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Synthesis and Rearrangement of 4-Imino-4 *H*-3,1-benzoxazines

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Summary. N-Acylanthranilamides react with dibromotriphenylphosphorane in the presence of triethylamine as HBr captor to give 4-imino-4 *H*-3,1-benzoxazines in good yields. If the reaction is carried out without acid acceptor, N-acetylanthranilamides yield 2-methyl-4-quinazolones, whereas N-benzoylanthranilamides give 2-phenyl-4-imino-4 *H*-3,1-benzoxazines. It has also been found that 2-methyl-4-imino-4 *H*-3,1-benzoxazines rearrange under the influence of HCl or HBr into the respective 2-methyl-4-quinazolones; 2-phenyl-4-imino-4 *H*-3,1-benzoxazines, however, do not undergo such a rearrangement.

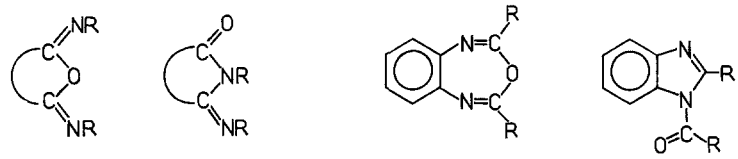
Keywords. 4-Imino-4 *H*-3,1-benzoxazines; Synthesis; Rearrangement; 4-Quinazolones.

Synthese und Umlagerung von 4-Imino-4 *H*-3,1-benzoxazinen

Zusammenfassung. Die Umsetzung von N-Acyl-anthranilsäure-amiden mit Triphenyldibromphosphoran in Gegenwart von Triethylamin als HBr-Akzeptor führt mit guten Ausbeuten zu 4-Imino-4 *H*-3,1-benzoxazinen. Wird die Reaktion ohne säurebindendes Mittel durchgeführt, dann entstehen aus N-Acetyl-anthranilsäure-amiden 2-Methylchinazolone-4, jedoch erhält man aus N-Benzoyl-anthranilsäure-amiden 2-Phenyl-4-imino-4 *H*-3,1-benzoxazine. 2-Methyl-4-imino-4 *H*-3,1-benzoxazine erleiden unter dem Einfluß von HBr oder HCl eine Umlagerung in entsprechende 2-Methylchinazolone-4, während 2-Phenyl-4-imino-4 *H*-3,1-benzoxazine zu einer solchen Umlagerung nicht befähigt sind.

Introduction

In previous papers [1] we have described intramolecular imidoylation reactions of N,N′-disubstituted diamides of dicarboxylic acids as well as of diamides derived from *o*-phenylenediamine. In both cases one of the two amide groups have been converted into an imidoylating agent by means of dibromotriphenylphosphorane (Ph_3PBr_2). It was shown that the primary products of the imidoylation reactions were O-imidoylated products **1** or **3**. If the reactions were carried out in the presence of triethylamine as HBr captor, the O-imidoylated products could be isolated in good yields; if, however, the reactions were performed without triethylamine, in general, N-imidoylated products **2** or **4** were obtained. The latter ones are most probably secondary products that arise from the rearrangement of the O-imidoylated precursors in strongly acidic reaction medium. It has also been found that both types of the O-imidoylation products rearrange under the influence of HBr or HCl into the respective N-imidoylation products.



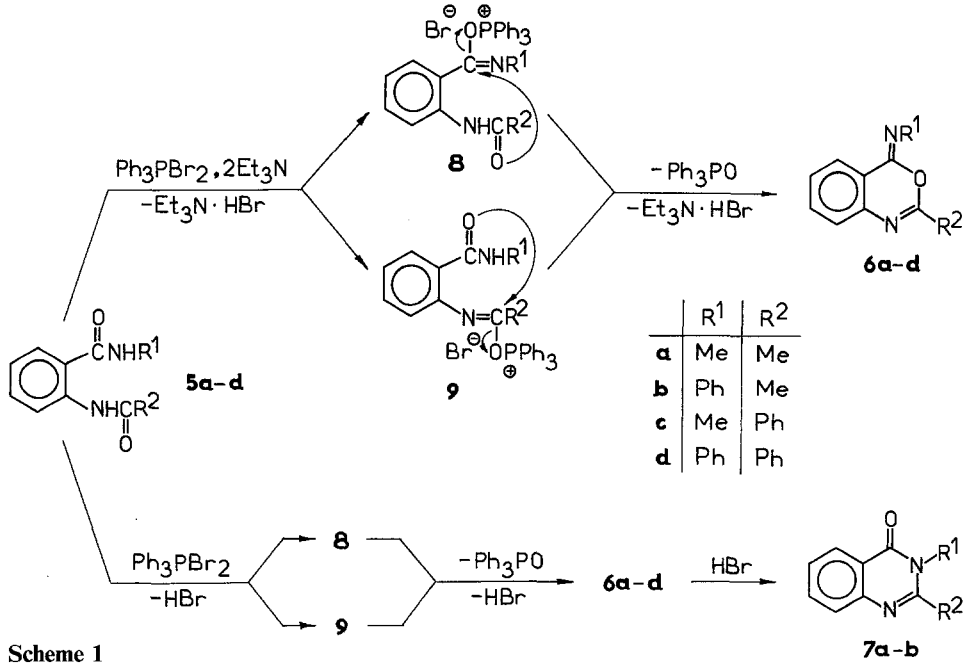
1 2 3 4

In the present paper we report similar reactions of diamides derived from an amino acid: the intramolecular O- and N-imidoylation of anthranilic acid diamides as well as the acid-catalysed O- to N-imidoylated product rearrangement. In this case the O-imidoylation results in the so far unknown interesting 4-imino-4 *H*-3,1-benzoxazine system.

Results and Discussion

Heating of the N-acylanthranilamides **5** with Ph_3PBr_2 in the presence of triethylamine in CH_2Cl_2 under reflux for 0.2–1 hour gave high yields of the expected intramolecular O-imidoylation products **6a–d** with the 4-imino-4 *H*-3,1-benzoxazine structure and are (as far as we know) unknown derivatives of the scarcely known 4 *H*-3,1-benzoxazine system. The structure of the obtained 4 *H*-3,1-benzoxazines was proved by means of spectroscopic methods (Table 2) as well as by rearranging some of them to 4-quinazolones **7**.

When N-acylanthranilamides and Ph_3PBr_2 were refluxed in CH_2Cl_2 without triethylamine, O-imidoylation products **6** or N-imidoylation products **7** (4-quinazolones) or a mixture of both were obtained (see Scheme 1 and Table 1). Thus, after one hour reaction time of N′-methyl-N-acetylanthranilamide (**5 a**) a mixture of 4 *H*-3,1-benzoxazine **6a** (27 %) and the 4-quinazolone **7 a** (53 %) was obtained.



Scheme 1

Table 1. Intramolecular O- and N-imidoylation of N-acylanthranilamides (**5a–d**) to 4-imino-4*H*-3,1-benzoxazines (**6**) and 4-quinazolones (**7**)

Amide	Condensing agent					
	$Ph_3PBr_2 + Et_3N$			Ph_3PBr_2		
	Time (h)	Yield (%)		Time (h)	Yield (%)	
		6	**7**		**6**	**7**
5a	0.2	92	–			
5a				1	27	53
5a				3	–	74
5b	1	84	–			
5b				3	–	65
5c	0.5	94	–			
5c				5	91	–
5d	1	95	–			
5d				5	51	–

Table 2. Physical and spectral properties of 4-imino-4*H*-3,1-benzoxazines

Compd. no.	M.p. (°C)	TLC R_f/solvent	IR (cm^{-1})	MS *m/s* (intensity)	^{1}H-NMR (δ)
6a	82–83	0.42/A 0.13/B 0.06/C	1691vs, 1650s 1236s, 1060s	174 (M^+, 40) 159 (100)	8.05 (d, 1H, 8.5Hz, H-5), 7.56–7.49 (m, 1H, H-7), 7.36–7.29 (m, 2H, H-6, H-8), 3.19 (s, 3H, CH_3N), 2.35 (s, 3H, CH_3C)
6b	44–45.5	0.63/A 0.51/B 0.44/C	1675vs, 1651m, 1242s, 1054s	236 (M^+, 23) 43 (100)	8.29 (d, 1H, 8Hz, H-5), 7.64–7.56 (m, 1H, H-7), 7.45–7.33 (m, 4H, H-6, H-8 and C_6H_5, H-3′, H-5′), 7.21–7.11 (m, 3H, other aromatic), 2.27 (s, 3H, CH_3)
6c	122.5–123.5	0.58/A 0.46/B 0.36/C	1687vs, 1629s, 1246m, 1063s, 1051s, 1023s	236 (M^+, 63) 235 (100)	8.23 (d, 2H, 7.5Hz, C_6H_5, H-2′, H-6′), 8.15 (d, 1H, 8.5Hz, H-5), 7.63–7.45 (m, 5H) and 7.37 (t, 1H, 8.5Hz) – other aromatic, 3.36 (s, 3H, CH_3)
6d	118.5–119	0.76/A 0.67/B 0.67/C	1676vs, 1625s, 1243s, 1062s	298 (M^+, 15) 77 (100)	8.33 (d, 1H, 8Hz, H-5), 8.01 (d, 2H, 7.5Hz, C_6H_5C, H-2′, H-6′), 7.65 (t, 1H, 7.5Hz, H-7), 7.26 (d, 2H, 8Hz, C_6H_5N, H-2″, H-6″), 7.20 (t, 1H, 7.5Hz, C_6H_5N, H-4″), 7.57–7.36 (m, 7H, other aromatic)

Table 3. The 4-imino-4*H*-3,1-benzoxazine (**6**) – 4-quinazolone (**7**) rearrangement

4-Imino-4*H*-3,1-benzoxazine	H*X*	H*X*:**6** molar ratio	Temp. (°C)	Reaction time (h)	Yield of **7** (%)
6a	HCl	1:1.5	25	120	93
6a	HCl	1:2.5	70	6	89
6a	HBr	1:2.5	70	6	82
6b	HCl	1:2.5	70	2	92
6c	HCl	1:2.5	70	12	–
6c	HBr	1:2.5	70	12	–
6d	HCl	1:2.5	70	12	–

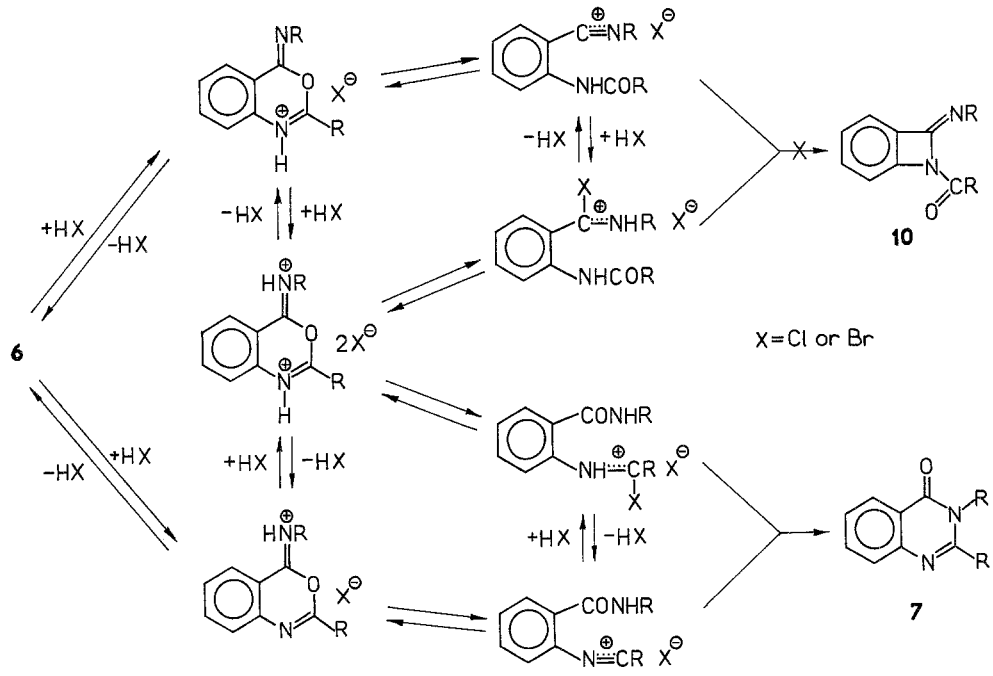
On prolonged reaction time (3 hours) only the 4-quinazolone **7a** was formed in 74% yield. Similarly, after 3 hours reaction from the N-acetylanthranilanilide **5b** only 4-quinazolone **7b** was obtained (65%). In contrast, refluxing of the N-benzoylanthranilamides **5c** or **5d** and Ph_3PBr_2 in CH_2Cl_2 without triethylamine for 5 hours gave only 4*H*-3,1-benzoxazines **6c** (91%) or **6d** (51%).

The results of these experiments suggest that – similarly as in the case of the intramolecular imidoylation reactions previously described [1] – the N-imidoylated products **7a** and **7b** are secondary products that arise from the acid-catalysed rearrangement of the O-imidoylated precursors **6a** or **6b**. In order to explain the obtained results it ought to be assumed that 2-methyl-4-imino-4*H*-3,1-benzoxazines (**6a–b**) rearrange easily to 4-quinazolones, whereas 2-phenyl-4-imino-4*H*-3,1-benzoxazines (**6c–d**) do not undergo such a rearrangement. Triethylamine, acting as a HBr captor, retardes the rearrangement of 2-methyl-4-imino-4*H*-3,1-benzoxazines.

In order to verify these assumptions, attempts have been made to rearrange 4-imino-4*H*-3,1-benzoxazines into 4-quinazolones: As expected, the 2-methyl-4-imino-4*H*-3,1-benzoxazines **6a** and **6b** rearranged smoothly under the influence of HCl or HBr into the respective 4-quinazolones and the rearrangement products could be isolated in fairly good yields (Table 3). In contrast, after heating of the solutions of 2-phenyl-4-imino-4*H*-3,1-benzoxazines **6c** or **6d** and HCl or HBr in CH_2ClCH_2Cl for 12 hours in sealed glass tubes at 70°C no traces of the respective 4-quinazolones have been detected in the reaction mixtures (IR, TLC), and the initial concentrations of the 4*H*-3,1-benzoxazines did not undergo any essential changes.

The failure to rearrange 2-phenyl-4-imino-4*H*-3,1-benzoxazines might be due to the better thermodynamic stability of the protonated 2-phenyl-4-imino-4*H*-3,1-benzoxazines if compared with the respective protonated 2-phenyl-4-quinazolones, though this does not seem to be very probable. Anyhow, attempts to rearrange 2-phenyl-4-quinazolones **7c** and **7d** into the respective 4*H*-3,1-benzoxazines in the presence of HCl have failed so far (see Experimental).

The effect of the substituent at the 2-position on the possibility to rearrange 4-imino-4*H*-3,1-benzoxazines may be explained in terms of the mechanism of analogous rearrangements of O-imidoylation products **1** and **3** as suggested previously [1]. According to this mechanism, the rearrangement consists in the opening of the ring of the protonated O-imidoylation product by cleavage of the C – O bond, after which the ring closes again in consequence of the formation of the new C – N bond (Scheme 2).



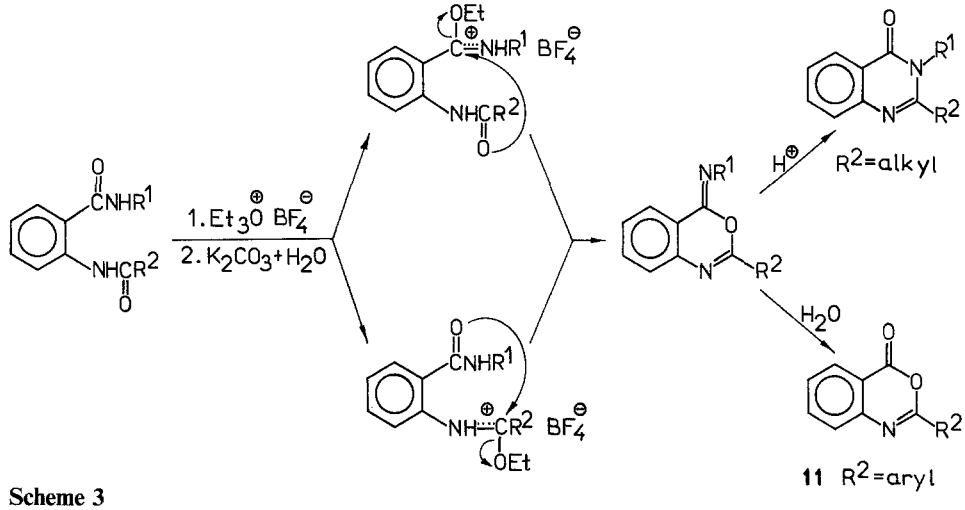
Scheme 2

The mechanism involves α-haloiminium or nitrilium cation intermediates. The electron-donating substituents at the α-carbon stabilize the resulting cations and thereby facilitate the rearrangement. According to the results of Ugi et al. [2] concerning the hydrolysis of imidoyl chlorides, the methyl group at the α-carbon stabilizes the nitrilium cation much more effectively than the phenyl group. Thus, differences in the ability of 2-methyl- and 2-phenyl-4-imino-4*H*-3,1-benzoxazines to rearrangement are connected, as might be assumed, with the difference between the electron-donating ability of the methyl and phenyl group. In previous papers [1c–d] we have described a similar effect of substituents on the susceptibility of N,N′-dimethyl- and N,N′-diphenylphthalimidic anhydrides to rearrangement.

The cleavage of the C4 – O bond of protonated 4-imino-4*H*-3,1-benzoxazines might bring about their rearrangement into the benzo-2*H*-azetidine system **10**. The formation of the latter one, however, is probably thermodynamically unfavourable because of the strain of the 2*H*-azetidine ring.

It is of interest to compare the results presented in this paper with those reported by Kato et al. [3] concerning the cyclodehydration of N-acylanthranilamides by triethyloxonium tetrafluoroborate. N-acetyl-, N-propion- and N-butyranthranilamides, when refluxed with triethyloxonium tetrafluoroborate in CH_2Cl_2, yield 2-alkyl-4-quinazolones, whereas, under the same reaction conditions N-aroyl anthranilamides give 2-aryl-4*H*-3,1-benzoxazin-4-ones **11**.

Kato et al. assume that 2-aryl-4*H*-3,1-benzoxazin-4-ones are formed by the hydrolysis of 2-aryl-4-imino-4*H*-3,1-benzoxazines, though they did not provide any proof for the formation of these intermediates. Taking into account our results it is to be supposed that 4-imino-4*H*-3,1-benzoxazines are the intermediates in the reaction of N-acylanthranilamides with triethyloxonium tetrafluoroborate independently of the structure of the substrate (Scheme 3); 2-alkyl-4-imino-4*H*-3,1-benzoxazines finally rearrange in acidic reaction medium into 2-alkyl-4-quinazolones, whereas 2-aryl-4-imino-4*H*-3,1-benzoxazines, which are not apt to rearrange, hydrolyse to 4*H*-3,1-benzoxazin-4-ones during workup of the reaction mixture.



Scheme 3

Experimental

Melting points, determined in capillary tubes, are uncorrected. IR spectra were recorded on a Zeiss Specord-M 80 spectrophotometer; the measurements were carried out, unless otherwise noted, in CH_2Cl_2 (0.2 *M*) using cells of 0.075 mm thickness. ^{1}H-NMR spectra were obtained at 300 MHz on a Varian XL-VXR 300 spectrometer in $CDCl_3$ using *TMS* as an internal standard. Mass spectra were obtained with a Gas Chromatograph-Mass Spectrometer LKB 2091 with ionization energy 70 eV. Elemental analyses were determined on a Perkin-Elmer 240 MC-1 apparatus and are in satisfactory agreement with the calculated values (C ± 0.4%, H ± 0.25%, N ± 0.25%). Reactions and chromatographic resolutions were monitored by TLC on 0.25 mm thick Kieselgel G (Merck) sheets, activated prior to use for 0.5 h at 105°C; the spots were visualized with iodine vapour. The following solvents were used for TLC: A-ethyl acetate; B and C-benzene/ethyl acetate in the ratios 2 : 1 and 5 : 1 (*v*/*v*), respectively. Silica gel (0.063–0.2 mm, International Enzymes Ltd), activated before use for 2 h at 200°C was used for column chromatography.

The purification of triphenylphosphine, bromine, triethylamine and the applied solvents as well as the preparation of solutions of HCl or HBr in CH_2ClCH_2Cl has been described in our previous papers [1].

The preparation and properties of the following compounds have been described in the literature: N-methyl-*o*-aminobenzamide [4], N-phenyl-*o*-aminobenzamide [5], 2-phenyl-3-methyl-4-quinazolone [6], 2,3-diphenyl-4-quinazolone [7].

Diamides of Anthranilic Acid (**5a–d**) *(General Procedure)*

To a stirred solution of N-methyl-*o*-aminobenzamide (3.00 g, 20 mmol) or N-phenyl-*o*-aminobenzamide (4.24 g, 20 mmol) and triethylamine (4.2 ml, 30 mmol) in benzene (40 ml) a solution of acetyl chloride (1.56 ml, 22 mmol) or benzoyl chloride (2.55 ml, 22 mmol) in benzene (10 ml) was added dropwise at 40°C; then the reaction mixture was allowed to cool and stand overnight. The precipitated mixture of diamide and triethylamine hydrochloride was collected by filtration, the precipitate was shaken with water (50 ml) and the crude diamide was filtered again. Recrystallization from ethanol (**5a–c**) or ethyl benzoate (**5d**) afforded the following pure diamides:

5a: 2.52 g, 66%; m.p. 177–177.5°C, Lit. [4], m.p. 171–172°C; IR (cm^{-1}, KBr): 3 317 m, 3 265 m (NH), 1 665 s, 1 631 vs (amide I), 1 526 s br (amide II).

5b: 2.93 g, 58%; m.p. 183.5–184.5°C, Lit. [6], m.p. 167–168°C, Lit. [8], m.p. 177–178°C; IR (cm^{-1}, KBr): 3 292 m (NH), 1 654 vs br (amide I), 1 523 vs br (amide II).

5c: 4.20 g, 83%; m.p. 167–168°C, Lit. [6], m.p. 181°C; IR (cm^{-1}, KBr); 3 324 m (NH), 1 641 s br (amide I), 1 527 vs br (amide II).

5d: 4.72 g, 75%; m.p. 278–280°C, Lit. [9], m.p. 280°C; IR (cm^{-1}, KBr): 3 284 m (NH), 1 657 vs (amide I), 1 544 s, 1 525 s (amide II).

4-Imino-4 H-3,1-benzoxazines (**6a–d**) (General Procedure)

To a solution of triphenylphosphine (1.26 g, 4.8 mmol) in CH_2Cl_2 (18 ml) a solution of bromine (0.77 g, 4.8 mmol) in CH_2Cl_2 (2 ml) was added at room temperature under argon atmosphere. After 30 min triethylamine (1.67 ml, 12 mmol) and diamide **5** (4 mmol) were added and the mixture was refluxed under argon for the time given in Table 1. At the end of the reaction the reaction mixture was diluted with benzene (20 ml), the precipitated triethylamine hydrobromide was filtered off and the filtrate was evaporated to dryness in vacuo. The benzoxazine **6a** was isolated from the residue by sublimation (60–65°C/0.01–0.02 mm Hg). The sublimate was recrystallized from hexane. The benzoxazines **6b–d** were isolated by column chromatography; elution was effected with benzene. The obtained benzoxazines **6b–d** were recrystallized from benzene-hexane.

Reactions of Anthranilic Acid Diamides (**5a–d**) *with* Ph_3PBr_2

The reactions were carried out as described above for the synthesis of benzoxazines **6a–d**, but without triethylamine. At the end of the reaction, the reaction mixture was cooled to about 0°C, then it was made alkaline with triethylamine (1.67 ml, 12 mmol) and diluted with benzene (20 ml). The precipitated triethylamine hydrobromide was filtered off and the solvent was removed in vacuo. From the obtained residue the products were isolated in the following way:

Procedure A: The mixture of the benzoxazine **6a** and the quinazolone **7a** was obtained by sublimation of the residue at 65°/0.01–0.02 mm Hg. The sublimate (0.561 g) contained about 33% of the benzoxazine **6a** and 66% of the quinazolone **7a** (IR), which corresponds to yields of 27% for **6a** and 53% for **7a**.

Procedure B: The quinazolone **7a** was isolated from the residue by sublimation (65°C/0.01–0.02 mm Hg). Recrystallization of the sublimate from hexane afforded pure **7a** (0.516 g, 74%), m.p. 109–110°C, Lit. [10], m.p. 111°C, R_f 0.25/A, 0.09/C. IR (cm^{-1}, CH_2ClCH_2Cl): 1 676 vs (C=O), 1 606 vs (C=N), Lit. [10], (cm^{-1}, melt): 1 672 vs, 1 593 vs. ^{1}H-NMR (δ, ppm): 8.16 (d, 1H, 8 Hz, H-5), 7.77–7.23 (m, 3H, other aromatic), 3.57 (s, 3H, CH_3N), 2.57 (s, 3H, CH_3C).

Procedure C: The quinazolone **7b** was isolated from the residue by column chromatography; elution was effected with benzene. Recrystallization of the crude product from benzene-hexane afforded pure **7b** (0.618 g, 65%), m.p. 145–146°C, Lit. [3], m.p. 145–146°C, R_f 0.49/A, 0.30/B. IR (cm^{-1}, CH_2ClCH_2Cl): 1 685 vs (C=O), 1 607 s (C=N). ^{1}H-NMR (δ, ppm): 8.20 (d, 1H, 8 Hz, H–5), 7.76–7.11 (m, 8H, other aromatic), 2.22 (s, 3H, CH_3).

Procedure D: The benzoxazines **6c** and **6d** were isolated as described above for the synthesis of benzoxazines.

Acid-Catalysed Rearrangement of 4-Imino-4 H-3,1-benzoxazines (**6a–d**) *to 4-Quinazolones*

To a solution of 4-imino-4*H*-3,1-benzoxazine (2 mmol) in CH_2ClCH_2Cl was added an about 0.4 *M* solution of HCl or HBr in CH_2ClCH_2Cl containing 3 or 5 mmol of acid (Table 3). The benzoxazine was dissolved in such a volume of CH_2ClCH_2Cl that the total volume of the reaction mixture amounted to about 20 ml. The reaction mixture was sealed in a glass tube and maintained at 25 or 70°C for the time given in Table 3. The reaction mixture was then made alkaline with triethylamine (0.83 ml, 6 mmol), and the progress of rearrangement was monitored by IR and TLC. No formation of the quinazolones **7c** and **7d** from the benzoxazines **6c** and **6d** has been detected. In order to isolate the

quinazolone **7a** or **7b** the reaction mixture was diluted with benzene (20 ml), the precipitated triethylamine hydrobromide or hydrochloride was filtered off and the filtrate was evaporated to dryness in vacuo. From the residue the quinazolones were isolated as described above in the Procedure B or C.

Attempts to Rearrange the Quinazolones **7c** *and* **7d** *into the Benzoxazines* **6c** *and* **6d**

The experiments were carried out similarly as in the case of the rearrangement of benzoxazines, applying 2 mmol of quinazolone and 5 mmol of HCl. The reaction mixtures were sealed in glass tubes, kept for 12 h at 70°C and then made alkaline with triethylamine (0.83 ml, 6 mmol). No formation of the respective benzoxazines has been detected (IR, TLC).

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