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Novel Synthesis and Rearrangement of 3,1,5-Benzoxadiazepines

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N,N′-Diacyl-*o*-phenylenediamines react with dibromotriphenylphosphorane in the presence of triethylamine as HBr captor to give 3,1,5-benzoxadiazepines in good yields. If the reaction is carried out without acid acceptor the initially formed 3,1,5-benzoxadiazepine finally rearranges into 1-acylbenzimidazole. It has also been found that the isolated 2,4-dimethyl-3,1,5-benzoxadiazepine rearranges under the influence of hydrogen bromide into 1-acetyl-2-methylbenzimidazole.

(Keywords: 3,1,5-Benzoxadiazepines; Synthesis; Rearrangement)

Neue Synthese und Umlagerung des 3,1,5-Benzoxadiazepins

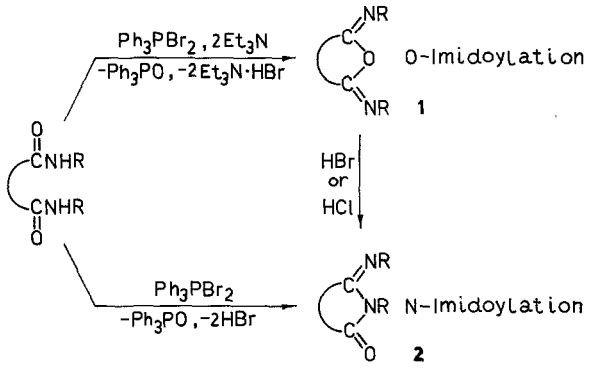
Die Umsetzung von N,N′-Diacyl-*o*-phenylendiaminen mit Triphenyldibromphosphoran in Gegenwart von Triethylamin als HBr-bindendes Mittel führt mit guten Ausbeuten zu den 3,1,5-Benzoxadiazepinen. Wird die Reaktion ohne säurebindendes Mittel durchgeführt, dann erleidet das anfänglich entstandene 3,1,5-Benzoxadiazepin eine Umlagerung in 1-Acylbenzimidazol. Es wurde auch gefunden, daß das isolierte 2,4-Dimethyl-3,1,5-benzoxadiazepin unter dem Einfluß des Bromwasserstoffs in 1-Acetyl-2-methylbenzimidazol umgelagert wird.

Introduction

In the previous papers [1, 2] we have described two types of the cyclodehydration of N,N′-disubstituted diamides of dicarboxylic acids (Scheme 1). Treatment of the diamides with dibromotriphenylphosphorane (Ph_3PBr_2) in the presence of triethylamine leads to the products of intramolecular O-imidoylation of the amide group (**1**) [1], which may be regarded as anhydrides of hypothetical imidic acids, a so far unknown class of imidic acid derivatives. In contrast, when the reaction was carried out without triethylamine, the intramolecular N-imidoylation products **2** having the ω-iminolactam structure were obtained [2]. It has

also been found [1] that the O-imidoylated products rearrange under the influence of acids into the N-imidoylated ones. The results of these investigations lead to a conclusion that the N-imidoylated products must be regarded as secondary products, arising from rearrangement in strongly acidic reaction medium of O-imidoylated precursors; when the reaction is carried out in the presence of HBr captor, the rearrangement of the O-imidoylated product is restrained.

Scheme 1



In the present paper we wish to report closely similar transformations: the intramolecular O- and N-imidoylation of diamides derived from *o*-phenylenediamine and the acid-catalysed O- to N-imidoylated product rearrangement. The O-imidoylation results in this case in the interesting 3,1,5-benzoxadiazepine system.

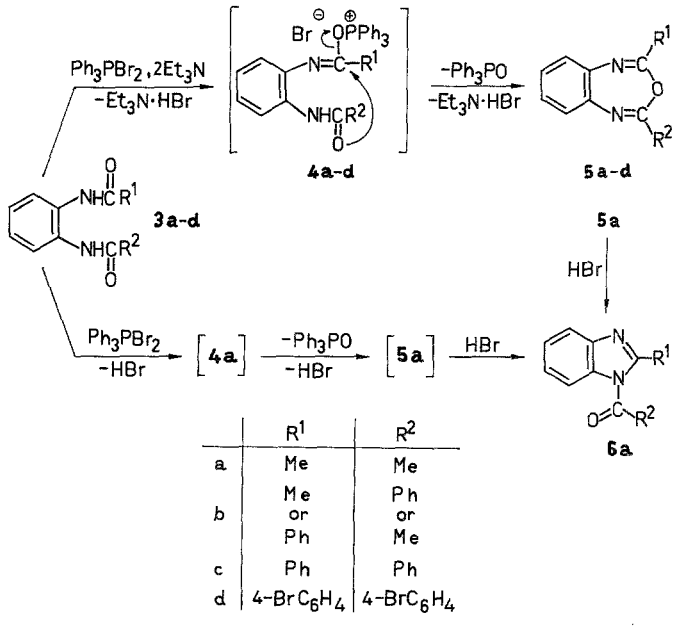
Results and Discussion

The heating of the N,N′-diacyl-*o*-phenylenediamines **3** with Ph_3PBr_2 in the presence of triethylamine in CH_2Cl_2 under reflux for 0.25–2.5 hours gave good yields of the expected intramolecular O-imidoylation products (**5 a–d**), which have the 3,1,5-benzoxadiazepine structure (see Scheme 2 and Table 1). The 3,1,5-benzoxadiazepines synthesized were identified on the basis of elemental analysis, spectroscopic properties, and by a comparison of the physical and spectroscopic properties with literature data. So far, only a few 3,1,5-benzoxadiazepines have been described [3–7], while monocyclic 3,1,5-oxadiazepines are unknown as yet [8]. The only described method of obtaining of 3,1,5-benzoxadiazepines is the photoisomerization of quinoxaline 1-oxides **7** (Scheme 3) [3–8], with the

photoisomerization products initially being mistakenly ascribed the 1a*H*-oxazirino[2,3-a]quinoxaline structure **8** [4]. At present, the structure of photoisomerisation products is beyond doubt; it has been proved, among others, by the X-ray diffraction method [5]. The cyclodehydration of N,N′-diacyl-*o*-phenylenediamines by the Ph_3PBr_2-triethylamine system is a new effective method of synthesis of 3,1,5-benzoxadiazepines.

The nature of intermediate in this reaction is open to question, but in known dehydration reactions using this type of phosphorus reagents acyloxyphosphonium salts analogous to **4a–d** have been implicated as intermediates [9].

Scheme 2



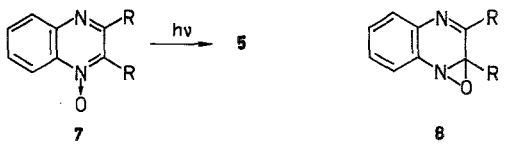
	R^1	R^2
a	Me	Me
b	Me or Ph	Ph or Me
c	Ph	Ph
d	4-BrC_6H_4	4-BrC_6H_4

When a mixture of N,N′-diacetyl-*o*-phenylenediamine (**3a**) and Ph_3PBr_2 in CH_2Cl_2 was heated under reflux for 1 hour without triethylamine, 1-acetyl-2-methylbenzimidazole **6a** was obtained in 76% yield (Scheme 2). It has also been found (IR, TLC) that after 2 minutes of heating the reaction mixture contained mainly 2,4-dimethyl-3,1,5-benzoxadiazepine **5a** and trace amounts of benzimidazole **6a**, whereas after 15 minutes of heating mainly benzimidazole **6a** besides small amounts of benzoxadiazepine **5a** was observed (see Fig. 1). This experi-

Table 1. *3,1,5-Benzoxadiazepines prepared*

Benzoxa-diazepine	Reaction time (h)	Yield (%)/ work up procedure	M.p. (°C)		TLC R_f/sol-vent	Spectral data
			Found	Lit.		
5a	0.25	52/A	70–72	71–73 [3]	0.25/A	IR (cm^{-1}, CH_2Cl_2): 1 704 vs (C=N), 1 125 vs (C—O—C), Lit. [3] (nujol mull): 1 705 vs; NMR (δ, $CDCl_3$): 7.13 (s, 4 H, aromatic), 2.23 (s, 6 H, CH_3), Lit. [3] (CCl_4): 7.1 (s, aromatic), 2.2 (s, CH_3)
5b	0.5	68/A	45.5–47		0.42/A	IR (cm^{-1}, CH_2Cl_2): 1 693 vs (C=N), 1 155 vs (C—O—C); NMR (δ, $CDCl_3$): 8.3–8.1 (m, 2 H, C_6H_5, H-2, H-6), 7.65–7.15 (m, 7 H, other aromatic), 2.26 (s, 3 H, CH_3)
5c	1	74/B	100–101	98–99 [4]	0.64/B 0.68/C	IR (cm^{-1}, CH_2Cl_2): 1 666 s (C=N), 993 vs (C—O—C), Lit. [4] (KBr): 1 667 s, Lit. [5] (KBr): 1 670; NMR (δ, $CDCl_3$): 8.3–8.1 (m, 4 H, C_6H_5, H-2, H-6), 7.6–7.1 (m, 10 H, other aromatic), Lit. [6] ($CDCl_3$): 8.3–8.2 (C_6H_5, H-2, H-6), 7.5–7.1 (other aromatic)
5d	2.5	72/C	193–195	194–196 [5]	0.66/C	IR (cm^{-1}, KBr): 1 666 vs (C=N), 998 s (C—O—C), Lit. [5] (KBr): 1 670; NMR (δ, $CDCl_3$): 8.08 (d, 4 H, 8 Hz, 4-BrC_6H_4, H-2, H-6), 7.64 (d, 4 H, 8 Hz, 4-Br—C_6H_4, H-3, H-5), 7.5–7.3 (m, 4 H, other aromatic)

Scheme 3



ment proves that the N-imidoylation product **6a** arises from rearrangement of the O-imidoylated precursor **5a** (Scheme 2), with the rearrangement probably being catalysed by HBr; triethylamine, acting as a HBr captor, restrains this rearrangement. The conclusion was confirmed by the HBr-catalysed rearrangement of the isolated benzoxadiazepine **5a** to benzimidazole **6a** in CH_2ClCH_2Cl at 25°. As in the case of the imidic anhydride-ω-iminolactam rearrangement previously described [1], the rearrangement rate is strongly dependent on the molar ratio of HBr to benzoxadiazepine. With a HBr to benzoxadiazepine molar ratio of 0.5 : 1,

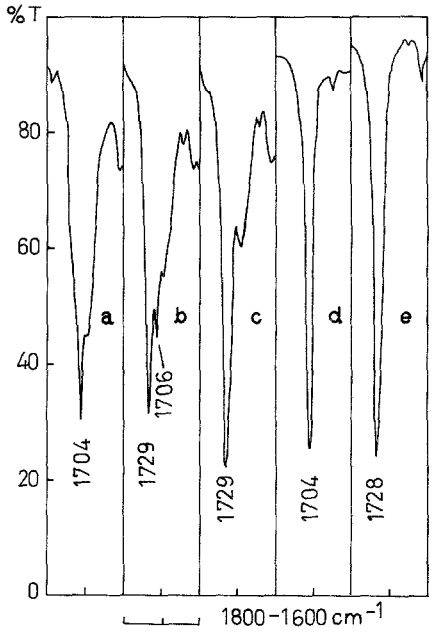
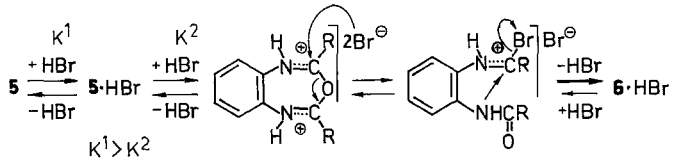


Fig. 1. The changes of the IR spectrum in the course of the reaction of N,N′-diacetyl-*o*-phenylenediamine (**3a**) with Ph_3PBr_2; a, b and c—the reaction mixture basified with triethylamine after, respectively, 2, 15 and 60 minutes of reaction; d and e, respectively, 0.2 *M* solutions of 2,4-dimethyl-3,1,5-benzoxadiazepine (**5a**) and 1-acetyl-2-methylbenzimidazole (**6a**) in CH_2Cl_2

the disappearance of benzoxadiazepine **5a** and constant concentration of benzimidazole **6a** were achieved after about 48 hours, whereas with a molar ratio of these reagents equal to 1.5 : 1, the rearrangement was already completed after about 90 minutes. The rapid increase of the rearrangement rate with rising the molar ratio of HBr to **5a** can be explained by assuming the diprotonation of benzoxadiazepine as a necessary condition of rearrangement. A tentative rearrangement mechanism embodying these findings is formulated in Scheme 4. The acid-catalysed rearrangement of 3,1,5-benzoxadiazepines to 1-acylbenzimidazoles has not yet been described, though *Kaneko* et al. [4] mentioned that they had obtained 1-benzoyl-2-phenylbenzimidazole from 2,4-diphenyl-3,1,5-benzoxadiazepine (which was mistakenly considered by them to be the corresponding 1a*H*-oxazirino[2,3-a]quinoxaline **8**) by boiling in aqueous methanol.

Scheme 4



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 100 MHz on Tesla BS 576 A *Fourier* transform NMR spectrometer using *TMS* as an internal standard. 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 ± 0.23%, N ± 0.21%). Reactions and chromatographic resolutions were, with two exceptions, monitored by TLC on 0.25 mm thick Kieselgel G (Merck) sheets, activated prior to use for 0.5 hour at 105°; the spots were visualized with iodine vapour. Only in the case of compounds **5a** and **6a**, ready-made Silufol UV 254 plates (Kavalier) were applied, and the spots were viewed by short-wave ultraviolet light (254 nm). 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 hours at 200° was used for column chromatography.

The purification of triphenylphosphine, bromine and triethylamine has been described in the previous papers [1, 2]. All the solvents used were carefully purified and dried. CH_2Cl_2 and CH_2ClCH_2Cl were washed with aqueous $NaHCO_3$, dried over $CaCl_2$, distilled from P_2O_5 and stored over molecular sieves 4 Å. Benzene and hexane were dried over Na, distilled from Na and stored over molecular sieves 4 Å. The hygroscopic nature of the benzoxadiazepines **5a** and **5b** made it essential to carry out the manipulations with these compounds in a dry box.

The preparation and properties of the following compounds are described in the literature: **3a** [10], N-acetyl-*o*-phenylenediamine [11], **6a** [12]. Hydrogen bromide was prepared by the action of bromine upon tetrahydronaphthalene and absorbed in CH_2ClCH_2Cl at 0°.

N-Acetyl-N'-benzoyl-o-phenylenediamine (**3b**)

A mixture of N-acetyl-*o*-phenylenediamine (1.5 g, 10 mmol), triethylamine (1.4 ml, 10 mmol) and benzoyl chloride (1.22 ml, 10.5 mmol) in benzene (50 ml) was heated under reflux for 3 h. The precipitated mixture of diamide **3b** and triethylamine hydrochloride was collected by filtration, shaken with water (50 ml) and the crude diamide was filtered again. Recrystallization from aqueous ethanol afforded pure **3b** (2.1 g, 83%); m.p. 158.5–159°. IR (cm^{-1}, KBr): 3 240 m br (NH), 1 669 s, 1 651 vs (amide I), 1 520 s (amide II).

N,N'-Dibenzoyl-o-phenylenediamine (**3c**) *and N,N'-Di(p-bromobenzoyl)-o-phenylenediamine* (**3d**)

A solution of benzoyl chloride (7.0 g, 50 mmol) in benzene (25 ml) was added dropwise to a solution of *o*-phenylenediamine (2.48 g, 23 mmol) and triethylamine (7 ml, 50 mmol) in boiling benzene (100 ml). The mixture was heated under reflux for 2 h and then was allowed to cool and stand overnight. The precipitated mixture of diamide **3c** and triethylamine hydrochloride was collected by filtration, the precipitate was shaken with water (100 ml) and the crude diamide was filtered again. Recrystallization from ethanol/*DMF* afforded **3c** (5.51 g, 76%); m.p. 305–306° (dec.), Lit. [13], m.p. 306°. IR (cm^{-1}, KBr): 3 264 m br (NH), 1 662 vs (amide I), 1 528 s (amide II).

In an analogous manner, from *p*-bromobenzoyl chloride (11.0 g, 50 mmol), diamide **3d** (8.55 g, 78%) was obtained; m.p. 262–264° (ethanol/*DMF*). IR (cm^{-1}, KBr): 3 276 w br (NH), 1 653 vs (amide I), 1 536 s (amide II).

3,1,5-Benzoxadiazepines (**5a–d**) *(General Procedure)*

To a solution of triphenylphosphine (1.10 g, 4.2 mmol) in CH_2Cl_2 (18 ml) a solution of bromine (0.67 g, 4.2 mmol) in CH_2Cl_2 (2 ml) was added at room temperature under argon atmosphere. After 30 min triethylamine (1.46 ml, 10.5 mmol) and diamide **3** (4 mmol) were added and the mixture was refluxed under argon for the time given in Table 1. Depending on the properties of the benzoxadiazepine synthesized (vapour pressure, solubility in CH_2Cl_2), one of the three following procedures of isolation of the product was used:

Procedure A: The reaction mixture was diluted with hexane (20 ml), the precipitated triethylamine hydrobromide was filtered off, the filtrate was evaporated to dryness in vacuo and the residue was sublimed at 60–65°/0.05–0.07 mm Hg (cold finger, − 20°). The sublimate was crystallized from hexane.

Procedure B: The reaction mixture was diluted with benzene (20 ml), the precipitated triethylamine hydrobromide was filtered off, the filtrate was evaporated to dryness in vacuo and the residue was chromatographed on a column packed with 25 ml of silicagel eluting with benzene. Chromatographically pure benzoxadiazepine was recrystallized from cyclohexane.

Procedure C: The benzoxadiazepine and triethylamine hydrobromide precipitated from the reaction mixture was collected by filtration and extracted three times with 15 ml of boiling benzene. The extract was evaporated to dryness in vacuo and the residue was recrystallized from benzene/CCl_4.

1-Acetyl-2-methylbenzimidazole **6 a**

To a solution of triphenylphosphine (1.10 g, 4.2 mmol) in CH_2Cl_2 (18 ml) a solution of bromine (0.67 g, 4.2 mmol) in CH_2Cl_2 (2 ml) was added at room temperature under argon atmosphere. After 30 min N,N'-diacetyl-*o*-phenylenediamine (0.77 g, 4 mmol) was added and the mixture was refluxed under argon. After 2, 15 and 60 min 1 ml of the reaction mixture was drawn, the sample was alkalized with 0.1 ml of triethylamine and the reaction progress was monitored by IR and TLC. After drawing the last sample, the reaction mixture was worked up according to the procedure A given above. Sublimation and recrystallization of the sublimate from benzene/hexane afforded pure 1-acetyl-2-methylbenzimidazole [0.45 g, 76%, m.p. 84.5–85.5°, Lit. [12], m.p. 85–86°, R_f 0.22 (solvent A)], which was identified (IR, TLC, mixed m.p.) with an authentic sample of 1-acetyl-2-methylbenzimidazole obtained by acetylation of 2-methylbenzimidazole according to *Bistrzycki* and *Przeworski* [12].

Acid-catalysed Rearrangement of 2,4-Dimethyl-3,1,5-benzoxadiazepine (**5 a**) *to 1-Acetyl-2-methylbenzimidazole* (**6 a**)

To a solution of the benzoxadiazepine **5 a** (0.174 g, 1 mmol) in CH_2ClCH_2Cl was added an about 0.4 *M* solution of HBr in CH_2ClCH_2Cl containing 0.5 mmol of HBr (experiment A) or 1.5 mmol of HBr (experiment B). The benzoxadiazepine was dissolved in such a volume of CH_2ClCH_2Cl that the total volume of the reaction mixture amounted to about 10 ml. The reaction mixture was maintained at 25°. After 20, 45 and 90 min and 3, 6, 12, 24, 48 and 96 h 1 ml of the reaction mixture was drawn, the sample was made alkaline with 0.05 ml of triethylamine and the progress of rearrangement was monitored by IR and, additionally, by TLC (solvent A). Complete disappearance of the benzoxadiazepine bands at 1 706 and 1 120 cm^{-1} and constant intensity of the 1-acetyl-2-methylbenzimidazole band at 1 728 cm^{-1} was achieved in experiment A after 48 h, and in experiment B after 90 min. Experiment B was repeated on twice-as-large scale without sampling of the reaction mixture. After 90 min the reaction mixture was made alkaline with triethylamine (0.5 ml, 3.6 mmol), diluted with hexane (20 ml), the precipitated triethylamine hydrobromide was filtered off, the filtrate was evaporated to dryness in vacuo and the residue was sublimed at 60–65°/0.05–0.07 mm Hg (cold finger, − 20°). Recrystallization of the sublimate from benzene/hexane afforded pure 1-acetyl-2-methylbenzimidazole [0.205 g, 59%, m.p. 84–85°, Lit. [12], m.p. 85–86°, R_f 0.22 (solvent A)], which was identified (IR, TLC, mixed m.p.) with an authentic sample of 1-acetyl-2-methylbenzimidazole.

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