

Interconversion of 3-Acylaminobenzisoxazoles and 3-(2-Hydroxyphenyl)-1,2,4-oxadiazoles

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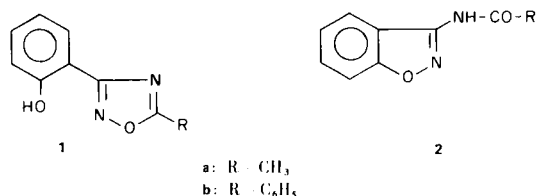
Interconversion of 3-(2-hydroxyphenyl)-1,2,4-oxadiazoles (**1**) and 3-acylaminobenzisoxazoles (**2**) was observed in the presence of base carboxylate anion, triethylamine, alkali hydroxide, alcoholate. With proton transferring reagents (carboxylate, triethylamine) the equilibrium $1 \rightleftharpoons 2$ is dependent on the substituent R; with anionic reagents (hydroxy anion, ethoxyl anion) the less basic anion of **1** is preferred. Alcohol effects further transformation of this anion and the alcohol adduct anion (**6**) is subject both to hydrolysis and alcoholysis (**7**) to yield 3-amino-benzisoxazole (**3**).

Katritzky's general scheme (1) for the ring transformation of five membered heterocycles gave impetus to a number of further investigations.

The first example of this type of transformation was given by Ponzio (2) and this was just the conversion of 1,2,4-oxadiazole into 1,2,5-oxadiazole. Other transformations of 1,2,4-oxadiazoles have been reported by others (3), as well as from this laboratory (4).

With 3-(2-hydroxyphenyl)-1,2,4-oxadiazoles (**1**) (5) prepared from salicylamidoxime, we anticipated the possibility of the unreported NCO \rightarrow CCO transformation. One example of reversed ring transformation starting from 3,6-diacetylaminobenzisoxazole was accomplished by aqueous alkali (6). The CNO \rightarrow CCO type conversion of 1,2,5-oxadiazoles to isoxazoles was described by Cusmano (7).

Ring transformation of two representatives of the system **1** (R = CH₃ and C₆H₅) was effected on one hand with bases which are not supposed to ionize the phenolic hydroxyl (e.g. sodium salts of carboxylic acids) and on the other, with those which were expected to produce this anion (alkali hydroxide, alcoholate).



Conversion of **1a** (R = CH₃) to **2a** (6) has already been observed on boiling in absolute ethanol in the presence of catalytic amounts of sodium acetate, but yields did not exceed 50% with 2 molar equivalents of sodium acetate.

In the presence of one molar equivalent of triethylamine in protic or polar aprotic solvents (ethanol, formamide, DMF) **1a** also underwent ring transformation.

However, compound **1b** (R = C₆H₅) remained practically unchanged with catalytic amounts of sodium benzoate. Isolable amounts of **2b** could be obtained with at least one mole of sodium benzoate in methanol in which the salt is more soluble. In crossing experiments, the reaction **1a** \rightarrow **2a** could also be performed with sodium benzoate and the formation of **1b** or **2b** could not be detected by tlc. This excluded the possibility of a dependence of the structure of the products on the quality of the salt.

Transformation **1** \rightarrow **2** is an equilibrium process, the position of which is substituent dependent. This was demonstrated by carrying out the process in the opposite direction (**2** \rightarrow **1**).

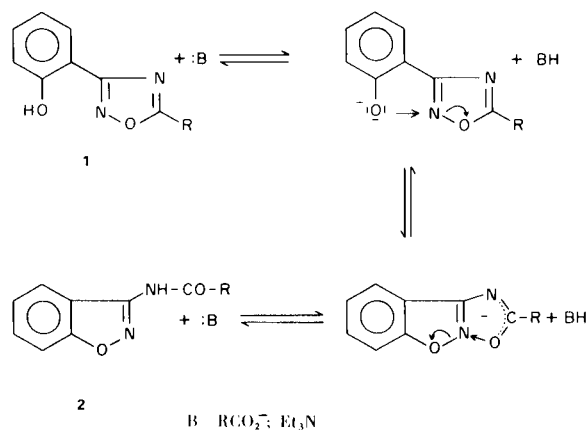
With the carboxylate or triethylamine catalyzed reaction, we obtained the neutral form of the products, i.e., their preparation did not require acidification. With aqueous alkali or alcoholic alcoholate, however, the formation of anions was anticipated and in fact a different course of the reaction was observed which was also dependent on the nature of the base. Transformation of **1** and **2** was performed first in aqueous sodium hydroxide solution. All four compounds gave mainly the oxadiazoles (**1**), and 10-18% of **2** could be isolated. These results are somewhat different from the previous one with respect to the methyl substituted compounds.

Alcoholate-promoted-transformation of both pairs was performed with one molar equivalent of the base in alcoholic solution, but work-up differed depending upon whether R was methyl or phenyl. When starting from **1b** or **2b** evaporation of the reaction mixture was followed

by acidification with a slight excess of dilute acetic acid and the product which was insoluble in hot water (65-70% of **1b**) was filtered off. 3-Aminobenzisoxazole (**3**) (15-17%) crystallized from the filtrate. The low m.p. of **1a** precluded this way of separation, so in this case the reaction product was crystallized from water without neutralization. This gave 50-55% of **3**; acidification of the mother liquor afforded 20-25% of **1a**. Acidification of the reaction mixture with anhydrous acetic acid and work-up by solvent extraction gave similar results. The appearance of **3** is unexpected since it is not formed in aqueous alkali.

No **3** was obtained in a blank experiment without alcoholate and only very little was formed with catalytic amounts (7 mole %) of alcoholate. This supported the assumption that the formation of **3** requires one molar equivalent of alcoholate and does not take place during work-up with water as shown by the presence of NH_2 -absorption in the ir spectrum of the crude product obtained after evaporation of the reaction mixture.

The basic reagents, triethylamine and carboxylate anion, are proton acceptors and their conjugate acids, proton donors, in the ring transformation reaction $1 \rightleftharpoons 2$. This role requires the cooperation with a protic or dipolar aprotic solvent as demonstrated by the fact that the establishment of the equilibrium $1a \rightleftharpoons 2a$ was extremely slow when triethylamine was also used as a solvent.



The process of $1 \rightleftharpoons 2$ may be regarded as a special enol \rightleftharpoons keto equilibrium in which the participating groups are different and the formation of one species involves the disappearance of the other.

The effect of substituent R on the position of the equilibrium can be interpreted in terms of a stabilization conjugated diene system (**8**) of the 1,2,4-oxadiazole of **1b** by interaction with the phenyl ring.

In aqueous alkali the equilibrium is shifted in favor of the phenolate and is essentially independent from the nature of the group R because the anion of **1** is a weaker

TABLE I

Starting Comp.	Reagent (molar ratio)	Solvent	Time hours	T°	Product, yield %	Recovery %	Notes
I	1a sodium acetate [a] 0.05; b) 2.0]	Ethanol	8	80	2a : a) 29% b) 54%	a) 48% b) 29%	
II	1a triethylamine [a-c] 1.0]	a) Ethanol b) FA c) DMF d) Et_3N	8	80-100	2a : a-c) 47-50% d) 12%	a-c) ~30% d) 78%	
III	1a sodium benzoate (2.0)	Methanol	8	65	2a : 53%	21%	tlc: 1b -; 2b -
IV	1b sodium benzoate [a] 0.05; b) 2.0]	Methanol	8	65	2b : a) tlc traces b) 9%	a) 86% b) 68%	
V	2a a) sodium acetate (2.0) b) triethylamine	a) Ethanol b) triethylamine	a) 8 b) 12	80 90	1a : a) 41% b) 48%	a) 40% b) 23%	
IV	2b sodium benzoate (0.05)	Ethanol	8	80	1b : 90%	tlc traces	
VII	1a or 2a 1b or 2b sodium hydroxide (1.1)	Water	until dissolving	80-90 100	1a : 63-67%; 2a : 15-17% 1b : 64-67%; 2b : 11-18%		isolation: after acidification
VIII	1a or 2a sodium hydroxide (~2.0)	Water	8	80	1a : 23-25%; 3 : 50-52%		3 dissolves in hot water
IX	1a or 2a sodium ethoxide (1.0)	Ethanol	8	80	1b : 65%; 3 : 15-17%		
X	1b or 2b sodium ethoxide (1.0)	Ethanol	8	80			

base than that of **2**. Though their interconversion did not permit the exact determination of the pK_a values of **1a** and **2a**, the pH dependence of their uv spectra indicated that the formation of the anion of **1a** began at pH 8.4 and that of **2a** at pH 12.0 (9).

In order to be able to interpret the alcoholate promoted transformation it was necessary to answer the following questions: a) Why is the equilibrium despite the lower basicity of **1** shifted to the benzisoxazole side? b) What kind of processes are associated with deacylation in the anhydrous medium? c) Why is deacylation an equilibrium reaction even in the presence of equimolecular alcoholate?

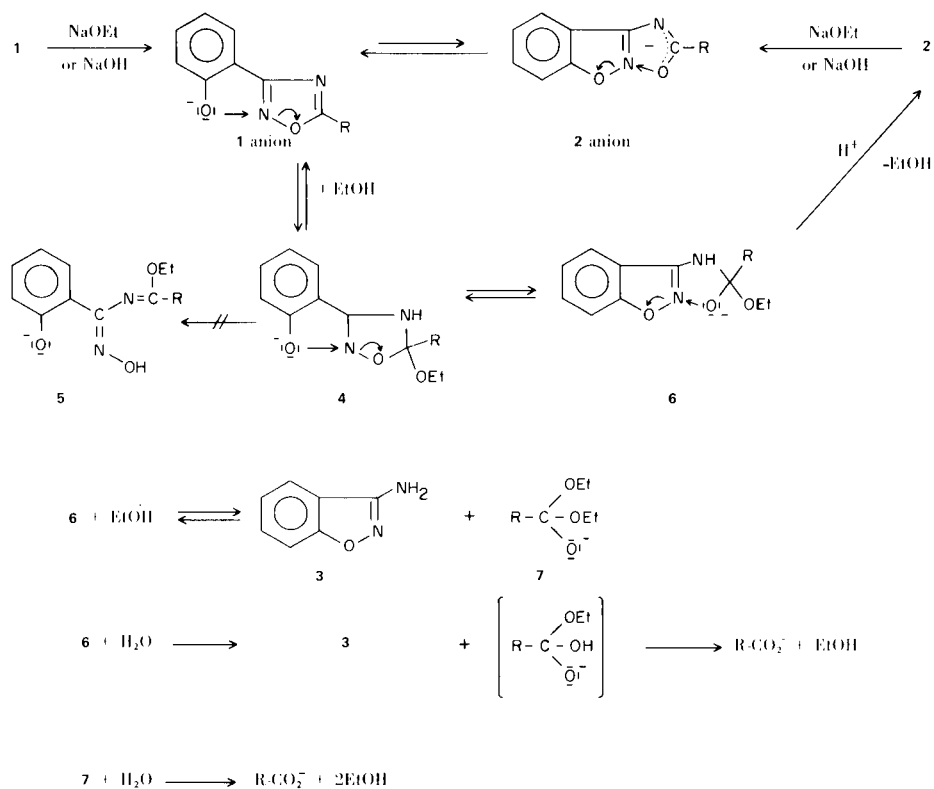
The process which may lead from the phenolate anion to the anion of a benzisoxazole derivative and which is the reverse of the one observed in water cannot be rationalized by solvent effect. The limited nucleophilic character of the solvated phenolate anion (10) in water would only inhibit such unfavorable transformation which is associated with an increase of basicity. The relative basicity of the anions **1** and **2** remain essentially the same when changing from water to alcohol. Since a rapid acid-base equilibrium and the predominance of the phenolate anion was expected, the reaction of **2a** was followed by uv spectroscopy.

By comparing absorption maxima at 335 nm (9), it was found that under the action of alcoholate on **2a** the

maximum concentration of **1a** is established within a few minutes at boiling point and in about 30 minutes at room temperature. By acidification and extraction with light petroleum, 68% of **1a** could be isolated at the time of the highest concentration of the corresponding anion. Consequently, **3** is not formed directly from the anion of **2** but *via* a phenolate anion of **1**. The next anionic species formed on the way to the product cannot be that of **2**, but one which has a comparable or lower basicity than the phenolate itself. This species is characterized by the following features: 1) its formation is dependent on alcohol, since it does not take place in water; 2) its existence or transformation enables the cleavage of the acyl group in alcohol; 3) as it is formed from the phenolate anion, it is related to the oxadiazole structure of the latter.

It is supposed that addition of alcohol to the N^4-C^5 -bond of the oxadiazole ring takes place (11) to give **4**, in which the center C^5 has iminoester character. The presence of a phenyl substituent on this atom antagonizes this addition by conjugative stabilization of the oxadiazole system. Further transformation of **4** cannot lead to the acyclic anion **5** because in this case benzisoxazole formation could not be explained.

This requires the presence of an electron-attracting group promoting the heterolysis of the N-O bond (*e.g.* oxime-ester) as well as the attack of a phenolate ion (12).



These conditions are given with **4** from which the formation of the amide-acetal type benzisoxazole anion **6** can be assumed.

Considering the structure of the anion **6** it is possible to explain the deacylation by alcoholate. This is an iminoester derivative since its conjugate acid (**6** + H⁺) is nothing else than the intermediate in the known transformations of iminoesters to amine and ester or to amide and alcohol, respectively. The iminoester character of anion **6** also involves the possibility of its alcoholysis (*cf.* the conversion of iminoesters to orthoesters). The alcoholysis of **6** gives the orthocarboxylic diester anion **7** and **3**.

The route from the anion of **2** to **6** by direct addition of alcohol is unlikely since the attack of a nucleophile (alcohol) is inhibited by the negative charge dispersed by mesomeric interaction over the triad N-C-O.

The equilibrium ratio of **1** and **3** in alcoholic alcoholate is similar to that of **1** and **2** in the presence of proton transmitting reagents. Despite this apparent agreement the equilibrium of anions is controlled both in this case and in that in aqueous solution by their relative basicity and this remains essentially unchanged by the addition of alcohol to **1** to form **4**, the process on which the formation of anions **6** and **7** is dependent. This elementary step, however, is influenced by the C⁵-R substituent. Basicity of anions **6** and **7**, respectively, falls according to our experience between that of acetate and phenolate. This is also in accord with theory, since the hypothetical conjugated acids of **6** and **7** respectively, will be substantially weaker than acetic acid due to the absence of electron-attracting and mesomeric effects of the carbonyl group. The ion-equilibrium character of the process is also supported by the fact that increasing the amount of alcoholate to two molar equivalents does not improve the yield of **3**.

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EXPERIMENTAL

Melting points are uncorrected. Compounds **1a**, **1b** (**5**), and **2b** (**6**) are known.

1) 3-Benzoylaminobenzisoxazole (**2b**).

This compound was prepared by reaction of **3** with 1 mole of benzoyl chloride, yield 65%, m.p. 140-141° (from carbon tetrachloride).

Anal. Calcd. for C₁₄H₁₀N₂O₂: C, 70.57; H, 4.23; N, 11.76. Found: C, 70.49; H, 4.41; N, 11.89.

2) Transformation of **1** in the Presence of Carboxylate.

a) Compound **1a** (R = CH₃) and Catalytic Amount of Sodium Acetate.

Compound **1a** (17.6 g., 0.1 mole) and fused sodium acetate

(0.5 g.) was refluxed in ethanol (150 ml.) for 8 hours. Evaporation, trituration with water (150 ml.), and filtration gave the crude product (16.7 g., m.p. 65-135°). Repeated recrystallization from acetonitrile gave **2a** (4.45 g., 25%), m.p. 160-161°. Evaporation of the acetonitrile mother liquor extraction of the residue (11.65 g.) with light petroleum (100 ml. + 4 x 50 ml.) and recrystallization of the undissolved material (2.4 g., m.p. 120-145°) from acetonitrile gave more of **2a** (0.8 g., 4%). Compound **1a** crystallized from the light petroleum (8.25 g., 48%), m.p. 73-74°.

b) Compound **1b** (R = C₆H₅) and 2 Molar Equivalents of Sodium Benzoate.

Compound **1b** (4.76 g., 0.02 mole) and sodium benzoate (5.76 g., 0.04 mole) were refluxed in methanol (120 ml.) for 8 hours. Evaporation, trituration with water (50 ml.), and extraction of the residue (4.55 g.) with hot light petroleum (3 x 50 ml.) gave **1b** (2.85 g., 58%), m.p. 124-125° which crystallized from the solvent. Undissolved material (1.45 g., m.p. 103-106°) was further extracted with light petroleum (8 x 10 ml.), the residue (0.6 g.) recrystallized from carbon tetrachloride to give **2b** (0.43 g., 9%), m.p. 140-141°. Compound **2b** was identical with an authentic sample by ir and m.m.p. Evaporation of the light petroleum extracts gave more **1b** (0.5 g., 10.5%).

3) Reactions of **1** with Aqueous Alkali.

A solution of **1a** (1.76 g., 0.01 mole) in 1*N* sodium hydroxide (11 ml.) prepared by heating on the steam bath was left to stand 24 hours in a stoppered flask. No precipitation of **3** was observed. Acidification with acetic acid and the usual work-up gave 25% of almost pure **2a**, m.p. 152-155°, 17% of the pure product, and 63% of **1a**.

4) Reaction of **1** in Ethanolic Sodium Ethoxide.

To an alcoholic solution of **1a** (5.28 g., 0.03 mole) that of metallic sodium (0.691 g., 0.03 mole) was added and the solution refluxed for 8 hours. Evaporation and crystallization from water (50 ml.) gave 2.04 g. (51%) of **3**, m.p. 110-112°. Acidification of the mother liquor with acetic acid gave 36% of crude **1a** (24% of m.p. 73-74° after purification). Similar results were obtained by fractional crystallization (with light petroleum) of the product which was obtained by acidification of the alcoholic reaction mixture (absolute alcohol was dehydrated with the diethylphthalate method; water < 0.05%) with anhydrous acetic acid prior to the evaporation (**3**, undissolved in light petroleum, is in this case somewhat contaminated with **2a**) (13).

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(13) By this experiment it was proved that there is also a direct formation of **3** in the alcoholic system. Furthermore, the protonation of **6** in anhydrous medium goes according to the process iminoester-hydrate \rightarrow amide + alcohol to **2**.