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Synthesis and Ring Transformation of Novel Tetracyclic Fused as-Triazines**

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Summary. Eight new tetracyclic fused as-triazines (**4** – **6**, **8**, **11** – **13**, and **15**) have been synthesized by conversion and subsequent ring transformation of 1,2-diaminoisoquinolinium (**2**) and -quinolinium salts (**9**) with 4-benzoyl-5-phenylfuran-2,3-dione (**1**). Selective alkylations of the new products revealed that these reactions are governed mainly by the electronic density of the lone pairs as well as by steric effects.

Keywords. Ring transformation; as-Triazines, fused; Alkylation; Regioselectivity; Calculation, AM1; Annelation effect.

Synthese und Ringtransformierung neuer tetracyclischer kondensierter as-Triazine

Zusammenfassung. Acht neue tetracyclische kondensierte as-Triazine (**4** – **6**, **8**, **11** – **13** und **15**) wurden durch Reaktion und nachfolgende Ringtransformierung von 1,2-Diaminoisochinolinium (**2**) bzw. -chinoliniumsalzen (**9**) mit 4-Benzoyl-5-phenylfuran-2,3-dion (**1**) dargestellt. Die selektiven Alkylierungen wiesen darauf hin, daß diese Reaktionen hauptsächlich sowohl durch die Elektronendichte der freien Elektronpaare als auch durch sterische Effekte beeinflußt werden.

Introduction

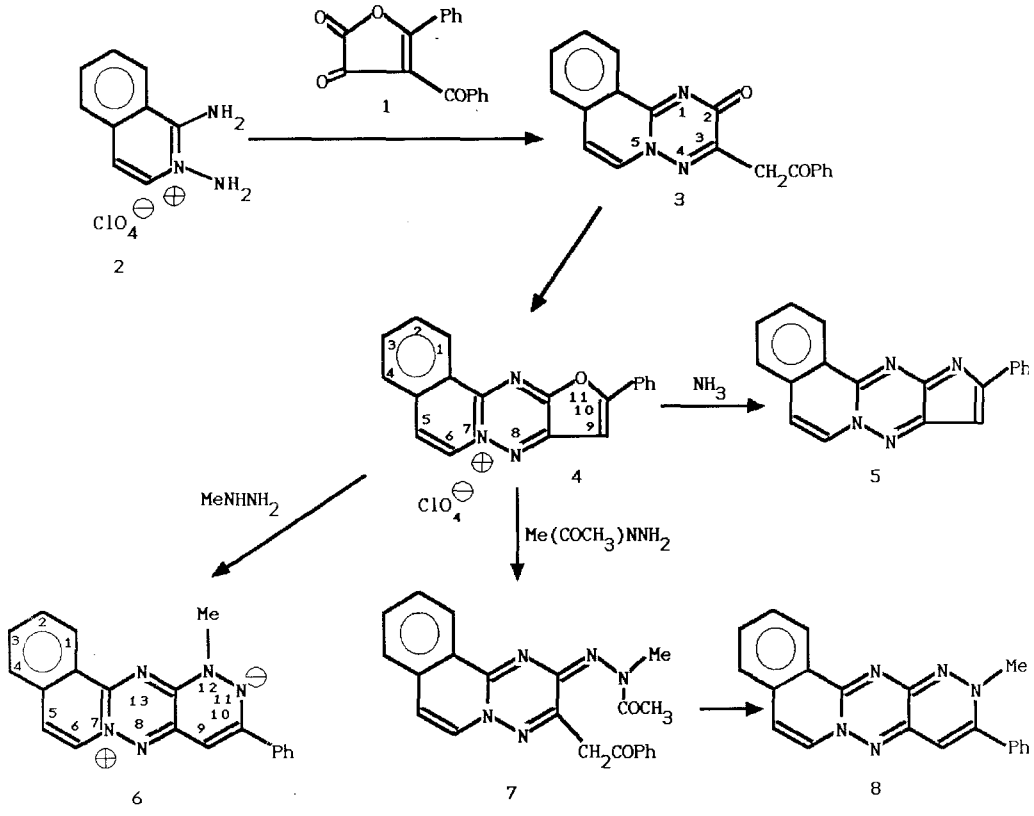
Recently we have reported [1, 2] that 1-amino-2-pyridonimine – generated in situ from 1,2-diaminopyridinium salt – easily reacts with 4-benzoyl-5-phenylfuran-2,3-dione to result in derivatives of the furo [2,3-e] pyrido [1,2-b]-as-triazinium system, which undergo ring transformations with nucleophilic reagents to give a series of derivatives of new fused heterocyclic ring systems. We also described that these ring transformation products – each containing several nitrogen atoms in the ring – react selectively with alkylating reagents and this selectivity was found in satisfactory correlation with the lone pair densities of the hetero atoms [4].

** Dedicated to em. Univ. Prof. Dr. E. Ziegler on the occasion of his 80th birthday

As a continuation of these studies we decided now to extend this synthetic method onto ring systems containing one additional fused benzene ring, where the selectivity problem with alkylation of the synthesized polycyclic ring systems seemed of particular interest.

Results and Discussion

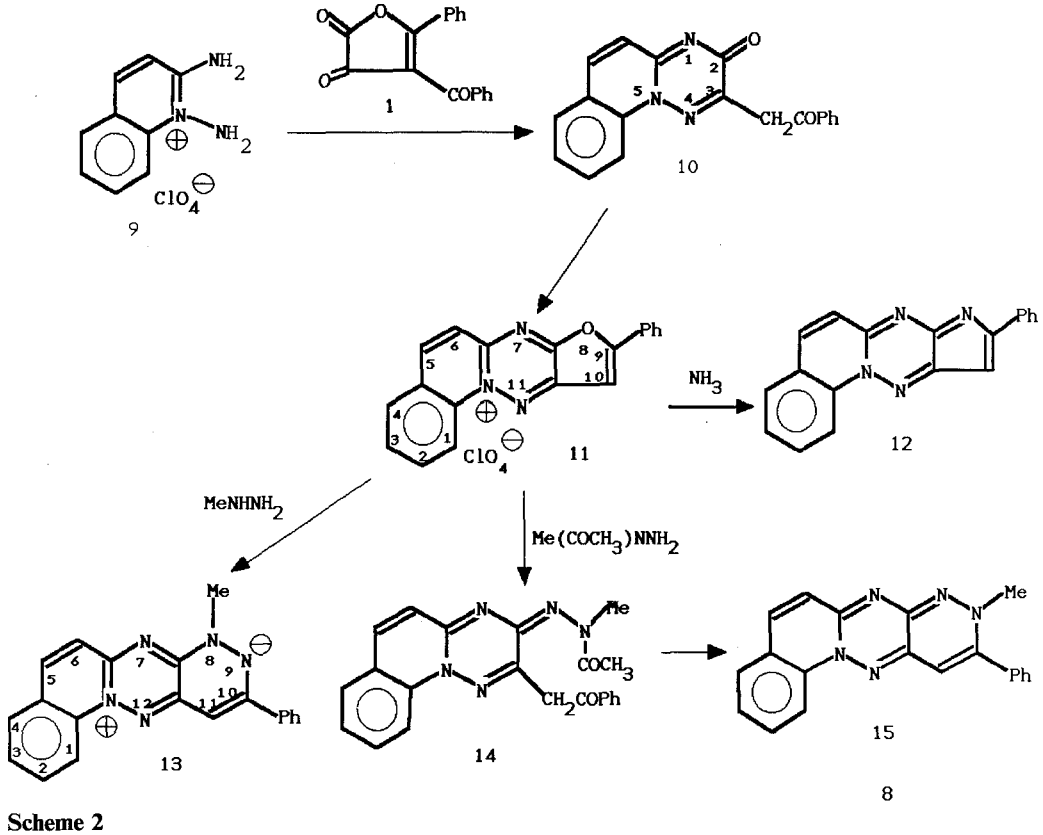
The two benzologues of 1,2-diaminopyridinium salt: 1,2-diaminoisoquinolinium perchlorate (**2**) and 1,2-diaminoquinolinium perchlorate (**9**) have been recently prepared [3]. These compounds reacted with 4-benzoyl-5-phenylfurane-2,3-dione (**1**) under basic conditions in analogy as described for the corresponding pyridinium compound [2] and afforded the substituted triazinone compounds **3** and **10**, respectively, which were cyclized by polyphosphoric acid to the desired new tetracyclic salts: furo[2,3-e]quinolino[1,2-b]-as-triazinium perchlorate (**11**) and furo[2,3-b]isoquinolino[2,1-b]-as-triazinium perchlorate (**4**) (Scheme 1).



Scheme 1

Both new furo-as-triazinium salts were treated with ammonium hydroxide, methyl hydrazine and 1-methyl-1-acetylhydrazine in order to accomplish ring transformations [2]. Thus, in the case of ammonia, the furo moiety was replaced by the pyrrol ring using the elaborated synthetic route [2] via opening of the furane ring. As expected, two new tetracycles, namely 2-phenylpyrrolo[2,3-e]isoquinolino[2,1-b]as-triazine (**5**) and 2-phenylpyrrolo[2,3-e]quinolino[1,2-b]-as-triazine (**12**) were isolated in good yields as deep red crystals.

Reaction of **4** and **11** with methylhydrazine and 1-methyl-1-acetyl-hydrazine allowed the synthesis of differently (i. e. 1- and 2-methyl) substituted pyridazino[3,4-e]isoquinolino[2,1-b]-triazines and pyridazino[3,4-e]quinolino[1,2-b]-as-triazines (**6**, **8**, and **13**, **15**, respectively). These ring transformations were found to proceed in analogous manner compared to the described tricyclic derivatives [2]. Thus, the 1-methyl substituted zwitterions **6** and **13** were formed directly upon reaction of the starting salts **4** and **11** with methyl hydrazine, whereas reaction of these salts (**4** and **11**) with 1-methyl-1-acetylhydrazine gave first the ring opened intermediates **7** and **14** which then were cyclized by acid to give the neutral quinonoide 2-methyl compounds **8** and **15** (Scheme 2).



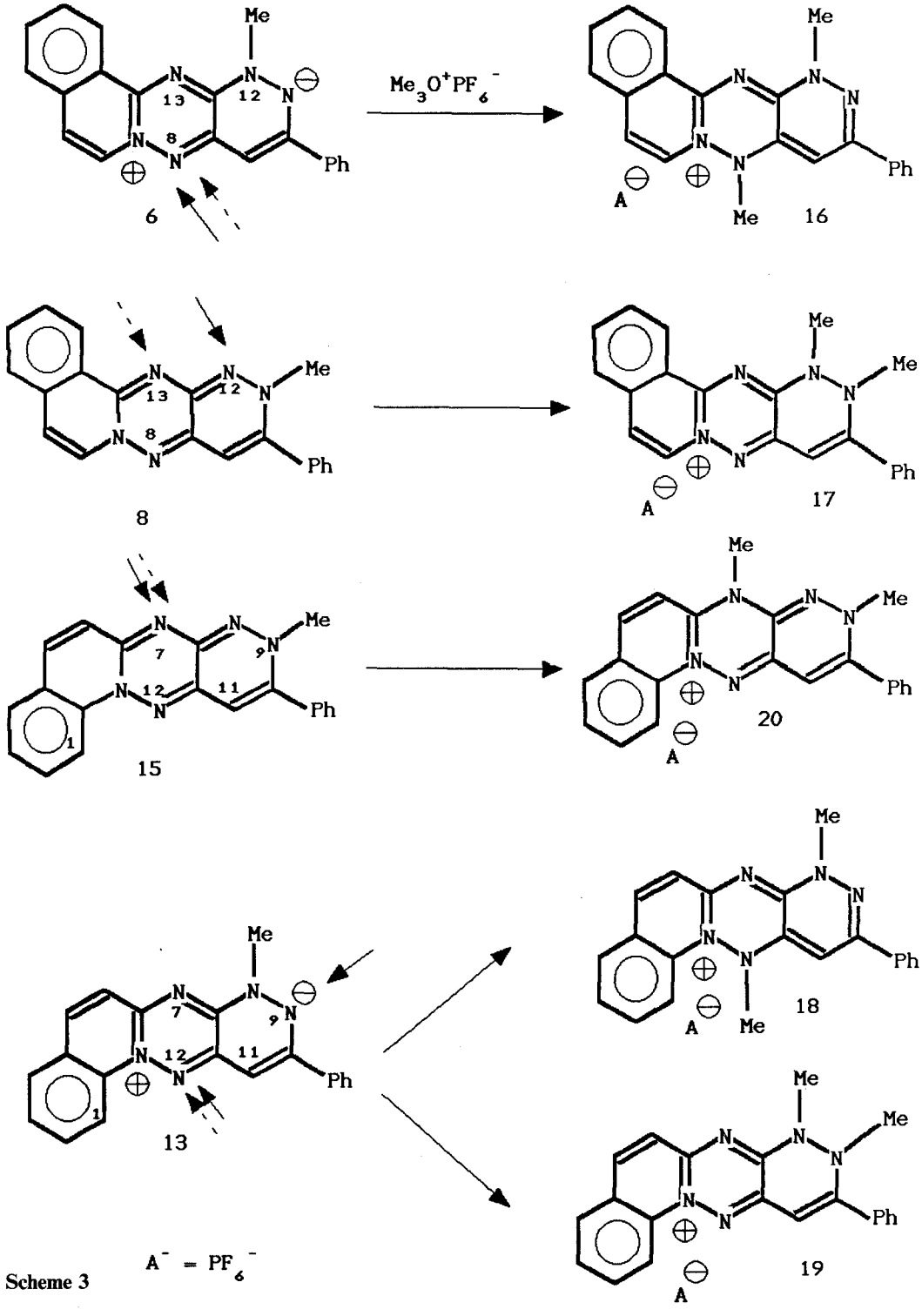
Scheme 2

Table 1. Comparison of the first UV maxima (in acetonitrile, 25°C) of the new tetracyclic ring systems and tricyclic derivatives

		Pyrrole-fused		1-*Me*-Pyridazine-fused*		2-*Me*-Pyridazine-fused*	
Tetracycles	Isoquinoline-fused	(**5**)	496 nm	(**6**)	692 nm	(**8**)	642 nm
	Quinoline-fused	(**12**)	502 nm	(**13**)	660 nm	(**15**)	666 nm
Tricyclic analogues [4]			490 nm		585 nm		631 nm

* Numbering according to the monocyclic pyridazine ring

Comparison of the colours of the new tetracyclic ring transformation products with those of the tricyclic analogues is in good agreement with the presence of the additional fused benzene ring; i. e. the red colour of the pyrrolo compounds **5** and **12**, the deep green colour of the zwitterions **6** and **13**, the violet colour of the



Scheme 3

quinonoide **8** and **15** indicates a distinct bathochromic shift compared to the tricyclic analogues as also shown by the first UV maxima of these compounds (Table 1).

As outlined above we were interested in the reactivity of the new tetracyclic ring transformation products towards alkylating agents (e. g. trimethyloxonium hexafluorophosphat). As we have previously shown [4], in cases where several ring-nitrogens of a nitrogen-containing heterocyclic compound can be alkylated, the preference of reactivities of these nitrogen atoms can be correlated with the electronic densities of their lone pairs. With the new tetracyclic compounds, however, a definite steric hindrance arises (e. g. N-13 in compounds **6** and **8** and similarly N-12 in derivatives **13** and **15**) which can change the reactivity sequence (Scheme 3). The alkylation reactions of tetracycles **6**, **8**, **13**, and **15** were carried out under the same conditions as described for other cases [4]. Workup of these reaction mixtures indicated that – with the exception of zwitterion **13** – one product was obtained in each case, whereas **13** afforded a mixture of two alkyl substituted salts. The structures of the new methyl derivatives were elucidated by NMR spectroscopy using the DNOE technique and revealed formation of the following structures:

(a) The zwitterion **6** and the neutral system **15** gave selectively 8-methyl (**16**, irradiation of H-9 gave NOE at methyl attached to N-8) and 7-methyl salts (**20**, NOE observed at H-6 when irradiated at the N-7 methyl). The sites of these alkylations are the same as those of the corresponding tricycles described earlier [4], and, thus, one can conclude that the presence of the additional benzene rings, which are far enough from the reaction sites, did not exert any influence on the selectivity of these reactions. In Scheme 3, the positions corresponding to those where alkylation was experienced with tricyclic analogues [4] are marked by dotted line arrows, and the present findings are marked by continuous line arrows.

(b) The neutral tetracycle **8** gave also one product (**17**) only, and was, however, alkylated selectively rather at N-12 (continuous arrow) than N-13 (dotted line arrow). This structure was supported by the NOE effect at the vicinal N-methyl groups. This difference is obviously due to the steric hindrance of the annelated benzene ring.

(c) The zwitterionic compound **13**, in contrast to the examples above, yielded a mixture of 12-(**18**) and 9-methyl salts (**19**). These structures were also supported by their NMR spectra: irradiation of N-12 methyl in **18** gave NOE at H-1 and H-11, whereas also a definite NOE was observed with the vicinal N-methyl groups in **19**. The attack of the reagent at N-12 corresponds to the methylation of the analogous tricycle, and the simultaneous reaction at N-9 is again a consequence of the presence of the annelated benzene ring fused to the pyridine moiety.

From the ^{1}H-NMR spectra of all reaction products remarkable differences within the chemical shift values of protons in structural units which seem nearly identical (e. g. H-6 in **4**, **6**, and **16**, see also the tricyclic analogues [2]) have been observed. This could be explained by the fact that the overall electronic situation in those molecules is not sufficiently represented by the usual molecular formulae. In particular, the status of hybridization of the nitrogen atoms should have a significant influence on the electronic environment of their neighbouring atoms.

Among the alkylations of the new tetracyclic system, the result with compound **8**, where a completely new selective alkylation was observed, seemed of particular interest: in order to rationalize this finding we carried out AM1 molecular orbital analysis and calculated the lone pair electronic densities ($c^2_{n\text{-HOMO}}$ coefficients) of

11, whereas also a definite NOE was observed with the vicinal N-methyl groups in **19**. The attack of the reagent at N-12 corresponds to the methylation of the analogous tricycle, and the simultaneous reaction at N-9 is again a consequence of the presence of the annelated benzene ring fused to the pyridine moiety.

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Table 2. Electronic distribution of the highest occupied π (HOMO) and the highest *n* orbital (*n*-HOMO) as well as net charges of compound **8** (Standard geometry was assumed which was optimized using the MM2 method. For simplicity, the methyl group was replaced by a hydrogen atom. *n*-HOMO was found as the second orbital below π-HOMO differing by 2.23 eV)

Atom	c^2_{HOMO}	$c^2_{n\text{-HOMO}}$	q_{net}
N-8	0.12	0.15	−0.11
N-13	0.11	0.28	−0.29
N-12	0.10	0.18	−0.07

The data shown in Table 2 reveal that N-13 has the highest *n*-HOMO density followed by N-12. Since N-13 is sterically fairly hindered as discussed above, N-12 has the most probable chance for the attack of the electrophile. Furthermore, in accordance with other similar cases [5], neither the π-HOMO densities nor the q_{net} partial charges show any correlation with the experimental findings.

The authors feel that these results provide a novel convincing evidence for the importance of the annelation effect in polyfused heterocyclic systems as well as for the correlation between lone pair electronic densities and selective alkylation reactions.

Further research with linearly fused related ring systems is in progress.

Experimental Part

Melting points were determined on a Büchi apparatus and are uncorrected. The IR spectra were recorded with a Nicolet 205 FT apparatus. The UV spectra were measured using a HP 8452 A spectrometer. The NMR spectra were registered on Varian EMX-360, XL-200, and XL-400 equipments. *TMS* was used as internal standard. The quantum chemical calculations were carried out by a PC AT computer.

3-(Benzoylmethyl)-2 H-isoquinolino[2,1-b]-as-triazine-2-one (**3**)

To a mixture of 1,2-diamino-isoquinolinium perchlorate (**2**, 5.2 g, 20 mmol), acetonitrile (30 ml), and aqueous sodium hydroxide (1.6 g in 3 ml water), a solution of 4-benzoyl-5-phenyl-2,3-furandione (**1**, 5.56 g, 20 mmol) in toluene (60 ml) was added at room temperature. The mixture was stirred for 60 min, then evaporated and the residue was treated with ethanol (100 ml) and 10 % hydrochloric acid (40 ml), and refluxed 4 h. Ice/water (200 ml) was then added, and the reaction mixture was neutralized with 10% sodium hydroxide solution. The precipitated product was filtered off, washed with ethanol, and recrystallized from acetic acid. The yield was 4.1 g (65%). M. p. 244°C. $C_{19}H_{13}N_3O_2$ (315.34). Calc. C 72.38, H 4.16, N 12.96; found C 72.44, H 4.22, N 13.02. IR (KBr) 3 460, 3 100, 2 940, 2 910, 1 685, 1 652, 1 590, 1 560, 1 500, 1 470, 1 330, 1 280, 1 210, 1 140, 790, 760, 700 cm^{-1}. ^{1}H-NMR (60 MHz, *TFA*): 8.9 (d, 1 H, H-11), 8.5 (d, 1 H, H-6), 8.4-7.6 (m, 9 H, H-7,8,9,10, H-phenyl), 4.9 (s, 2 H, H-CH_2) ppm.

3-(Benzoylmethyl)-2 H-quinolino[1,2-b]-as-triazine-2-one (**10**)

The experimental procedure was as described for **3**. From **9** (instead of **2**) 4.45 (70%) of **10** were obtained. M. p. 241°C. $C_{19}H_{13}N_3O_2$ (315.34). Calc. C 72.38, H 4.16, N 12.96; found C 72.44, H 4.26, N 12.85. IR (KBr) 3 250, 3 090, 3 060, 3 000, 2 960, 2 920, 1 687, 1 655, 1 610, 1 580, 1 520, 1 470, 1 450, 1 400, 1 380, 1 340, 1 220, 1 185, 1 170, 1 160, 1 130, 1 000, 840, 760, 690 cm^{-1}. ^{1}H-NMR (60 MHz, *TFA*): 8.9 (d, 2 H, H-6,11), 8.3 – 7.5 (m, 9 H, H-7,8,9,10, H-phenyl), 4.95 (s, 2 H, H-CH) ppm.

10-Phenylfuro[2,3-e]isoquinolino[2,1-b]-as-triazinium Perchlorate (**4**)

A mixture of **3** (3.15 g, 10 mmol) and polyphosphoric acid (50 g) was stirred at 150 – 160°C for 2 h. The cooled slurry was diluted with 200 ml of ice/water and was then treated with 5 ml of 70% perchloric acid, yielding a yellow precipitate. Filtration, washing with ethyl acetate, and recrystallization from nitromethane/ethyl acetate yielded 2.60 g (65.5%) **4**. M. p. >300°C. $C_{19}H_{12}ClN_3O_5$ (397.79). Calc. C 57.37, H 3.04, N 10.56; found C 57.53, H 3.03, N 10.62. IR (KBr) 3 120, 3 100, 1 610, 1 560, 1 540, 1 490, 1 470, 1 450, 1 410, 1 400, 1 300, 1 110, 1 080, 810, 770, 750, 670, 610 cm^{-1}. ^{1}H-NMR (60 MHz, *TFA*): 9.6 (d, 1 H, H-1), 9.1 (d, 1 H, H-6), 8.7 – 7.8 (m, 9 H, H-2,3,4,5, H-phenyl), 7.7 (s, 1 H, H-9) ppm.

9-Phenylfuro[2,3-e]quinolino[1,2-b]-as-triazinium Perchlorate (**11**)

Prepared as described above, from **10** the yield of **11** was 2.10 g (52.8%). M. p. >300°C. $C_{19}H_{12}ClN_3O_5$ (397.79). Calc. C 57.37, H 3.04, N 10.56; found C 57.02, H 3.10, N 10.47. IR (KBr) 3 130, 3 110, 3 080, 1 630, 1 610, 1 580, 1 560, 1 530, 1 490, 1 460, 1 360, 1 310, 1 270, 1 160, 1 090, 1 000, 880, 820, 760, 680 cm^{-1}. ^{1}H-NMR (60 MHz, *TFA*): 9.5 (d, 1 H, H-1), 9.0 (d, 1 H, H-5), 8.5 – 7.5 (m, 9 H, H-2,3,4,6, H-phenyl), 7.8 (s, 1 H, H-10) ppm.

10-Phenylpyrrolo[2,3-e]isoquinolino[2,1-b]-as-triazine (**5**)

To a suspension of **4** (0.8 g, 2 mmol) in acetonitrile (5 ml), conc. ammonium hydroxide (1 ml) was added, whereupon a yellow solid immediately precipitated. After filtration this solid was suspended

in 10 ml of pyridine, and a few crystals of *p*-toluenesulfonic acid were added, and heated for 15 min at reflux. The resulting red mixture was then poured onto 50 ml of ice/water. The precipitated solid was filtered off and recrystallized from dimethylformamide. The yield was 0.36 g (63%). M. p. >300°C. $C_{19}H_{12}N_4$ (296.34). Calc. C 77.04, H 4.08, N 18.91; found C 77.28, H 4.15, N 19.04. IR (KBr) 3 070, 3 110, 1 680, 1 640, 1 570, 1 530, 1 460, 1 450, 1 410, 1 400, 1 330, 1 230, 1 140, 1 040, 720, 680 cm^{-1}. UV/VIS (CH_3CN) 496 (3.09), 470 (3.14), 326 (4.79) 232 nm ($lg \varepsilon = 4.43$). ^{1}H-NMR (200 MHz, *DMSO-d_6*): 9.14 (d, 1 H, H-1), 8.72 (d, 1 H, H-6), 8.40 (m, 2 H, H-2',6'), 8.12 (d, 1 H, H-4), 7.96 (m, 2 H, H-2,3), 7.84 (d, 1 H, H-5), 7.57 (m, 3 H, H-3',4',5'), 7.46 (s, 1 H, H-9) ppm.

9-Phenylpyrrolo[2,3-e]quinolino[1,2-b]-as-triazine (**12**)

Using **11** instead of **4**, under an equal procedure the yield of **12** was 0.39 g (65%). M. p. 252–255°C. $C_{19}H_{12}N_4$ (296.34). Calc. C 77.04, H 4.08, N 18.91; found C 77.19, H 4.09, N 19.05. IR (KBr) 3 060, 3 030, 3 000, 2 920, 1 630, 1 610, 1 575, 1 510, 1 460, 1 440, 1 410, 1 390, 1 330, 820, 760, 720, 680, 670 cm^{-1}. UV/VIS (CH_3CN) 502 (2.92), 468 (3.03), 328 (4.78), 278 (4.27), 204 nm ($lg \varepsilon = 4.59$). ^{1}H-NMR (200 MHz, *DMSO-d_6*): 9.06 (d, 1 H, H-1), 8.42 (d, 1 H, H-6), 8.40 (m, 2 H, H-2',6'), 8.20 (d, 1 H, H-4), 8.00 (t, 1 H, H-3), 7.86 (d, 1 H, H-5), 7.82 (t, 1 H, H-2), 7.56 (m, 3 H, H-3',4',5'), 7.50 (s, 1 H, H-10) ppm.

12-Methyl-10-phenylpyridazino[3,4-e]isoquinolino[2,1-b]-as-triazinium-11-ide (**6**)

A suspension of **4** (0.4 g, 1 mmol) in acetonitrile (4 ml) was treated with methylhydrazine (0.5 ml), whereupon a dark solution was formed and green crystals commenced to precipitate. Water (5 ml) was added, and the product was filtered off, and recrystallized from acetonitrile. The yield was 0.26 g (81%). M. p. 178–179°C. $C_{20}H_{15}N_5$ (325.38). Calc. C 73.82, H 4.65, N 21.52; found C 73.90, H 4.66, N 21.71. IR (KBr) 3 090, 3 050, 2 990, 2 940, 1 630, 1 570, 1 540, 1 510, 1 490, 1 400, 1 340, 1 290, 1 250, 1 200, 800, 790, 755, 690, 670, 660 cm^{-1}. UV/VIS (CH_3CN): 692 (2.89), 424 (4.05), 396 (4.03), 330 (4.68), 292 (4.40), 252 nm ($lg \varepsilon = 4.28$). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.98 (d, 1 H, H-1, $J = 8.3$ and 1.0 Hz), 7.49 (m, 1 H, H-3, $J = 7.5$, 7.0 and 1.0 Hz), 7.49 (m, 2 H, H-2',6'), 7.36 (m, 1 H, H-2, $J = 8.3$, 7.0 and 1.3 Hz), 7.34 (m, 1 H, H-4, $J = 7.5$ and 1.3 Hz), 7.32 (m, 3 H, H-3',4',5'), 6.68 (d, 1 H, H-6, $J = 7.3$ Hz), 6.51 (d, 1 H, H-5, $J = 7.3$ Hz), 4.65 (s, 1 H, H-9), 3.14 (s, 3 H, H-NCH_3) ppm.

8-Methyl-10-phenylpyridazino[3,4-e]quinolino[1,2-b]-as-triazinium-9-ide (**13**)

Starting from **11** and following the above procedure the yield of **13** was 0.24 g (75%). M. p. 206°C. $C_{20}H_{15}N_5$ (325.38). Calc. C 73.82, H 4.65, N 21.52; found C 73.85, H 4.71, N 21.51. IR (KBr) 3 060, 2 940, 1 620, 1 540, 1 490, 1 470, 1 430, 1 400, 1 350, 1 330, 1 290, 1 260, 1 210, 1 175, 1 150, 920, 820, 770, 760, 690 cm^{-1}. UV/VIS (CH_3CN): 660 (2.81), 404 (4.10), 336 (4.62), 322 (4.63), 246 nm ($lg \varepsilon = 4.37$). ^{1}H-NMR (400 MHz, $CDCl_3$) 7.83 (d, 1 H, H-1, $J = 8.5$ and 1.0 Hz), 7.49 (m, 2 H, H-2',6'), 7.42 (m, 1 H, H-2, $J = 8.5$, 7.0 and 1.3 Hz), 7.30 (m, 3 H, H-3',4',5'), 7.29 (d, 1 H, H-4, $J = 7.5$ and 1.3 Hz), 7.29 (d, 1 H, H-5, $J = 9.1$ Hz), 7.17 (m, 1 H, H-3, $J = 7.5$, 7.0 and 1.0 Hz), 6.17 (d, 1 H, H-6, $J = 9.1$ Hz), 4.76 (s, 1 H, H-11), 3.03 (s, 3 H, H-NCH_3) ppm.

2-(-Acetyl-2-methylhydrazono)-3-benzoylmethyl-2 H-isoquinolino[2,1-b]-as-triazine (**7**)

To a suspension of perchlorate salt **4** (0.4 g, 1 mmol) in acetonitrile (3 ml), 1-acetyl-1 methylhydrazine (0.18 g, 2 mmol) was added dropwise during 30 min. The resulting clear solution was stirred for 2 h, diluted with water (20 ml) and extracted with dichloromethane (3 × 20 ml). After evaporation of the organic solvent the residue was recrystallized from ethyl acetate. The yield was 0.30 g (78%). M. p. 170°C. $C_{22}H_{19}N_5O_2$ (385.43). Calc. C 68.56, H 4.97, N 18.17; found C 68.70, H 4.86, N 18.12. IR (KBr) 3 070, 2 950, 2 920, 1 680, 1 660, 1 610, 1 520, 1 480, 1 450, 1 420, 1 370, 1 330, 1 290, 1 200, 1 130, 1 000,

785, 760, 690, 630 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): 8.68 (d, 1 H, H-11), 8.05 (m, 2 H, H-4',8'), 7.70–7.45 (m, 7 H, H-6,8,9,10,5',6',7'), 6.83 (d, 1 H, H-7), 4.40 (s, 2 H, H-1'), 3.41 (s, 3 H, H-N-CH_3), 1.90 (s, 3 H, H-C-CH_3) ppm.

2-(2-Acetyl-2-methylhydrazono)-3-benzoylmethyl-2 H-quinolino[1,2-b]-as-tiazine (**14**)

From the perchlorate **11** under analogous reaction conditions **14** was obtained. The yield was 0.27 g (70%). M. p. 158°C. $C_{22}H_{19}N_5O_2$ (385.43). Calc. C 68.56, H 4.97, N 18.17; found C 68.62, H 4.96, N 18.22. IR (KBr) 3 050, 3 000, 2 970, 2 920, 1 690, 1 650, 1 630, 1 610, 1 540, 1 480, 1 450, 1 410, 1 370, 1 330, 1 300, 1 220, 1 130, 990, 760 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.26 (d, 1 H, H-6, J = 8.2 and 1.0 Hz), 8.06 (m, 2 H, H-4',8'), 7.74 (d, 1 H, H-10, J = 9.3 Hz), 7.64 (m, 1 H, H-7, J = 8.2, 7.0 and 1.3 Hz), 7.62 (m, 1 H, H-9, J = 7.5 and 1.3 Hz), 7.61, 7.52 (m, 3 H, H-5',6',7'), 7.42 (m, 1 H, H-8, J = 7.5, 7.0 and 1.0 Hz), 6.95 (d, 1 H, H-11, J = 9.3 Hz), 4.48 (s, 2 H, H-1'), 3.34 (s, 3 H, H-N-CH_3), 1.89 (s, 3 H, H-C-CH_3) ppm. ^{13}C-NMR ($CDCl_3$): 194.86 (C-2'), 171.60 (C-3''), 151.03 (C-2), 147.92 (C-5 a), 146.37 (C-3), 137.90 (C-10), 137.42 (C-11 a), 136.53 (C-3'), 133.62 (C-7), 131.55 (C-6'), 128.78 (C-5',7'), 128.34 (C-4',8'), 128.34, 125.60 (C-8, C-9), 122.42 (C-11), 122.21 (C-9 a), 42.07 (C-1'), 34.56 (C-N-2''-CH_3), 21.47 (C-4''-CH_3).

11-Methyl-10-phenyl-7 H-pyridazino[3,4-e]isoquinolino[2,1-b]-as-triazine (**8**)

To a solution of **7** (0.19 g, 0.5 mmol) in ethanol (3 ml) aqueous hydrogen bromide (40%, 0.5 ml) was added, and refluxed for 2 h. The mixture was then diluted with water (10 ml) and neutralized with 10% sodium hydroxide solution to pH = 8–9. Extracted with chloroform (3 × 30 ml) the organic solvent was evaporated, and the residue was recrystallized from acetonitrile. The yield was 0.11 g (68%). M. p. 177°C. $C_{20}H_{15}N_5$ (325.38). Calc. C 73.82, H 4.65, N 21.52; found C 73.83, H 4.64, N 21.55. IR (KBr) 3 040, 3 010, 2 950, 1 630, 1 610, 1 590, 1 570, 1 550, 1 530, 1 500, 1 360, 1 330, 1 300, 1 280, 1 210, 780, 770, 760, 700, 670 cm^{-1}. UV/VIS (CH_3CN): 642 (2.30), 584 (2.53), 538 (2.57), 402 (4.15), 382 (4.19), 320 (4.24), 270 nm (lg ε = 4.58). ^{1}H-NMR (200 MHz, $CDCl_3$): 8.20 (d, 1 H, H-1), 7.50–7.20 (m, 8 H, H-2,3,4, H-phenyl), 6.55 (d, 1 H, H-6), 6.18 (d, 1 H, H-5), 4.43 (s, 1 H, H-9), 2.90 (s, 3 H, H-N-CH_3) ppm.

9-Methyl-10-phenyl-13 H-pyridazino[3,4-e]quinolino[2,1-b]-as-triazine (**15**)

As described for **7**, from the hydrazone **14** the yield of **15** was 0.12 g (69%). M. p. 225–226°C. $C_{20}H_{15}N_5$ (325.38). Calc. C 73.83, H 4.65, N 21.52; found C 73.84, H 4.73, N 21.45. IR (KBr) 3 050, 3 040, 2 990, 2 920, 1 630, 1 570, 1 560, 1 490, 1 440, 1 420, 1 360, 1 330, 1 280, 1 220, 810, 745, 710 cm^{-1}. UV/VIS (CH_3CN): 666 (2.47), 606 (2.64), 554 (2.65), 404 (4.36), 382 (4.36), 298 (4.58), 228 nm (lg ε = 4.36). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.59 (d, 1 H, H-1, J = 8.2 and 1.0 Hz), 7.41 (m, 2 H, H-2',6'), 7.33 (m, 1 H, H-2, J = 8.2 and 7.0 and 1.3 Hz), 7.24 (m, 3 H, H-3',4',5'), 7.23 (m, 1 H, H-4, J = 7.5 and 1.3 Hz), 7.15 (d, 1 H, H-5, J = 9.3 Hz), 7.05 (m, 1 H, H-3, J = 7.5 and 7.0 and 1.0 Hz), 6.13 (d, 1 H, H-6, J = 9.3 Hz), 4.58 (s, 1 H, H-11), 2.86 (s, 3 H, H-N-CH_3) ppm. ^{13}C-NMR ($CDCl_3$): 155.70, 155.49 (C-10, C-7 a), 150.91 (C-11 a), 137.43, 134.08 (C-13 a, C-6 a), 136.80 (C-5), 134.08 (C-1'), 130.94 (C-2), 129.65 (C-4'), 128.89 (C-2',6'), 127.67 (C-4), 127.36 (C-3',5'), 123.05 (C-3), 122.61 (C-5 a), 121.89 (C-6), 114.20 (C-1), 99.64 (C-11), 42.38 (C-N-9-CH_3).

General Procedure for Methylation of **6**, **8**, **13**, *and* **15** *with Trimethyloxonium Hexafluorophosphate*

To a suspension of the appropriate starting compound **6**, **8**, **13**, or **15** (100 mg, 0.3 mmol) in abs. dichloromethane, trimethyloxonium hexafluorophosphate (60 mg, 0.35 mmol) was added and the suspension was stirred at room temperature for 24 h. Diethyl ether was then added, the solid precipitate was filtered off and separated by preparative layer chromatography (silica, chloroform-methanol 9 : 1 as eluent). All methylated products gave satisfactory elementary analysis (within ±0.4%).

8,12-Dimethyl-10-phenylpyridazino[3,4-e]isoquinolino[2,1-b]-as-triazinium Hexafluorophosphate (**16**)

The yield was 80 mg (55%). M.p. 200–204°C. ^{1}H-NMR (400 MHz, CD_3CN) 8.58 (d, 1 H, H-1, J=8.4 Hz), 7.91 (m, 1 H, H-3, J=7.6 and 7.0 Hz), 7.88 (m, 2 H, H-2',3'), 7.82 (d, 1 H, H-4, J=7.6 Hz), 7.76 (m, 1 H, H-2, J=8.4 and 7.0 Hz), 7.57 (d, 1 H, H-6, J=7.5 Hz), 7.54 (m, 3 H, H-3',4',5'), 7.34 (d, 1 H, H-5, J=7.5 Hz), 6.82 (s, 1 H, H-9), 3.96 (s, 3 H, H-N-12-CH_3), 3.53 (s, 3 H, H-N-8-CH_3) ppm. ^{13}C-NMR (CD_3CN) 155.73, 155.15, 153.72, 145.27 (C-12 a, C-10, C-8 a, C-4 a), 136.81 (C-13 a), 136.11 (C-3), 134.47 (C-1'), 132.16 (C-4'), 130.76 (C-2), 130.16 (C-2',6'), 128.03 (C-4), 127.73 (C-1), 127.57 (C-6), 127.37 (C-2',6'), 125.08 (C-1 a), 116.70 (C-5), 107.98 (C-9), 46.88 (C-CH_3-N-8), 43.54 (C-CH_3-N-12).

11,12-Dimethyl-10-phenylpyridazino[3,4-e]isoquinolino[2,1-b]-as-triazinium Hexafluorophosphate (**17**)

The yield was 45 mg (31%). M.p. 240–244°C. ^{1}H-NMR (400 MHz, CD_3CN) 8.68 (d, 1 H, H-1, J=8.0 Hz), 7.98 (m, 1 H, H-3, J=7.0 and 7.5 Hz), 7.93 (d, 1 H, H-4, J=7.5 Hz), 7.82 (m, 1 H, H-2, J=8.0 and 7.0 Hz), 7.60 (m, 2 H, H-2',6'), 7.58 (m, 1 H, H-4'), 7.57 (d, 1 H, H-6, J=7.2 Hz), 7.54 (m, 2 H, H-3',5'), 7.49 (d, 1 H, H-5, J=7.2 Hz), 5.77 (s, 1 H, H-9), 3.57 (s, 3 H, H-CH_3-N-12), 3.22 (s, 3 H, H-CH_3-N-11) ppm.

Mixture of 8,12-Dimethyl-10-phenylpyridazino[3,4-e]quinolino[1,2-b]-as-triazinium Hexafluorophosphate (**18**) *and 8,9-Dimethyl-10-phenylpyridazino[3,4-e]quinolino[1,2-b]-as-triazinium Hexafluorophosphate* (**19**)

Methylation of **13** yielded 75 mg (51%) of a mixture of **18** and **19** in a ratio of 2:1. Separation on preparative layer allowed isolation of the major product **18**: 35 mg (24%). M.p. 195–197°C. ^{1}H-NMR (400 MHz, CD_3CN): 8.28 (d, 1 H, H-5, J=9.2 Hz), 8.14 (d, 1 H, H-1, J=8.3 and 1.0 Hz), 7.98 (m, 2 H, H-2',6'), 7.96 (m, 1 H, H-2, J=8.3, 7.2 and 1.3 Hz), 7.96 (d, 1 H, H-4, J=7.5 and 1.3 Hz), 7.85 (s, 1 H, H-11), 7.63 (m, 1 H, H-3, J=7.5, 7.2 and 1.0 Hz), 7.60 (m, 3 H, H-3',4',5'), 7.19 (d, 1 H, H-6, J=9.2 Hz), 4.14 (s, 3 H, H-CH_3-N-8), 3.41 (s, 3 H, H-CH_3-N-12) ppm. ^{13}C-NMR (CD_3CN) 157.50, 155.34, 153.95, 145.98 (C-10,7 a,11 a,13 a), 143.73 (C-2), 137.02 (C-6 a), 134.78 (C-5), 134.17 (C-1'), 132.36 (C-4), 130.75 (C-3), 130.34 (C-3',5'), 127.76 (C-4'), 127.57 (C-2',6'), 126.47 (C-4 a), 122.70 (C-6), 119.84 (C-11), 115.53 (C-1), 51.26, 44.09 (C-CH_3-N).

^{1}H-NMR (400 MHz, CD_3CN) analysis of the minor component revealed the presence of **19**: 8.37 (d, 1 H, H-1, J=8.5 and 1.0 Hz), 8.29 (d, 1 H, H-5, J=9.2 Hz), 7.95 (m, 2 H, H-2',6'), 7.93 (d, 1 H, H-4, J=7.5 and 1.3 Hz), 7.91 (m, 1 H, H-2, J=8.5, 7.2 and 1.3 Hz), 7.69 (m, 1 H, H-3, J=7.5, 7.2 and 1.0 Hz), 7.60, 7.55 (m, 3 H, H-3',4',5'), 7.17 (d, 1 H, H-6, J=9.2 Hz), 5.86 (s, 1 H, H-11), 3.49 (s, 3 H, H-CH_3-N-8), 3.21 (s, 3 H, H-CH_3-N-9) ppm. ^{13}C-NMR (CD_3CN) 162.60, 154.20, 152.18, 146.90 (C-10,7 a,11 a,13 a), 142.89 (C-2), 137.90 (C-6 a), 134.46 (C-5), 133.98 (C-1'), 133.08 (C-4), 130.37 (C-3), 130.43 (C-3',5'), 129.00 (C-4'), 128.69 (C-2',6'), 126.12 (C-4 a), 121.78 (C-6), 117.34 (C-1), 102.16 (C-11), 44.96 (C-CH_3-N-9), 36.86 (C-CH_3-N-8).

7,9-Dimethyl-10-phenylpyridazino[3,4-e]quinolino[1,2-b]-as-triazinium Hexafluorophosphate (**20**)

The yield was 75 mg (51%). M.p. 255–260°C. ^{1}H-NMR (400 MHz, CD_3CN) 8.27 (d, 1 H, H-5, J=9.4 Hz), 8.21 (d, 1 H, H J=8.5 Hz), 7.88 (d, 1 H, H-4, J=7.6 Hz), 7.85 (m, 1 H, H-2, J=8.5 and 7.0 Hz), 7.62 (m, 1 H, H-3, J=7.6 and 7.0 Hz), 7.55 (m, 3 H, H-3',4',5'), 7.44 (m, 2 H, H-2',6'), 7.05 (d, 1 H, H-6, J=9.4 Hz), 5.41 (s, 1 H, H-11), 3.22 (s, 3 H, H-CH_3-N-9), 3.10 (s, 3 H, H-CH_3-N-7) ppm.

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