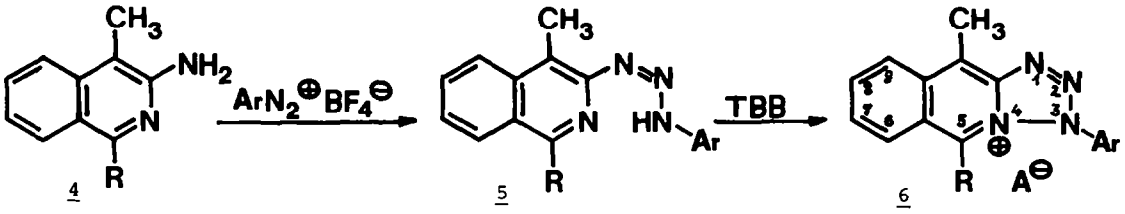
	Ar	R
a	p-Br-C_6H_4-	H
b	p-Br-C_6H_4-	Br
c	p-CH_3O-C_6H_4-	Br

	Ar	R
a	p-Br-C_6H_4-	H
b	p-Br-C_6H_4-	C_2H_5O
c	p-CH_3O-C_6H_4-	C_2H_5O

with diazonium salt was expected to yield the corresponding triazene. Unexpectedly, however, instead of the triazene coupling, formation of 3-amino-4-arylazoisoquinolines (2) were observed. These new, red-coloured, azo compounds, on the other hand, proved to be suitable starting materials for subsequent ring closure when treated with aromatic aldehyde. Thus, reaction of 2a with anisaldehyde afforded a derivative of the imidazo(4,5-c)isoquinoline ring system (3a)[4]. In cases of 1-bromo-substituted azo compounds, the ring closure reaction was accompanied by solvolysis which led to the formation of ethoxy derivatives 3b, c.

This finding showed that position 4 in 3-aminoisoquinoline (1) is more active than the exo nitrogen atom in electrophilic reactions such as diazo coupling. To offset the undesired azo coupling route, amino derivatives blocked by methyl group in position 4 (4a, b) were then used to obtain the desired triazene coumpounds.

We found that reaction conditions used in earlier studies[2] (weakly basic water--alcohol solution) yielded a mixture of decomposition products only; in the presence of hydrophosphate buffer (pH 4-5), however, the triazene coupling took place and 1-(3-isoquinolyl)-3-aryltriazenes (5) could be isolated as yellow crystals.

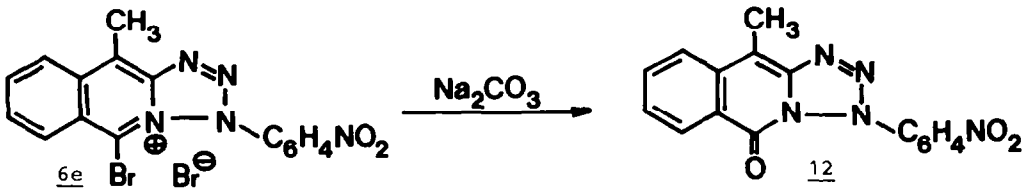


	Ar	R
a	p-Br-C_6H_4-	H
b	p-Cl-C_6H_4-	H
c	p-F- C_6H_4-	H
d	p-NO_2-C_6H_4-	H
e	p-NO_2-C_6H_4-	Br

	Ar	R
a	p-Br-C_6H_4-	H
b	p-Cl-C_6H_4-	H
c	p-F- C_6H_4-	H
d	p-NO_2-C_6H_4-	H
e	p-NO_2-C_6H_4-	Br
f	p-NO_2-C_6H_4-	morph.

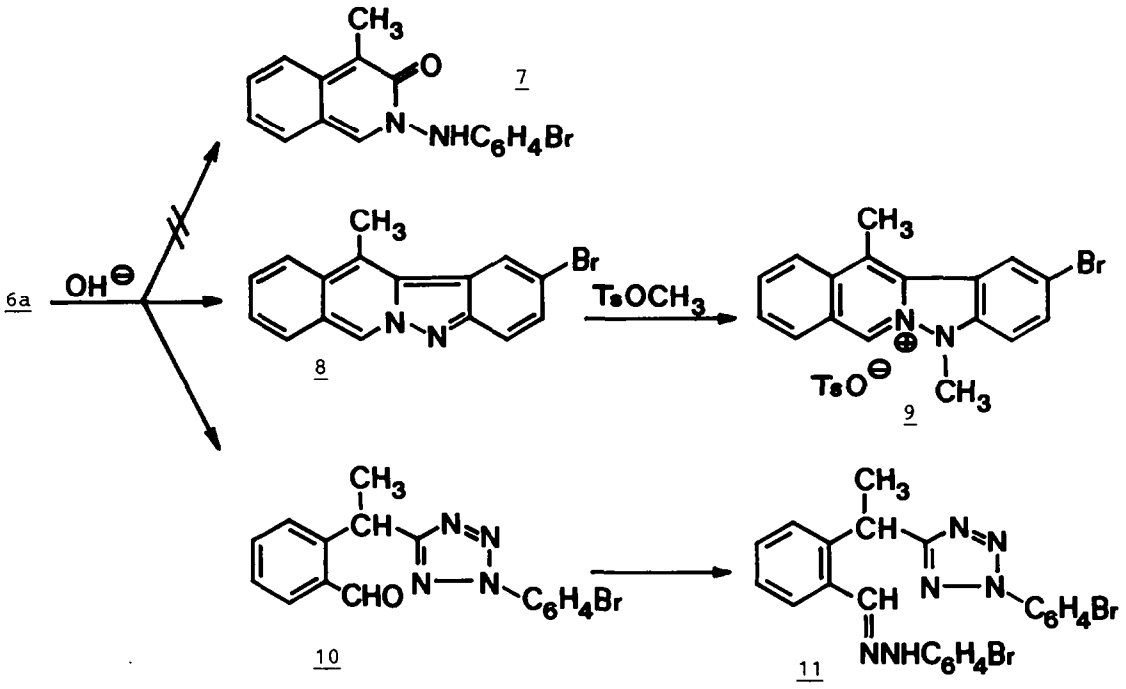
Cyclization of triazenes 5 by 2,4,4,6-tetrabromocyclohexa-2,5-dien-1-one[5] (TBB) proceeds under surprisingly mild conditions (even at -10°C) compared to the angularly annelated cases (boiling dichloromethane)[2]. The new tetrazolium bromides or fluoroborates (6) were stable compounds, on reaction with sodium dithionite they afforded the starting triazenes (5)[6].

Interestingly, while p-nitrophenyl substituted triazenes were found to be unreactive in the presence of TBB in earlier cases[2], triazenes 5d, e gave the corresponding tetrazolium salts (6d, e) in a few minutes. The preparative importance of this finding is that, in this way, tetrazolium salts having very reactive bromine atom in position 5 (adjacent to the positively charged nitrogen) become readily available which, in turn, may serve as starting materials for introduction of novel substituents in that position. Thus, for instance, reaction of 6e with morpholine gave 10-methyl-5-morpholino-3-p-nitrophenyltetrazolo(1,5-b)isoquinolinium bromide (6f) whereas the reaction with aqueous sodium carbonate solution yielded 10-methyl-3-p-nitrophenyltetrazolo(1,5-b)isoquinolin-5(4H)-one (12).



As reported in our previous paper[2], reaction of the angularly fused tetrazolo-(1,5-a)quinolinium or tetrazolo(5,1-a)isoquinolinium salts with tetramethylammonium hydroxide (TMAH) resulted in nitrogen elimination and formation of N-anilino-quinolones and isoquinolones, respectively. Experiments in this study have shown that the linearly fused tetrazolium salt (6) reacts in an entirely different way. Its treatment with TMAH at room temperature gives immediately a deeply coloured solution accompanied by slow gas evolution and deposition of a yellow precipitate. The IR spectrum of this solid product excluded the formation of an N-anilinoiso-quinoline structure (7) (no carbonyl band) expected on the basis of earlier cases[2].

200 MHz proton spectrum of this product displayed an AMX and an ABXY multiplet



pattern (δ_H 7.65 to 8.66 ppm) attributable, resp., to tri- and disubstituted aromatic ring protons, a methyl signal (δ_H 3.41 ppm) and an "isolated" one-proton resonance at 9.76 ppm heavily broadened through long range couplings with ABXY and Me protons ($J_{H,Me}$ = 1.03 Hz). These findings, together with other spectral evidence, indicated that the ring closure occurred via N_2-elimination and that the product molecule may be represented by one of the alternative structure shown in Fig. 1 (a or b). In terms of proton NMR, these structures differ primarily in the number of bonds separating the unsaturated CH at 9.76 ppm and the Me protons. While the 1.03 Hz may be readily accounted for the assuming four-bond coupling pathway, ^4J (H-7,Me), available in b (Fig. 1), mechanistic considerations obviously favour structure a where, however, the interacting protons are separated by six chemical bonds, ^6J (H-7, Me), an unusually large distance for sizable couplings to be observed.

Fig. 1 Alternative structures for the product obtained by reaction of 6a with TMAH

An unambiguous distinction between a and b (Fig. 1) was inferred from C-13 NMR spectra (50 MHz) of the product. Assignment of the proton-bearing carbon atoms was conveniently performed by means of two-dimensional (2D) heteronuclear chemical shift correlation experiment[7], whereas quaternary C atoms were identified through their long range couplings with neighbouring protons ($^nJ_{CH}$, n = 2,3,4) in a series of pulsed selective polarization transfer ("selective INEPT") experiments[8]. For each proton site, two separate INEPT runs were performed in which the pertinent delay times ($\Delta_1 \sim \Delta_2$ = 1/2 ($^nJ_{CH}$) for CH pairs and 1/4 ($^nJ_{CH}$) for Me group)[8] were adjusted such to give optimum polarization transfer via the smaller $^2J_{CH}$ and $^4J_{CH}$ (~0.5 to 2 Hz) and via the larger vicinal $^3J_{CH}$ couplings (~3 to 8 Hz).

Evaluation of the carbon-proton coupling pathways deduced from these experiments has led to a consistent labelling of each carbon and proton site of the molecule. The particular finding that quaternary carbon atoms resonating at 133.29 (C-12a) and 134.80 ppm (C-11a) are vicinally coupled to both the CH at 9.76 ppm and the Me protons has settled the molecular structure as portrayed by structure a in Fig. 1.

Compound 8 could be readily methylated by p-toluenesulphonic acid methyl ester to give pale yellow tosylate salt 9. Extraction of the mother liquor obtained after the isolation of 8 with dichloro methane gave a second product as colourless crystals. Proton NMR (60 MHz) unambiguously indicated the formation of α-(2-p-bromophenyltetrazolyl-5)-o-ethyl benzaldehyde (10) in 40 per cent yield. Formation of 10 is strongly reminiscent of some reactions of the bicyclic tetrazolo(5,1-a)-pyridinium system[2] leading to the opening of the pyridine ring. It seems very like that the anion attacks the linearly fused tetrazolium system at C-5 and the resulting intermediate undergoes a ring opening process as shown in Fig. 2. The presence of the aldehyde function in 10 was also verified experimentally by preparing the stable crystalline p-bromophenylhydrazone 11.

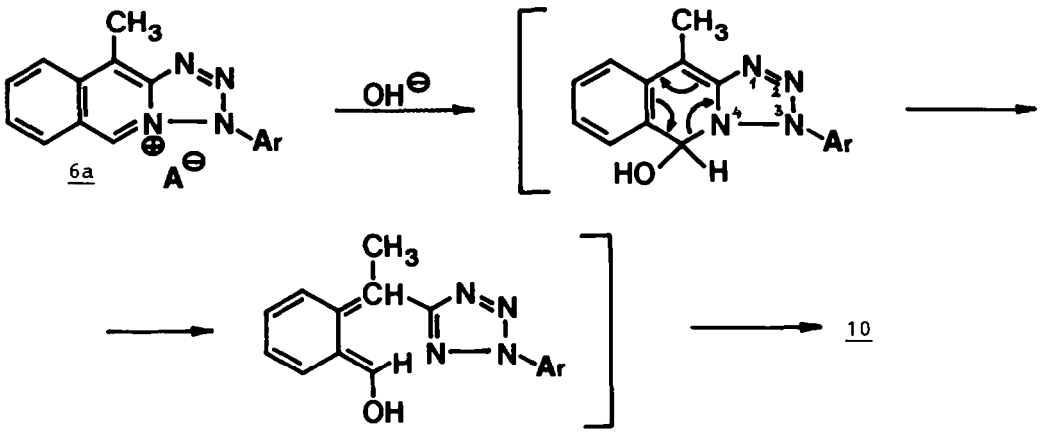
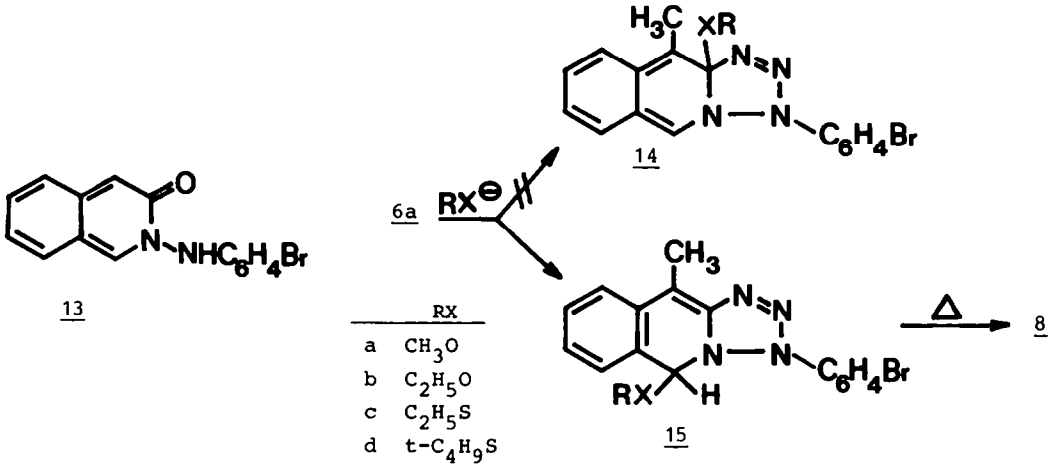


Fig. 2. Proposed mechanism of formation of α-(2-p-bromophenyltetrazolyl-5)-o-ethyl benzaldehyde (10)

As shown by these results, the linearly fused tricyclic tetrazolium salt has an ambident reactivity towards hydroxide anion which results in the simultaneous formation of aldehyde 10 and tetracycle 8. This ambidency can be rationalized by assuming that the nucleophilic reagent (in a similar manner to other cases[2]) attacks the heteraromatic cation both at C-5 and C-10a; the former attack yields product 10 while the latter leads to the intermediate formation of 7 followed by subsequent ring closure/water elimination step giving 8. In order to verify this contention, N-p-bromophenylaminoisoquinolin-3(2H)-one (13) was prepared by independent synthesis[9] and was subsequently treated with TMAH using the same conditions as with

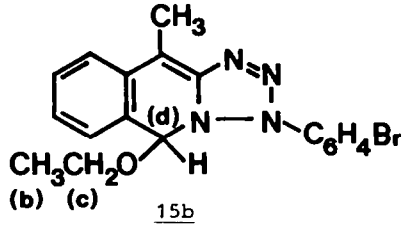
synthesis of 8. Contrary to our expectations, no reaction could be detected and the starting material was recovered in quantitative yield. Consequently, compound 7 cannot be regarded as the intermediate of tetracycle 8. A solution to this problem could finally be obtained by studying the reaction of the linearly fused tetrazolo (1,5-a)isoquinolinium salt (6) with alcoholates and thioalcoholates.



We found that treatment of the acetonitrile solutions of 6 with sodium alcoholates or a mixture of mercaptan and sodium alcoholate gave rapidly a red solution followed by the separation of deep red crystals. As shown by proton NMR, these products contain alkoxy and alkylthio group, respectively, and, by treatment with acid, can be reconverted to the starting material. These two pieces of evidence revealed that the new red coloured compounds were pseudo bases (the addition products of the nucleophile anion and the tetrazolium cation) and formation of either of the two possible structures (14, or 15) could be anticipated. Distinction between 14 and 15 was readily available from the carbon-13 NMR spectra of the product molecules. As shown by the chemical shift data in Table 1, both the ethoxy and the ethylthio groups are attached to a proton-bearing carbon atom, a finding that verifies structure 15 and clarly discards 14 as an alternative structure[10].

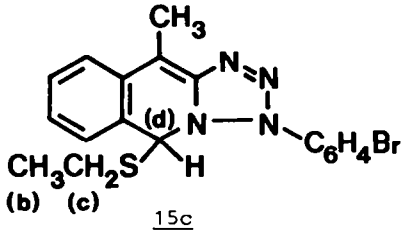
The new pseudo bases (15a-d) proved to be fairly stable in the crystalline state (several weeks) whereas their solutions underwent rapid decomposition even at room temperature. When 15 was added to boiling toluene, the initial red colour disappeared rapidly, a yellow solution formed, and a few minutes later, crystals of

Table 1. ^{13}C-NMR chemical shifts of relevant proton-bearing carbon atoms in 15b and 15c (δppm) (C_6D_6, 25°C)



15b

(a)	11.0
(b)	15.4
(c)	65.1
(d)	85.8



15c

(a)	11.2
(b)	15.2
(c)	27.0
(d)	68.4

2-bromo-12-methylindazolo(2,3-b)isoquinoline (8) separated in farily good yield. The occurrence of this reaction (formation of 8 from 15 in aprotic solvent) suggests that formation of 15-like base has to be anticipated also in the reaction with hydroxide ion as shown in Fig. 3. In other words, the hydroxy-analogue of 15 (Fig.3; RX = OH) can be considered as a common intermediate in reactions leading to 8 and 10, respectively.

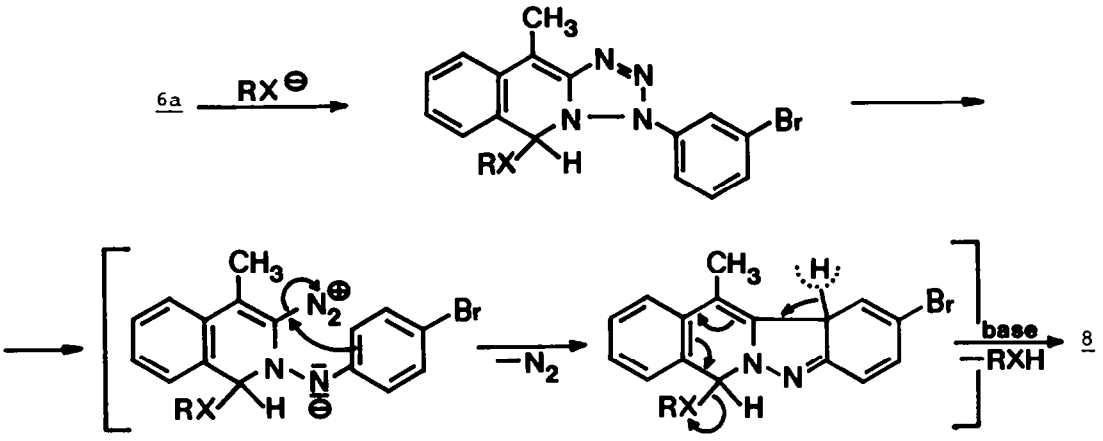


Fig. 3. Supposed mechanism of formation of the indazolo(2,3-b)-isoquinoline ring system (8)

Comparison of the reactivities of the linearly fused tetrazolium salt (8) with those of related bicyclic and angularly fused tricyclic systems studied earlier[2] shows that, in each case, regioselective nucleophilic reactions take place and the selectivity depends strongly on the type of annelation. Since mechanistic consideration suggested that the formation of pseudo bases constitutes the first step of the conversions, it seemed of interest to compare the estimated stabilities of the conversions. In Fig. 4, to types of pseudo bases corresponding to attack of nucleophile at both positions adjacent to the positively charged nitrogen are portrayed for the four ring systems using Clar's notation for the separated π-electron sextets[11]. From the inspection of this Figure it can be seen that both

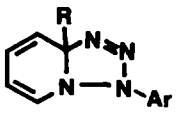
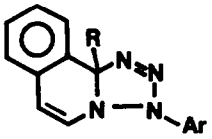
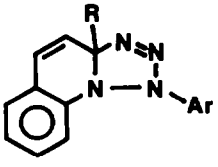
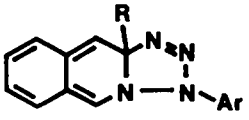
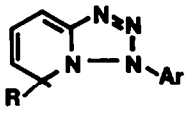
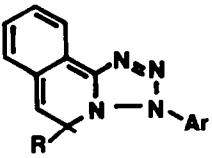
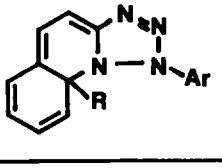
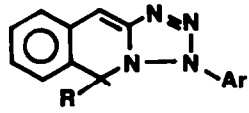
Type	tetrazolo-(1,5-a)pyridinium	tetrazolo-(5,1-a)isoquinolinium	tetrazolo-(1,5-a)quinolinium	tetrazolo-(1,5-b)isoquinolinium
A				
B				

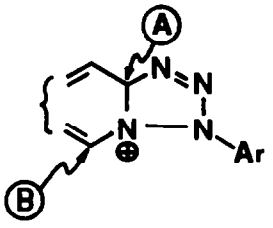
Fig. 4. Comparison of stabilities of pseudo bases obtained by reaction of differently annelated tetrazolium salts with nucleophile (R^-)

types of pseudo bases with the bicyclic system are equally stable, whereas an essential difference is to be expected with the tricyclic compounds: in the case of the angularly fused rings pseudo base of type A, while with the linearly annelated system pseudo base of type B (i.e. those types having one circle in the valence bond representation) should be regarded as the more stable. In fact, this experimental study showed that only these preferred pseudo bases were formed in the tricyclic cases and the alternative routes could not have been observed in any case.

The above interpretation of the regioselective reactions of the differently annelated systems involves the supposition of a thermodynamic control in formation of the pseudo bases. When the question, however, is raised from the side of the starting azolium salt (kinetic control), interestingly, the same result can be obtained. For this purpose, CNDO/II calculations have been carried out for the electronic distribution in the heteroaromatic cations[12]. The c_{LUMO} coefficients and q_{net} charges for the two centres adjacent to the bridge head nitrogen(the most probable targets of the reagent) are summarized in table 2. From this comparison

Table 2. Electronic distribution in fused tetrazolium salts

Center	Value	tetrazolo (1,5-a) pyridinium	tetrazolo (1,5-a) quinolinium	tetrazolo (5,1-a) isoquinolinium	tetrazolo (1,5-b) isoquinolinium
A	c_{LUMO}	0.44	0.44	0.46	0.02
	q_{net}	+0.23	+0.24	+0.29	+0.19
B	c_{LUMO}	0.18	0.09	0.07	0.55
	q_{net}	+0.10	+0.12	+0.16	+0.10



For calculations, 3-aryl groups were neglected and were changed for hydrogen atoms. Geometry of the bicyclic tetrazolopyridinium systems has been determined earlier[13]. For the annelating benzene rings in the tricyclic systems, the common values of bond length and angles were taken.

it appears that both values are comparable in the case of bicyclic system. With the angularly fused tricyclic azolium systems, values belonging to the bridge head carbon atom are considerably higher than those calculated for the "α-carbon atom", whereas the situation dramatically changes in the case of the linearly fused system and the c value at the "α-carbon atom" became to be higher by one order of magnitude.

The authors believe that the observed nucleophilic reactivities of the differently annelated tetrazolium salts, the surprising dependency of the regioselectivity on the mode of annelation represents a novel example for the "annelation effect".

EXPERIMENTAL PART

Melting points were determined by a Büchi apparatus and are uncorrected. IR spectra were recorded on a Unicam SP-200, UV spectra on a Unicam SP-800 equipment.

60 MHz NMR spectra were obtained by a Varian EMX-360 spectrometer. The 200 (^{1}H) and 50.13 (^{13}C) MHz NMR spectra were recorded on a Bruker WP 200/SY instrument, at ambient temperature. Mass spectra were obtained with an AEI MS-902 spectrometer.

3-Amino-4-arylazoisoquinolines (2a-c)

A solution of 3-aminoisoquinoline or 3-amino-1-bromoisoquinoline (1), respectively, (7 mmol) in ethanol (80 ml) and water (60 ml) was treated with a solution of the appropriate aryldiazonium fluoroborate (7.5 mmol) in acetonitrile (10 ml) at 0°C. The mixture was stirred for 3 h, stored in a refrigerator overnight and the precipitated red solid was filtered. Recrystallization from benzene afforded red needles.

Compound 2a:

M.p. 236-37°C; 66%. Anal. Calc. for $C_{15}H_{11}N_4Br$ (327.20); C, 55.06; H, 3.63; N, 17.12; Br, 24.42. Found: C, 54.92; H, 3.54; N, 17.25; Br, 24.60. MS: 327(39), 155(13), 143(100). UV (EtOH): 466 (4.25), 330 (3.89). NMR (DMSO-d_6 + $CDCl_3$): δ 9.0 (s, 1H, H-1); 8.2 (s, NH); 8.8-7.2 (m, 8H, H-Ar).

Compound 2b:

M.p. 251-52°C; 64%. Anal. Calc. for $C_{15}H_{10}N_4Br_2$ (406.11): C, 44.36; H, 2.48; N, 13.8. Found: C, 44.12; H, 2.35; N, 13.61. UV (EtOH): 470 (4.27), 336 (3.84).

Compound 2c:

M.p. 229-31°C, 59%. Anal. Calc. for $C_{16}H_{13}N_4BrO$ (357.23): C, 53.80; H, 3.67; N, 15.69. Found: C, 53.69; H, 3.51; N, 15.82. UV (EtOH): 464 (4.33), 336 (3.84).

Imidazo(4,5-c)isoquinoline compounds (3a-c)

A solution of the appropriate 3-amino-4-arylazoisoquinoline (2) (4.3 mmol) in ethanol (100 ml) was mixed with anisaldehyde (0.59 g, 0.48 ml, 4.3 mmol) and with one drop of conc. hydrochloric acid and the mixture was refluxed for 3 h. The resulting reddish yellow solution was then evaporated, the residue was treated with triethylamine (0.5 ml) and water (30 ml) and the resulting precipitate was filtered off and recrystallized.

Compound 3a:

M.p. 233-35°C (BuOH), 46%. Anal. Calc. for $C_{23}H_{17}N_4BrO$ (445.34): C, 62.03; H, 3.85; N, 12.58; Br, 17.95. Found: C, 62.16; H, 3.60; N, 12.83; Br, 17.89. MS: 445(6), 274(100). UV (EtOH): 353 (4.22), 300 (4.21). NMR (DMSO-d_6 + $CDCl_3$): 10.35 (s, 1H, H-5); 9.15 (s, 1H, NH); 8.30-7.50 (m, 4H, H-Ar); 8.05 and 6.45 (AA'BB', 4H, methoxyphenyl); 7.30 and 7.00 (AA'BB', p-bromophenyl); 3.80 (s, 3H, CH_3).

Compound 3b:

M.p. 186-88°C (nitromethane), 45%. Anal. Calc. for $C_{25}H_{21}N_4BrO_2$ (489.39): C, 61.36; H, 4.33; N, 11.45. Found: C, 61.09; H, 4.22; N, 11.36.

Compound 3c:

M.p. 276.78 (BuOH), 35%. Anal. Calc. for $C_{26}H_{24}N_4O_3$ (440.51): C, 71.05; H, 5.28; N, 12.75. Found: C, 70.89; H, 5.12; N, 12.94.

3-Isoquinolyltriazenes (5)

Compounds 5a-c:

To a mixture of a solution of 3-amino-4-methylisoquinoline (4a)[14] (3.0 g, 1.9 mmol) in ethanol (120 ml) and a solution of sodium dihydrogenphosphate (4.0 g) in water (240 ml), a solution of the appropriate diazonium fluoroborate (2.0 mmol) in acetonitrile (10 ml) was added at once at 0 – -5°C and the resulting mixture was stored without stirring for 40 h in a refrigerator. Voluminous yellow precipitate was formed which was filtered and recrystallized from benzene. Yields, and physical data are given in table 3.

Compounds 5d,e:

To a solution of the appropriate amino compound (4a,b) (12.6 mmol) in glacial acetic acid (420 ml), ethanol (280 ml), sodium acetate hydrate (24 g) and crushed ice (280 g) were added and the resulting solution was mixed with a solution of 4-nitrophenyldiazonium fluoroborate (7.2 g, 32 mmol) in acetonitrile (10 ml) at -2°C. The mixture was allowed to stand and was worked up as described above. For data, see table 3.

Table 3. Characteristics of 3-isoquinolyltriazenes (5a-e)

No	R	Ar	Analysis		C	H	N	m.p.(°C); yield(%)	UV (EtOH) λ_{max} (log ε)
5a	H	4-Br-C_6H_4-	$C_{16}H_{13}N_4Br$ (341.23)	Calc.	56.32	3.84	16.42	190-91; 58	382(4.38) 354(4.37) 226(4.42)
				Found	56.10	3.60	16.24		
5b	H	4-Cl-C_6H_4-	$C_{16}H_{13}N_4Cl$ (296.77)	Calc.	64.76	4.42	18.88	187-88; 53	380(4.41) 356(4.40) 228(4.50)
				Found	64.52	4.17	18.95		
5c	H	4-F-C_6H_4-	$C_{16}H_{13}N_4F$ (280.31)	Calc.	68.56	4.67	19.99	167-68; 28	375(4.33) 349(4.37) 226(4.49)
				Found	68.37	4.52	19.84		
5d	H	4-NO_2-C_6H_4-	$C_{16}H_{13}N_5O_2$ (307.32)	Calc.	62.53	4.26	22.79	212-13; 75	402(4.57) 221(4.54)
				Found	62.41	4.10	22.98		
5e	Br	4-NO_2-C_6H_4-	$C_{16}H_{12}BrN_5O_2$ (386.23)	Calc.	49.76	3.13	18.13	181-82; 68	408(4.49)
				Found	49.61	2.95	17.87		

Tetrazolo(1,5-b)isoquinolinium salts (6)

Compounds 6a-c:

A solution of the appropriate triazene compound (5a-c) (6 mmol) in dichloro methane (40 ml) was treated with solid tribromophenol bromine (80 g, 19.5 mmol) at 0°C with stirring. Orange yellow crystals separated from the solution which was filtered in 30 min. This perbromide salt was suspended in nitromethane (20 ml) and the suspension was treated with cyclohexene (2 ml). The resulting cream coloured thick suspension was filtered off and the solid was recrystallized. Data for products are given in table 4.
The bromide salts could be converted to fluoroborates by treatment of their methanol—water solution with fluoroboric acid. (E.g. 6a, A = BF_4: m.p. 232-34°C.) ^{1}H-NMR (TFA) of compound 6a: δ 9.65 (s, 1H, H-5); 8.6-7.6 (m, 4H, H-Ar): 7.71 (s, 4H, H-p-bromophenyl); 3.45 (s, 3H, CH_3).

Compounds 6d,e:

A suspension of the appropriate triazene compound (5d or e) (1.8 mmol) in dimethyl fpr,a,ode (30 ml) was stirred at room temperature and was treated with solid tribromophenol bromine (3.0 g, 65 mmol). After 10 min, ether was carefully added to the red solution whereupon orange yellow perbromide salt separated. De-bromination with cyclohexene and further work-up was accomplished as described above. For data see table 4.

Compound 6f:

A suspension of 5-bromo-10-methyl-3-p-nitrophenyltetrazolo(1,5-b)isoquinolinium bromide (6e) in methanol (15 ml) was stirred in an ice bath and was treated with morpholine (3 ml). The starting material rapidly dissolved and a new suspension was formed. After few minutes, ether (15 ml) was added and the product was filtered. For data, see table 4.
IR (KBr): 3050 (CH-Ar); 2800 (CH-Alk); 1610, 1590, 1500 (C=C), C=N) cm^{-1}.

Reaction of 6a with hydroxide ion

Method (a). Formation of 2-bromo-12-methylindazolo(2,3-b)isoquinoline (8): A solution of 3-p-bromophenyl-10-methyltetrazolo(1,5-b)isoquinolinium fluoroborate (6a, A = BF_4) (2.0 g, 4.7 mmol) in acetonitrile (40 ml) was treated with a 10 per cent solution of tetramethylammonium hydroxide in water (16 ml) at room temperature and the mixture was stirred for 2 h. A deep red colour was developed at once which turned to deep yellow at the end of this period, a slow gas evolution could be observed and a fine precipitate was formed. The mixture was then filtered off, the solid product was recrystallized from pyridine (3 ml) to give 2-bromo-12-methylindazolo(2,3-b)isoquinoline (8) as brilliant yellow crystals (0.5 g, 35%) m.p. 239-40°C.

Table 4. Characteristics of tetrazolo(1,5-b)isoquinolinium salts (6a-f)

	R	Ar	Analysis		C	H	N	m.p.(°C); yield (%) (solvent of recryst.)	UV(EtOH) λ_{max}(log ε)
a	H	4-Br-C_6H_4-	$C_{16}H_{12}N_4Br_2$	Calc.	45.74	2.88	13.34	250-52; 61	358(3.98)
			(420.14)	Found	45.56	2.58	13.17	(W-Et)	277(4.18)
b	H	4-Cl-C_6H_4-	$C_{16}H_{12}BrClN_4$	Calc.	51.15	3.22	14.91	237-38; 63	356(4.12)
			(375.68)	Found	50.98	3.07	14.65	(W-Et)	275(4.36)
c	H	4-F-C_6H_4-	$C_{16}H_{12}N_4BrF$	Calc.	53.50	3.37	15.60	231-33; 60	354(4.45)
			(359.22)	Found	53.21	3.62	15.85	(ME/EE)	263(4.16)
d	H	4-NO_2-C_6H_4-	$C_{16}H_{12}BrN_5O$	Calc.	49.75	3.13	18.13	226-28; 55	362(4.19)
			(386.23)	Found	49.63	2.94	18.39	(NM)	233(4.63)
e	Br	4-NO_2-C_6H_4-	$C_{16}H_{11}Br_2N_5O_2$	Calc.	41.32	2.38	15.06	146-47; 33	394(3.58)
			(465.14)	Found	41.09	2.41	15.42	(DMF/EE)	270(4.37)
f	Mf	4-NO_2-C_6H_4-	$C_{20}H_{19}BrN_6O_3$	Calc.	50.97	4.06	17.83	136-38; 70	365(4.03)
			(471.34)	Found	50.68	4.24	17.54	(ME)	275(4.10)

Abbreviations: W-Et: 50% water–ethanol; ME methanol; EE: ethyl ether; NM: nitromethane; Mf: morpholino

Anal. Calc. for $C_{16}H_{11}N_2Br$ (311.20); C, 61.75; H, 3.56; N, 9.00. Found: C, 61.47; H, 3.32; N, 8.88. MS: 311(100); 230(9); 202(22); 101(13). ^{1}H-NMR (400 MHz, DMF-d_7-$CDCl_3$ = 1:1 solvent mixture): 9.36 (m, 1H, $J_{H,Me}$ = 1.03); 8.51 (dd, 1H, J_m = 1.7, J_p = 0.7, H-1); 8.24 (m, 1H, J_o = 8.3, J_m = 1.9, J_p = 0.5, H-11); 7.92 (m, 1H, J_o = 8,0, J_m = 2.0, J_p = 0.5, H-15); 7.70 (m, 1H, J_o = 8.85, J_p = 0.7, H-4); 7.66 (m, 1H, J_o = 8,0, J_m = 1.9, H-10); 7.52 (m, 1H, J_o = 8.0, J_m = 1.9, H-9); 3.26 (d, 3H, $J_{H,Me}$ = 1.03 Mh).

Owing to the limited solubility of the free base 8, ^{13}C and related ^{1}H-NMR spectra were recorded on the protonated form using TFA-d_1-$CDCl_3$ (1:1) solvent mixture with TMS as internal reference.

^{1}H-NMR ($\delta_H^{TFA-CDCl_3}$) 9.76 (1H, m, H-7); 8.66 (1H, m, H-1); 8.55 (1H, m, H-11); 8.31 (1H, m, H-8); 8.15 (1H, m, H-10); 8.01 (1H, m, H-9); 8.01 (1H, m, H-3); 7.65 (1H, m, H-4); 3.41 (3H, Me). Interproton couplings remained practically unchanged upon protonation.

^{13}C-NMR ($\delta_C^{TFA-CDCl_3}$): 139.87 (s, C4a); 137.08 (s, C3); 134.87 (d, C10); 134.80 (d, C3); 133.29 (s, C4); 132.17 (d, C9); 131.46 (s, C7a); 129.19 (d, C8); 128.36 (d, C7); 127.34 (d, C1); 126.94 (s, C12); 124.92 (d, C11); 120.01 (s, C12b); 118.93 (s, C1); 112.97 (d, C4); 14.92 (q, C12-Me). IR (KBr): 3000, 2900 (CH); 1610, 1580, 1490, 1480 (C=C, C=N) cm^{-1}. UV (CH_3CN): 394 (4.06); 374 (3.65); 314 (4.25); 304 (4.07); 290 (3.92). UV (TFA): 384 (4.14); 368 (4.03); 3.04 (4.24); 287 (4.22).

Method (b). Formation of α-(2-p-bromophenyltetrazolyl-5)-o-ethylbenzaldehyde (10): The mother liquor obtained as above was mixed with 50 ml of water then the mixture was extracted three times by dichloromethane. Evaporation of the organic solvent followed by crystallization from ether gave 0.65 g (40%) of product, m.p. 65-70°C. Anal. Calc. for $C_{16}H_{13}BrN_4O$ (357,23); C, 53.80; H, 3.67; N, 15.69; Br 22.37. Found: C, 53.52; H, 3.49; N, 15.41; Br, 21.95. ^{1}H-NMR ($CDCl_3$): δ 10.5 (s, 1H, CHO); 8.1-7.5 (m, 8H, H-Ar); 5.8 (q, 1H, -CH=); 1.9 (d, 3H, CH_3). IR (KBr): 3050, 2900, 2800 (CH); 1690 (C=O); 1600-1580 (C=C, C=N) cm^{-1}.

2- Bromo-5,12-dimethylindazolo(2,3-b)isoquinolinium tosylate (9)

A mixture of compound 8 (0.4 g, 1.3 mmol) and p-toluenesulfonic acid methyl ester (1 ml) was stirred at 120°C for 5 min. A solution was first formed then a thick mass of crystals deposited. The cold reaction mixture was filtered off, the product was washed with ether and recrystallized from ethanol to give 0.45 g (70%) of tosylate salt, m.p. 272-74°C.

Anal. Calc. for $C_{24}H_{21}BrN_2O_3S$ (497.43); C, 57.95; H, 4.26; N, 5.63; S, 6.45. Found: C, 57.68; H, 4.09; N, 5.37; S, 6.09. ^{1}H-NMR (TFA): δ 10.3 (s, 1H, H-7); 8.8-7.9 (m, 7H, H-Ar); 4.4 (s, 3H, N-Me); 3.3 (s, C-Me). IR (KBr): 3050, 2970 (CH); 1610, 1500, 1480 (C=C, C=N) cm^{-1}.

α-(2-p-Bromophenyltetrazolyl-5)-o-ethylbenzaldehyde p-bromophenylhydrazone (11)

A solution of aldehyde compound 10 (0.4 g, 1.1 mmol) in ethanol (10 ml) was first diluted with a little amount of water still to obtain a solution, then the mixture was treated with a solution of p-bromophenylhydrazine (0.3 g, 1.3 mmol) in 5 ml of 50 per cent ethanol. An oily precipitate was formed which slowly crystallized. After 2 days the product was filtered and crystallized from acetonitrile to give 0.34 g (58%) of product, m.p. 186-88°C.
Anal. Calc. for $C_{22}H_{18}Br_2N_6$ (526.27); C, 50.21; H, 3.45; N, 15.97; Br, 30.37. Found: C, 50.03; H, 3.20; N, 15.61; Br, 29.90.

10-Methyl-3-p-nitrophenyltetrazolo(1,5-b)isoquinolin-5(4H)one (12)

Solid 5-bromo-10-methyltetrazolo(1,5-b)isoquinolinium bromide (6e) (0.5 g, 1.4 mmol) was added to a 10 per cent solution of sodium carbonate in water (15 ml) with stirring and the mixture was stirred for an addition hour at room temperature. During this time an orange suspension was formed which was filtered and the solid product was crystallized from toluene to give 0.25 g (56%) of product, m.p.227-28°C.
Anal. Calc. for $C_{16}H_{11}N_5O_3$ (321.30); C, 59.81; H, 3.45; N, 21.80. Found: C, 59.82; H, 3.31; N, 2.59. IR (KBr): 3050, 2900 (CH); 1660 (C=O); 1620, 1590, 1490, 1410 (C=C, C=N); 1530, 1350 (NO_2) cm^{-1}.

Reaction of 6a with sodium dithionite

A solution of tetrazolium salt 6a (0.3 g, 0.7 mmol) in a mixture of acetonitrile (10 ml), methanol (20 ml) and water (20 ml) was treated with a solution of sodium dithionite (0.15 g, 0.8 mmol) in water (15 ml) containing sodium hydrogencarbonate (0.1 g) and the mixture was stirred at room temperature. Within few minutes, a deeply coloured mixture was first formed then a yellow solid precipitated which was filtered off in 20 min. The product proved to be identical (mp. and IR) with the authentic sample of triazene compound 5a.

Table 5. Characteristics of pseudobases 15a - d

No	Reagent used m.p.(°C); yield(%)	Analyses	^{1}H-NMR (δ ppm)
15a	Sodium methylate	$C_{17}H_{15}BrN_4O$ (371.26)	8.0-7.2 (m, 8H, H-Ar)
			5.85 (s, 1H, H-5)
	90-92; 76	Calc. C 54.99 H 4.07 N 15.09	3.15 (s, 3H, OCH_3)
		Found C 54.60 H 3.87 N 14.87	2.40 (s, 3H, CH_3)
			($CDCl_3$)
15b	Sodium ethylate	$C_{18}H_{17}BrN_4O$ (385.28)	8.2-7.0 (m, 8H, H-Ar)
			6.0 (s, 1H, H-5)
	82-84; 73	Calc. C 56.11 H 4.45 N 14.54	3.4 (q, 2H, CH_2)
		Found C 55.93 H 4.21 N 14.20	1.05 (t, 3H, CH_3-ethyl)
			2.50 (s, 3H, 10-Me)
			($CDCl_3$)
15c	Sodium mercaptan+ Sodium ethylate	$C_{18}H_{17}BrN_4S$ (401.35)	7.7-7.2 (m, 8H, H-Ar)
			6.2 (s, 1H, H-5)
	67-69; 68	Calc. C 53.87 H 4.27 S 7.99	2.40 (s, 3H, CH_3)
		Found C 53.61 H 4.69 S 7.01	2.35 (q, 2H, CH_2)
			1.0 (t, 3H, CH_3-ethyl)
			(C_6D_6)
15d	t-Butylmercaptan+ Sodium ethylate	$C_{20}H_{21}BrN_4S$ (429.40)	7.8-7.1 (m, 8H, H-Ar)
			6.0 (s, 1H, H-5)
	75-77; 47	Calc. C 55.94 H 4.93 S 7.47	2.4 (s, 3H, CH_3)
		Found C 55.61 H 4.69 S 7.01	1.1 (s, 9H, butyl-Me)
			(C_6D_6)

Preparation of pseudo bases 15a - d

A solution of tetrazolium salt 6a (0.5 g, 1.2 mmol) in acetonitrile (5 ml) was treated with a solution of the appropriate reagent (1.4 mmol) in ethanol (10 ml)[15] at 0°C. A deep red solution was formed at once followed by separation of red needles. The product was filtered and washed with cold ethanol. Date for products are summarized in table 5.

Formation of 8 from pseudobases 15a - d

Solid pseudobases 15a (1.0 g, 2.7 mmol) was added to boiling toluene (5 ml) and the reflux was continued for an additional 5 min. Brisk gas evolution was observed, the deep red colour changed to yellow and yellow crystals deposited. The cold mixture was then filtered to give 0.35 g (42%) of indazoloisoquinoline compound 8 which proved to be identical (m.p., UV, IR) with the sample obtained by the alternative route.
The same product could be isolated starting from compound 15b (48%), 15c (62%) and 15d (47%)

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REFERENCES AND NOTES

[1]Linearly fused isoquinolines. Part III. For Part II see: Gy. Hajós and A.Messmer, *J. Heterocycl. Chem.*, 15, 463-465 (1978).

[2]Fused azolium salts. Part IX. Previous papers of the series: Part VII. A. Messmer, Gy. Hajós, J. Fleischer and M. Czugler, *Monatsh.* 1227-1231 (1985); Part VIII. A. Messmer, A. Gelléri and Gy. Hajós, *Tetrahedron*, in press.

[3]In the course of our investigation with azide-tetrazole equilibria, we described the formation of this cation by protonation of the neutral tetrazolo(1,5-b)-isoquinoline: A. Messmer and Gy. Hajós, *J. Org. Chem.*, 46, 834-846 (1981).

[4]This type of ring closure is well known with naphthalene derivatives: O. Fischer, W. Meier, H. Schwappacher and J. Kracker, *J. prakt. Chem.*, 104, 102-122 (1922).

[5]V. Calo, F. Ciminale, L. Lopez and P.E. Todesco, *J. Chem.Soc.*(C), 1971,3652-3653.

[6]Similar behaviour was found in the case of bicyclic and angularly fused tricyclic tetrazolium salts: A. Messmer and A. Gelléri, *Angew. Chem.*, 77, 171 (1965).

[7]A. Bax, *J. Magn. Reson.*, 53, 517-520 (1983).

[8]A. Bax, *ibid.* 57, 314-318 (1984).

[9]J.O. Halford and B. Weissmann, *J. Org. Chem.*, 18, 30-35 (1953).

[10]Owing to the low stability of molecules 15b,c in the solution state, carbon-13 spectra had to be recorded with few transients. With the instrumentation available, this was sufficient to detect proton bearing carbon atoms only. The chemical shift data of carbon atoms (c) and (d), however, clearly demonstrate the formation of structure 15.

[11](a) E. Clar, *The Aromatic Sextet*, J. Wiley, New York, 1972; (b) Gy. Hajós, A. Messmer, A. Neszmélyi and L. Párkányi, *J. Org. Chem.*, 49, 3199-3203 (1984).

[12]J.A. Pople, D.P. Santry and G.A. Segal, *J. Chem. Phys.*, 43, Part 2, S-129-S-135 (1965).

[13]For the X-ray structure elucidation, see: K. Sasvári, M. Czugler and A. Gelléri, *Acta Cryst.*, B35, 2145-2149 (1979).

[14]H. Win and H. Tickelman, *J. Org. Chem.*, 32, 59-61 (1967).

[15]In the case of compound 15a, methanol was used as solvent.