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ON THE REACTION OF PRIMARY ALIPHATIC AMINES WITH 1,2-NAPHTHOQUINONE-4-SULFONIC ACID

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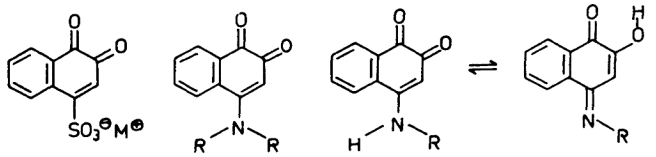
Primary amines react with 1,2-naphthoquinone-4-sulfonic acid to form violet dyes in a complex redox reaction. Their general structure 6 has been established by an independent synthesis.

The alkali metal salts of 1,2-naphthoquinone-4-sulfonic acid (NQS) form coloured condensation products with primary and secondary amines which are often used for colorimetric estimations[1a]. Comparable reactions have been reported with amino acids[1b] and serve among others for their quantitative analysis in biological material[2]. The resulting coloured product is generally formulated as a 4-amino-1,2-naphthoquinone 2; in the case of primary amines also tautomeric forms such as 3b have been considered[1].



1 2 a 3 b

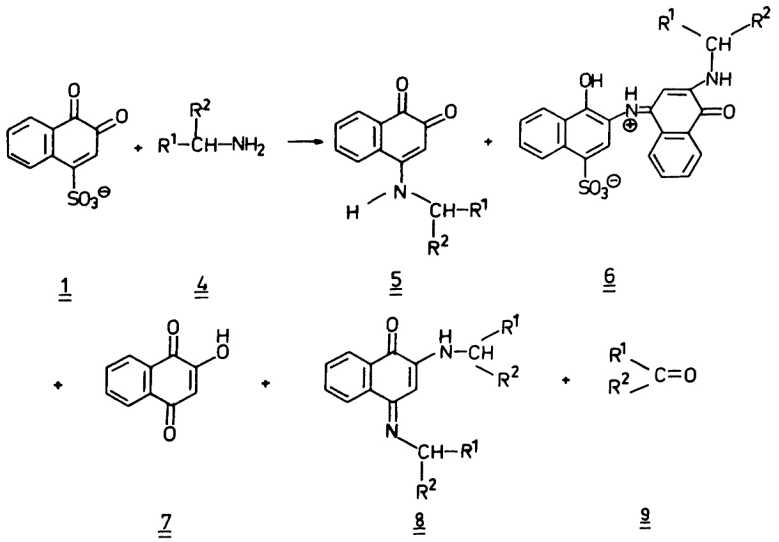
NQS reacts with secondary aliphatic amines as well as with primary and secondary aromatic amines substituting the sulfonic acid group to yield the corresponding 4-dialkylamino-, 4-arylamino- or 4-alkylarylamino-1,2-naphthoquinone 2 or 3[3]. With primary aliphatic amines, however, NQS forms a complex mixture of products, which contains, according to our observation, only minor amounts of 4-alkylamino-1,2-naphthoquinone 3[4)5].

All 4-amino-1,2-naphthoquinones are yellow; therefore the structures 2 and 3 by no way explain the violet colour observed in the reaction of primary aliphatic amines with NQS. On the other hand should it be impossible to detect a small impurity of a primary aliphatic amine in a secondary aliphatic amine[6] with NQS, if both reaction products had the same chromophoric system.

We, therefore, reacted equimolar quantities of methyl-, ethyl-, and isopropylamine with the sodium salt of NQS at room temperature in aqueous medium. Within a few minutes the colour changes from orange to dark violet and a complex mixture of products is formed, from which 5 to 9 could be identified; the main products

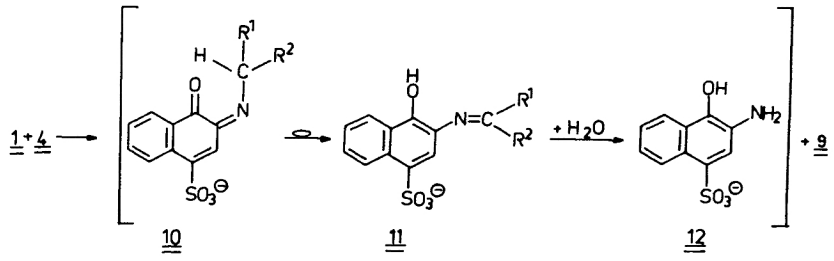
being 5, 6 and 9. After 15 minutes the reaction mixture is acidified with 5% hydrochloric acid until the violet colour changes to red, kept at 5°C for 12 hours and filtered. The violet black precipitate is thoroughly washed with Et_2O, CH_2Cl_2 and CH_3OH and consists mainly of 6: 6a (R = CH_3), yield 61%, mp. ~230°C (decomp.), ^{1}H-NMR(DMSO): δ 9.77 (d, NH), 8.9-7.5 (m, 9 H), 5.50 (s, 1 H), 2.78 (d, NCH_3); ^{13}C-NMR (pyridine-d_5): δ 181.1 (C=O), 156.7, 146.9, 146.4, 146.3, 135.1, 133.0, 130.5, 129.3, 128.2, 127.3, 126.2, 125.9, 125.6, 125.5, 125.1, 125.0, 124.8, 93.7 (C-Ar), 28.6 (NCH_3); 6b (R = C_2H_5), 72%, mp. decomp.: 6c [R = $CH(CH_3)_2$], 33%, mp. decomp. The filtrate is extracted with CH_2Cl_2, the organic phase evaporated and the residue sublimed to give 5, identified by an independent synthesis from 4-alkoxy-1,2-naphthoquinone and 4 according to lit[4]: 5a (R = CH_3), 30%; 5b (R = C_2H_5), 15%; 5c [R = $CH(CH_3)_2$], 25%. The side product 7 (yield ~2%) is formed through hydrolysis of 1 and/or 5. 5 may further react with an equimolar quantity of 4 yielding 8 (~1%).

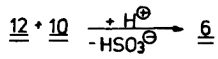
We have not been able to isolate any intermediate products. Corey and Achiwa[7], however, have found a comparable redox reaction, where primary aliphatic



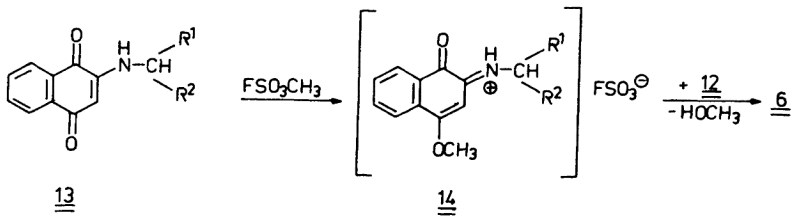
amines could easily be oxidised to the respective carbonyl compounds with 3,5-di-t-butylbenzoquinone. We assume, that the primary aliphatic amine attacks NQS at the carbonyl group of C-2 producing the Schiff base 10. This might rearrange by a 1,5-proton shift and aromatization of the second ring to the isomeric Schiff base 11, which could hydrolyse under aqueous reaction medium to the 3-amino-4-hydroxynaphthalene-1-sulfonic acid (12) and the carbonyl compound 9. Condensation of 12 with 10, which should become highly reactive after N-protonation, yields the violet coloured compound 6.

We have confirmed structure 6 through an independent synthesis. 1,4-naphthoquinone reacts with primary amines to yield 2-alkylamino-1,4-naphthoquinone 13[8], which on alkylation with methyl fluorosulfonate gave the salts 14.

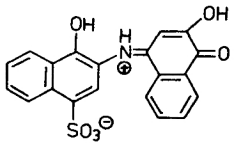




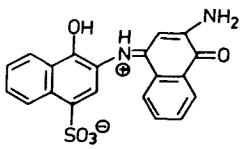
These salts condense with commercial 3-amino-4-hydroxynaphthalene-1-sulfonic acid (12) to give violet substance 6 in practically quantitative yield.



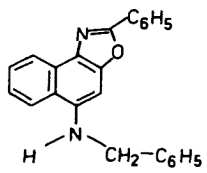
Structural details of the particular primary amine used may change the reaction course with NQS considerably. Thus, we obtained with benzylamine and NQS in addition to benzaldehyde and 30% 5 three violet substances. Among them the main product is 15 (~ 25% yield), while the expected 6 and 16[9] could only be identified in very small amounts (< 1%) in the ^{13}C-NMR spectrum of the crude violet substance from 15 through comparison with authentic samples. Besides that, we isolated the oxazole 17 (~ 1%)[10], whose structure was confirmed through an independent synthesis of the isomeric compound (position of N and O in the oxazole ring is exchanged). The way of formation of 15 is unclear; we could, however, show that 15 is neither a hydrolysis product of 6 or 16, nor a condensation product of NQS with 12. The isolation of the oxazole 17 further indicates, that a primary aliphatic amine can attack the NQS not only at C-4 and C-2 but also at C-1. These three possibilities explain, why so many products are formed in the reaction of NQS with primary aliphatic amines.



15



16



17

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   b. Reference 1a, p. 1018 and 1. suppl., p. 368.

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3) C.Grundmann in Methoden der Organischen Chemie (Houben-Weyl-Müller), 4. Ed., Vol. VII/3b, part II, p. 107-109, Thieme, Stuttgart 1979.

4) Therefore L.M.Fieser and M.Fieser, J.Am.Chem.Soc. 57, 491 (1935) state, that 4-alkylamino-1,2-naphthoquinones 3 are not accessible from primary aliphatic amines and NQS; they recommend to use 4-alkoxy-1,2-naphthoquinones instead of NQS.

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