Bacterial Aromatic Sulfonates - A *Bucherer* Reaction in Nature?

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Abstract: Aromatic sulfonic acids have been found in Nature only rarely as bacterial metabolites, mostly with the sulfonate group located on an oxygenated benzene ring. This suggests a mechanism of formation as it is discussed for the first step of a *Bucherer* reaction.

Keywords: Bacterial metabolites, sulfonates, *Bucherer* reaction.

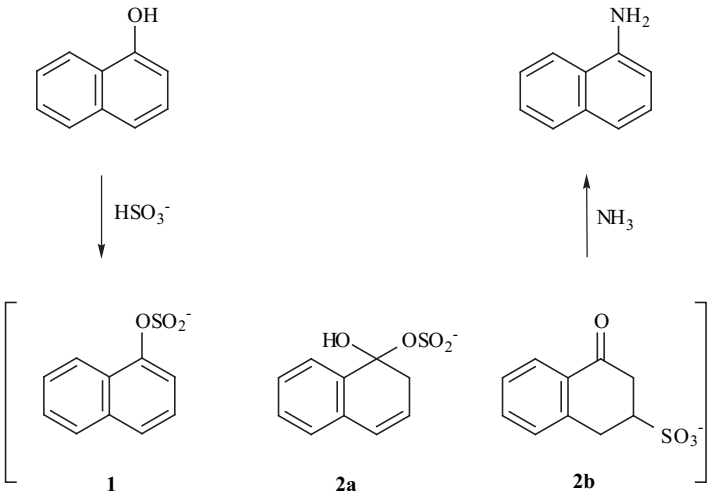
1. INTRODUCTION

Aliphatic sulfonic acids are common in Nature. Best known is cysteic acid (the oxidation product of cystein) from which other compounds are derived such as sulfoacetic acid and other C_2-compounds, or even sulfocarbohydrates (see e.g. [1]). Aromatic sulfonic acids, however, are scarce and so far only found to be produced by some bacteria. Since in every case oxygenated benzene rings are derivatized, a mechanism of formation in analogy to the first steps of the *Bucherer* reaction could be postulated.

The *Bucherer* reaction is hardly mentioned in recent text books of organic chemistry. This was different in the first half of the 20th century. It allowed a transformation of readily available aromatic hydroxy compounds into the corresponding amines (Scheme **1**) which were needed as starting materials for the azo dyes. A host of patents was the consequence. After World War II a few scientists used the spectroscopic methods now available to clarify the disputed mechanism of the reaction, but then the interest in the *Bucherer* reaction declined. It gained some importance again when its intermediacy was suggested for the biosynthesis of the bacterial pyoverdins (see below).

In 1904 *H. Th. Bucherer* had published a detailed account of his studies on the reciprocal transformation of aromatic hydroxy and amino compounds by the action of sulfites [2]. The mechanism of this reaction especially for α- and β-naphthol systems was long under discussion. *Bucherer* originally had assumed that a naphthol sulfite ester (**1**) was the reactive component [2], while *Woroshtzow* suggested in 1916 [3, 4] that the keto tautomer of the naphthol reacted with an oxygen atom of the hydrogen sulfite anion to give **2a.** A third formulation of the intermediate (**2b**) was proposed by *Bogdanow* in 1932 [5], which was proved to be correct by *Rieche* and *Seeboth* in a series of publications in 1960 [6] (Scheme **1**). For a review of this topic see [7].

Phenol can not be transformed into aniline in this way. For hydroquinone a tris-addition product was described (formulated as **3**) [8] which has not been investigated any further. Resorcinol, however, was studied in more detail. *Bucherer* could transform resorcinol into 3-aminophenol and 1,3-diaminobenzene by reacting it with ammonium sulfite and ammonia, and he again assumed the intermediacy of sulfite esters [2]. He noticed that three molecules of sulfite had been added [9]. Different proposals were made for the structure of this addition product. *Fuchs* and *Elsner* [10] proposed **4** mainly because in alkaline solution 2 moles of SO_2 were lost. The resulting compound was suggested to be



Scheme 1. Intermediates suggested for the *Bucherer* reaction of α-naphthol.

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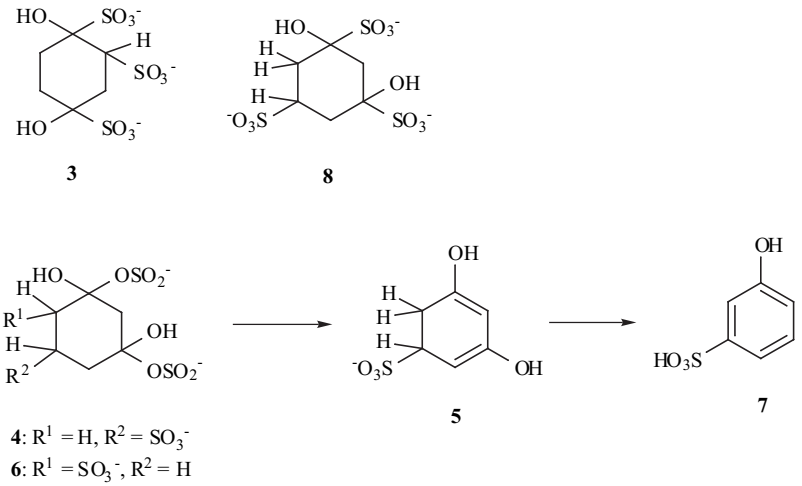
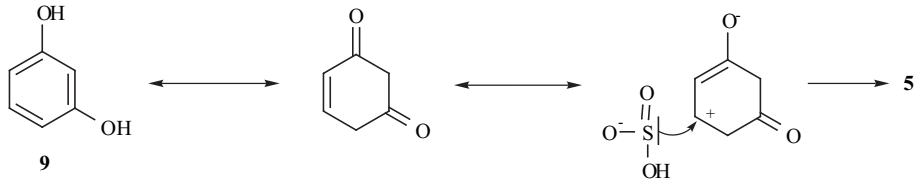


Scheme 2. Intermediates suggested for the *Bucherer* reaction of hydroquinone and resorcinol systems.



Scheme 3. Reaction of resorcinol with SO_3H^-.

5,6-dihydroresorcinol-5-sulfonic acid (**5**), while *Bucherer* [11] preferred the isomeric structure **6** for the tris-adduct. This question was finally settled in favor of **4** when it was shown [12] that **5** by the loss of H_2O could be transformed into **7**. Subsequently it was proposed that all three sulfite ions are bound to the cyclohexane ring by their sulfur atoms (**8**) [13-15] (Scheme **2**). Whatever the structure of the tris-adduct, for our purposes it is important that one hydrogen sulfite ion attacks the free 5-position of resorcinol with its sulfur atom yielding a sulfonic acid substituent (**9** → **5**), and that in a subsequent reaction one or both hydroxy groups can be replaced by amino functions [2, 16] (Scheme **3**).

2. THE PYOVERDIN CHROMOPHORE

Pyoverdins are the typical siderophores of the fluorescent species of the bacterial family Pseudomonadaceae *sensu stricto* [17]. They consist of three distinct structural parts, viz. a dihydroxyquinoline chromophore responsible for their fluorescence (**14**), a peptide chain comprising 6 to 12 amino acids bound to the chromophore carboxyl group, and a small dicarboxylic acid (or its monoamide) connected amidically to its NH_2-group (Fig. **1**). A fair amount of evidence has been assembled regarding the formation of the pyoverdin chromophore **14** suggesting the sequence depicted in Scheme 4: D-Tyrosine bound to the γ-carboxyl group of L-glutamic acid is condensed with L-2,4-diaminobutanoic acid to give the ferribactin chromophore **10**, which was shown [18] to be a precursor of **14**. Into the hydroxyphenyl ring of tyrosine two additional hydroxyl groups are introduced (**11**). For the ring closure giving the dihydropyoverdin ring **13**, the mechanism of a *Bucherer* reaction was proposed [19], as it is suggested by the discovery of dihydropyoverdin-7-sulfonic acids (**12**) [19, 20]. Dihydropyoverdins are readily dehydrogenated in the culture medium by atmospheric oxygen especially in slightly alkaline media [21].

3. PSEUDOALTEROBACTIN A/B AND PETROBACTIN SULFONATE

From two bacterial species, *Pseudoalteromonas sp.* KP20-4 and *Marinobacter hydrocarbonoclasticus*, catecholate siderophores (for a review see [22]) were obtained which carry a sulfonic acid residue next to the two catechol hydroxyl groups: pseudoalterobactin A (**15**) and B (**16**) (Scheme **5**) [23], and petrobactin sulfonate (**17**) (Fig. **2**) [24].

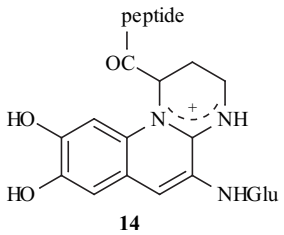
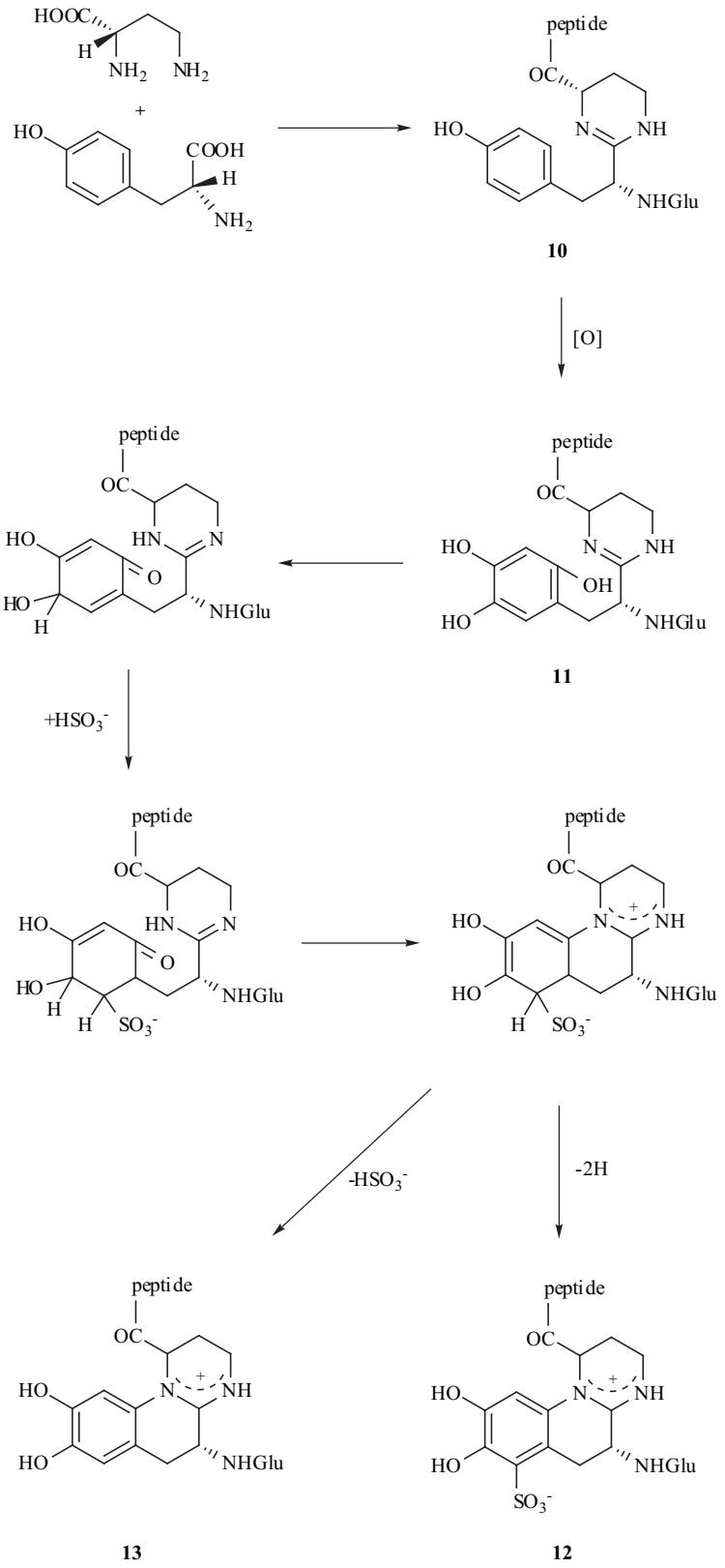


Fig. (1). General structure of pyoverdins.



Scheme 4. Suggested biosynthesis of the dihydropyoverdin chromophore.

As it has been formulated above for hydroquinone and resorcinol systems, addition of a sulfite ion to the keto form could be invoked. The last step must be loss of H_2 (as observed for the formation of **12** (and not of H_2O as for **7**).

4. AERUGINOSIN B

Aeruginosin A (**18**) [25] and B (**19**) [26, 27] (Scheme **5**) are red pigments of *Pseudomonas aeruginosa*. Little is

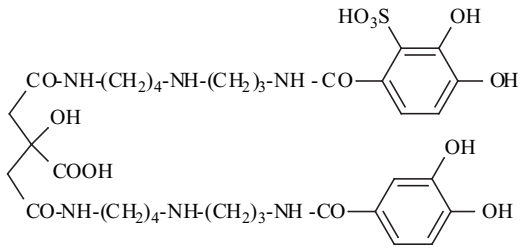


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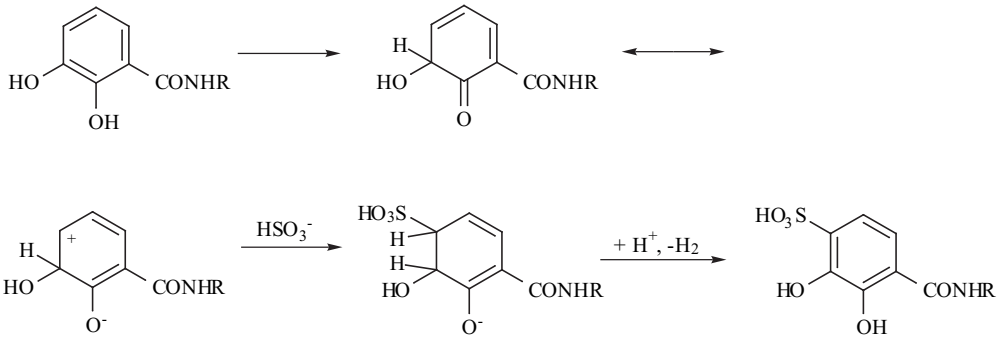
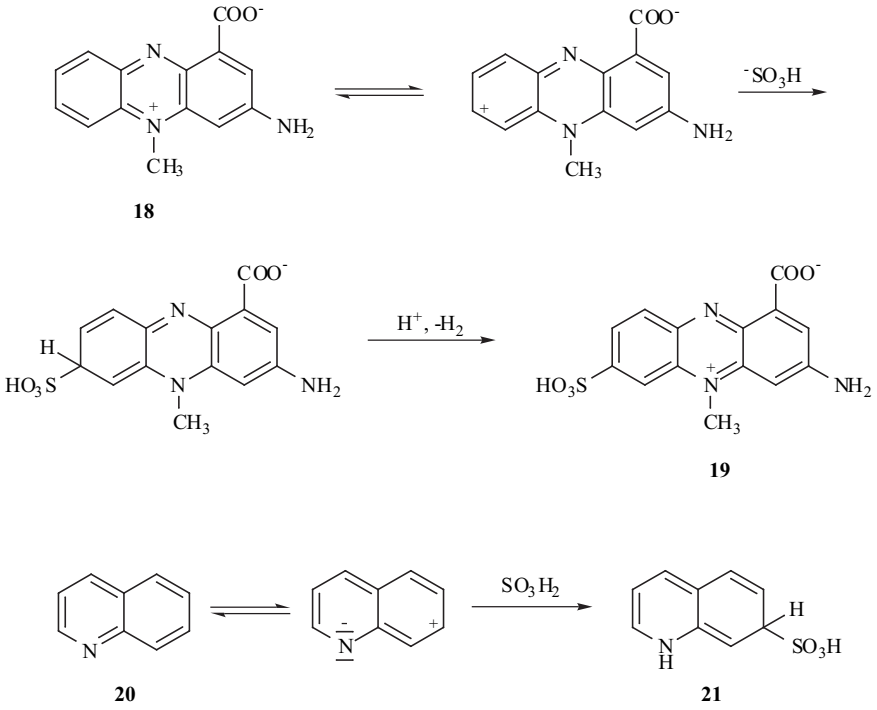
Fig. (2). Petrobactin sulfonate.



15: R = NH-$(CH_2)_4$-$CHNH_2$-CHOH-CH_2-CO-Asn-OHAsp-cyclo-(Lys-Lys-OHAsp-Gly)
16: R = NH-$(CH_2)_4$-$CHNH_2$-CHOH-CH_2-CO-Asn-OHAsp-cyclo-(Lys-Arg-OHAsp-Gly)

Scheme 5. Suggested formation of the pseudoalterobactins.

known regarding the reaction of sulfites with heterocyclic systems. As do many aliphatic and aromatic amines [28], also quinoline reacts with gaseous as well as with liquid SO_2 to give a 1:1 solid yellow addition compound melting at 53°C [29, 30]. Reaction of quinoline with SO_2 in aqueous solution and with aqueous $NaHSO_3$ gave, however, yellow crystals with a mp. 80-81°C. Form the combustion analysis data an elemental composition of $C_9H_7N.SO_2$ was calculated. By both procedures yellow crystals (mp. 127-129°C) were also obtained from 8-hydroxyquinoline. Combustion analyses suggested also here the addition of SO_2 ($C_9H_7O.SO_2$) [31]. In a subsequent publication the authors report the reaction of 6-hydroxy- and 8-hydroxyquinoline with aqueous NH_4HSO_3 giving the



Scheme 6. Hetrocyclic sulfonates.

corresponding aminoquinolines. In analogy to **2a** addition products of the hydrogensulfite ion (but formulated as ammonium sulfonates) to the respective keto forms were formulated as intermediates, without reference to the earlier combustion analysis data [32]. An explanation could be that under mild conditions (warming in a water bath [31]) a sulfite ester is obtained while under more drastic ones (7 hours in an autoclave at 150°C [32]) the quinoline analog of **2a** and subsequently aminoquinoline is formed.

For the hydroxyquinolines intermediates of type **2a** would be expected, but for unsubstituted quinoline the sequence **20** → **21** could be considered. In this context it is of interest that the equilibrium between quinoline and SO_2 was reported to be reached only comparatively slowly [29] which suggests a chemical modification. For the formation of aeruginosin B the sequence depicted in Scheme **6** can be proposed.

5. CONCLUSION

The *Bucherer* reaction consists of three steps, viz., the attack of a hydrogensulfite ion with its sulfur atom at a positive carbon center of specific aromatic systems to give a sulfonic acid, the exchange of a an oxygen function against a nitrogen function (or *vice versa*), and the loss of the hydrogen sulfite ion. Side reactions are the loss of H_2O or of H_2 with retention of the sulfonic acid group. The formation of aromatic sulfonates found to by produced by some bacteria could be explained in this way. Hydrogensulfite ions necessary for the addition reaction were shown [33] to be formed by the oxidative desulfurization of aliphatic sulfonates [1].

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