

REACTIONS OF HALOGENS WITH 5-HYDROXYBENZO(*a*)PHENAZINE

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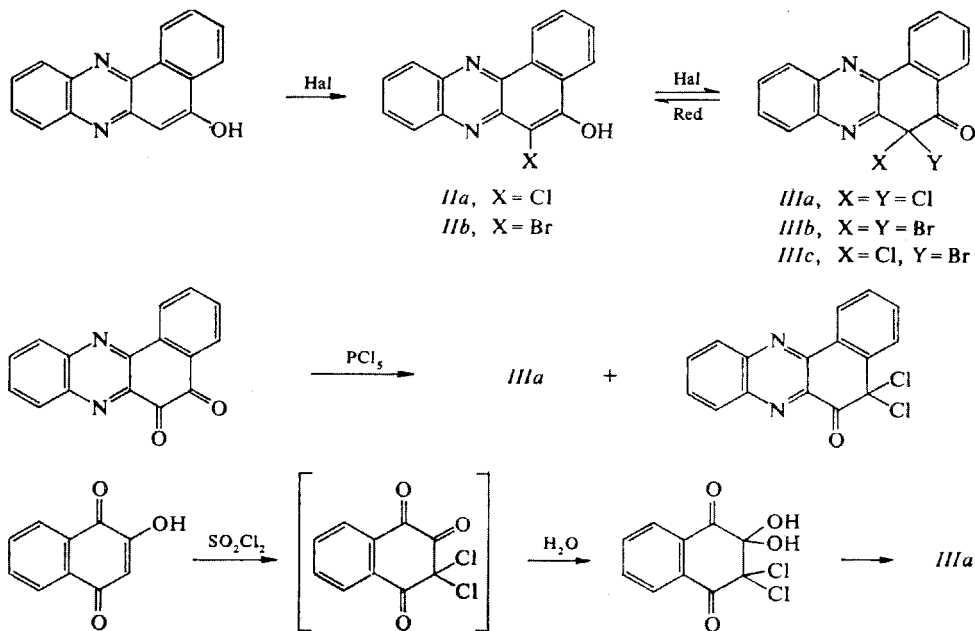
On reaction of chlorine with 5-hydroxybenzo[*a*]phenazine (*I*) in ethanol 6-chloro-5-hydroxybenzo[*a*]phenazine (*IIa*) and 6,6-dichloro-5-oxo-5,6-dihydrobenzo[*a*]phenazine (*IIIa*) are formed gradually. Compound *IIIa* is also formed on reaction of sulfuryl chloride with *I* and *IIa*. Its structure was proved by two independent routes. Bromination of *I* gives 6-bromo-5-hydroxybenzo[*a*]phenazine (*IIb*) and 6,6-dibromo-5-oxo-5,6-dihydrobenzo[*a*]phenazine (*IIIb*).

All halogeno derivatives of benzo[*a*]phenazine described so far have been prepared on condensation of halogen-substituted 1,4- and 1,2-naphthoquinones with 1,2-phenylenediamine¹. At direct chlorination of 5-hydroxybenzo[*a*]phenazine (*I*) in ethanol we detected now in the reaction mixture in addition to the known 6-chloro-5-hydroxybenzo[*a*]phenazine² (*IIa*) also a light yellow substance to which we assigned the structure of 6,6-dichloro-5-oxo-5,6-dihydrobenzo[*a*]phenazine (*IIIa*) on the basis of elemental analysis and the IR spectrum. Similarly, on bromination of *I* dibromo derivative *IIIb* has been obtained. A combined derivative, *IIIc*, was obtained on reaction of substance *IIa* with bromine. Using potentiometric control of bromination of *I* it was found that the reaction takes place in two separate steps; similar conclusions could also be made from a spectrophotometric study of the reaction³.

The structure of compound *IIIa* was confirmed by its preparation from 5,6-dioxo-5,6-dihydrobenzo[*a*]phenazine and phosphorus pentachloride in a mixture of benzene and xylene. In this reaction the isomeric 5,5-dichloro-6-oxo-5,6-dihydrobenzo[*a*]phenazine, described already in literature⁴, could also be formed. On comparison with an authentic sample we were able to prove its content, 1.5%, in the product chromatographically. The reaction mixture displayed thermochromy: in the cold it is blue-violet, on heating it turns orange. A similar effect was also described for the products of photoaddition of aromatic aldehydes to 5,6-dioxo-5,6-dihydrobenzo[*a*]phenazine, and it was explained by lactam-lactim tautomerism⁵. Compound *IIIa* was also obtained by condensation of 1,2-phenylenediamine with 2,2-dihydroxy-3,3-dichloro-1,4-dioxo-1,2,3,4-tetrahydronaphthalene. This compound was prepared by Zincke and Gerland⁶ on reaction of 2-hydroxy-3-chloro-1,4-naphthoquinone with chlorine in acetic acid. We have obtained it under the effect of sulfuryl chloride on 2-hydroxy-1,4-naphthoquinone. In the reaction 3,3-dichloro-1,2,4-trioxo-1,2,3,4-

-tetrahydronaphthalene is probably formed first, which is then hydrated during recrystallization. Sulfuryl chloride is also a good chlorinating agent for many heterocycles⁷. Compounds *I* and *IIa* also could be converted smoothly to *IIIa* with it. In several informatory experiments we could observe the formation of *IIIa* on reaction of 5,6-dioxo-5,6-dihydrobenzo[*a*]phenazine with thionyl chloride or sulfuryl chloride (in the case of sulfuryl chloride in a small amount only), further on reaction of *I* with thionyl chloride or phosphorus pentachloride, and on reaction of 6-chloro-5-hydroxybenzo[*a*]phenazine (*IIa*) with phosphorus pentachloride. We limited ourselves to the chromatographic proof of compound *IIIa* in the poorly separable mixture, and these results are not further treated in the experimental part. The last of the mentioned experiments is similar in its experimental conditions to the preparation of 5,6-dichlorobenzo[*a*]phenazine from *IIa* under the effect of phosphorus pentachloride in phosphorus oxychloride, described by Van Allan and Reynolds⁸. As no mention is made in the mentioned paper of the formation of compound *IIIa*, we investigated this reaction in greater detail. Using column chromatography we found that in addition to 5,6-dichlorobenzo[*a*]phenazine at least the same amount of compound *IIIa* is also formed.

During the preparative halogenation of *I* the low solubility of this compound in ethanol is of decisive importance. Dihalogeno derivatives *IIIa* and *IIIb* can be obtained in pure state, but monohalogeno derivatives *IIa* and *IIb* only in admixture



with *IIIa* or *IIIb*, respectively, so that a chromatographic separation is indispensable. Substance *IIIa* can be reduced to *IIa* with stannous chloride and hydrochloric acid in acetic acid. Reduction of *IIIb* could be carried out in the same manner, but it is accompanied by debromination of *IIb* to *I*, so that a reduction with phenylhydrazine in chloroform is more advantageous. Debromination of *IIb* takes partly place already on longer heating in ethanol or acetic acid, but especially easily in the presence of mineral acids. The method of debromination of *IIb* with a mixture of phenol and conc. sulfuric acid, mentioned in literature⁹, is quantitative.

EXPERIMENTAL

The melting points were determined on a Boetius block under a microscope and they are corrected. Unless stated otherwise the samples for analysis were dried at 110°C/1 Torr for one hour, over phosphorus pentoxide. For chromatography on loose layers silica gel L 40/100 Lachema was used. For column chromatography silica gel L 100/160 Lachema was purified on heating in a mixture of sulfuric acid and chromic acid, washing with water and activation at 150°C for 20 hours. During the recrystallization of compound *IIIa* approximately 0.5 ml of a solution of chlorine in acetic acid (8 g per 100 ml) was added. The IR spectra were measured in KBr on a Zeiss UR-20 spectrophotometer and the UV and visible light spectra on a Zeiss instrument Specord UV VIS in 96% ethanol and $1 \cdot 10^{-5}$ M concentration.

Chlorination of 5-Hydroxybenzo[a]phenazine (*I*)

a) Chlorine gas was introduced at 50°C under stirring into a solution of 200 mg of *I* in 200 ml of ethanol until the orange colour turned to red-violet. The mixture was poured into 400 ml of water, the precipitate was filtered off under suction, washed with a small amount of ethanol and dried at 80°C. Yield 170 mg. Fifty mg of this substance gave on chromatography on a 35×5 cm column with a mixture of benzene and acetone (10 : 1) 35 mg of pure chloro derivative *IIa* (after crystallization from ethanol-benzene 2 : 1). A small amount of dichloro derivative *IIIa* has not been isolated. The same is true for the weak zone of the unreacted compound *I*. Compound *IIa* melts at 267–270°C under decomposition. Literature either does not give the melting point², or it gives 268°C under decomposition⁸. The compound is identical with an authentic sample of *IIa* prepared from 2,3-dichloro-1,4-naphthoquinone², as shown by thin layer chromatography in benzene-acetone 14 : 6 (R_F 0.52).

b) Chlorine gas was introduced into a suspension of 1.00 g of compound *I* in 500 ml of ethanol at 50°C until decolorized. On cooling 700 mg of a yellow substance precipitated, and on dilution of the mother liquors with 500 ml of water another 350 mg were obtained. The sample for analysis was recrystallized from acetic acid under addition of chlorine. The substance melts under decomposition, within the 225–240°C range. UV and visible spectrum λ_{\max} (log ϵ): 207 nm (4.61), 235 nm (4.49), 244 nm (4.50), 276 nm (4.50), 332 nm (4.26). Infrared spectrum: 1704 (C=O), 1593 (C=C_{arom.}), 760 cm^{-1} (*o*-substituted benzene ring). For $\text{C}_{16}\text{H}_8\text{Cl}_2\text{N}_2\text{O}$ (315.2) calculated: 60.97% C, 2.56% H, 22.50% Cl, 8.89% N; found: 60.99% C, 2.46% H, 22.75% Cl, 8.76% N.

Bromination of 5-Hydroxybenzo[a]phenazine (*I*)

a) Bromine was added dropwise and under stirring at 50°C to a solution of 200 mg of compound *I* in 200 ml of ethanol until the orange colour turned to red-violet. The same working up procedure

as in the case of chlorination *a*) gave 230 mg of crude bromo derivative *IIB*. From 50 mg of this product 32 mg of pure material were obtained after chromatography and recrystallization. It was identical with an authentic sample according to thin-layer chromatography in benzene-acetone 14 : 6 (R_F 0.57). The substance decomposes from about 220°C up, without previous melting, and affords a yellow-brown sublimate which does not melt up to 350°C (literature⁹ gives 230°C as decomposition point).

b) Bromine was added dropwise at 50°C to a suspension of 1.00 g of compound *I* in 500 ml of ethanol, until the solution almost completely decolorized. Application of the same working up procedure as in the case of chlorination *b*) gave totally 1.10 g of orange dibromo derivative *IIIB*. A sample for analysis was recrystallized from acetic acid under addition of bromine. On heating the substance begins to darken from 160°C and it decomposes at about 200°C without previous melting. UV and visible spectrum, λ_{\max} (log ϵ): 207 nm (4.64), 238 nm (4.54), 246 nm (4.56), 276 nm (4.49), 328 nm (4.26). Infrared spectrum: 1695 (C=O), 1594 (C=C_{arom.}), 765 cm⁻¹ (*o*-substituted benzene ring). For C₁₆H₈Br₂N₂O (429.6) calculated: 47.56% C, 1.95% H, 39.55% Br, 6.93% N; found: 47.65% C, 2.00% H, 39.85% Br, 6.81% N.

6-Bromo-6-chloro-5-oxo-5,6-dihydrobenzo[*a*]phenazine (*IIIc*)

The procedure was similar to that applied in the bromination of *I*. From 1.00 g of substance *IIa* 1.05 g of a yellow product was obtained. A sample for analysis was crystallized from acetic acid under addition of bromine. From 160°C the substance darkened and melted under decomposition at about 200°C. UV and visible spectrum, λ_{\max} (log ϵ): 207 nm (4.60), 236 nm (4.51), 245 nm (4.49), 280 nm (4.46), 325 nm (4.25). Infrared spectrum: 1703 (C=O), 1593 (C=C_{arom.}), 759 cm⁻¹ (*o*-substituted benzene ring). For C₁₆H₈BrClN₂O (359.6) calculated: 53.43% C, 2.24% H, 7.79% N; found: 53.31% C, 2.12% H, 7.91% N.

Effect of PCl₅ on 5,6-Dioxo-5,6-dihydrobenzo[*a*]phenazine

Dioxo compound (300 mg), PCl₅ (3.20 g) and 40 ml of a benzene-xylene mixture 3 : 1 were refluxed for 5 minutes, then cooled (the colour turns on cooling from orange to blue-violet) and poured into 70 ml of icy water. After 5 minutes' stirring the unreacted starting material (20 mg) was filtered off on a fritted glass filter, the layers of the filtrate were separated and the organic layer washed twice with 70 ml of water, dried over CaCl₂ and evaporated in a vacuum (25 Torr) on a water bath. The residue was dissolved in 100 ml of benzene and chromatographed on a silica gel column (5 × 4 cm) in order to adsorb a further fraction of the unreacted dioxo compound and a small amount of 6-chloro-5-hydroxybenzo[*a*]phenazine (*IIa*). The volume of the eluate was 350 ml. Benzene was evaporated under reduced pressure, the residue triturated with 5 ml of light petroleum, the solution (suspension) was filtered under suction and the residue crystallized from 90% (v/v) acetic acid in the presence of chlorine. Yield 200 mg (55%) of a yellowish substance which according to chromatographic data and IR spectrum was identical with compound *IIIa* obtained on chlorination of 5-hydroxybenzo[*a*]phenazine (*I*). If working at elevated temperature (in xylene) and for a longer reaction time the pure product may be obtained only after chromatography on a long silica gel column. According to chromatographic comparison with authentic samples neither 5,6-dichlorobenzo[*a*]phenazine² nor 5-chloro-6-hydroxybenzo[*a*]phenazine⁴ is present among the by-products.

In the crude reaction product after vacuum evaporation of the organic layer (dried over CaCl₂) it was possible to prove also 5,5-dichloro-6-oxo-5,6-dihydrobenzo[*a*]phenazine⁴ (1.5%) by thin-layer chromatography in benzene, using an authentic sample for comparison. The authentic

sample was prepared by condensation of 2,2,3,3-tetrahydroxy-4,4-dichloro-1-oxo-1,2,3,4-tetrahydronaphthalene with 1,2-phenylenediamine. Detection was carried out by short exposure of the chromatogram to ammonia vapours and then to sulfur dioxide gas. Substance *IIIa* after reduction to *Ila* appeared as a strongly red spot (R_F 0.80), and the originally very weak yellow spot of the isomer (R_F 0.30) deepened its hue (reduction to 5-chloro-6-hydroxybenzo[*a*]phenazine). On subsequent exposure to hydrogen chloride gas the yellow spot of R_F 0.30 turned brown-yellow.

2,2-Dihydroxy-3,3-dichloro-1,4-dioxo-1,2,3,4-tetrahydronaphthalene

a) A mixture of 2.0 g of 2-hydroxy-1,4-naphthoquinone, 5.0 ml of sulfuryl chloride and 30 ml of glacial acetic acid was heated until dissolution, evaporated *in vacuo* on a water bath (25 Torr) and then again three times with 50 ml portions of benzene. The brownish syrup was refluxed for 5 minutes with a mixture of 120 ml of conc. hydrochloric acid and 10 ml of conc. nitric acid. On filtering 200 mg of a substance remained on the filter. It was not further investigated. After cooling of the filtrate 1.85 g of product precipitated, which was washed with a small amount of water and dried at room temperature. A sample for analysis was crystallized from the same mixture of concentrated acids and dried for one day at room temperature. The substance melted under liberation of water within the 80–108°C range. According to analysis it is an 0.5 hydrate. For $C_{10}H_6Cl_2O_4 \cdot 0.5 H_2O$ (270.1) calculated: 44.46% C, 2.61% H; found: 44.42% C, 2.50% H.

b) From 500 mg of 2-hydroxy-3-chloro-1,4-naphthoquinone on chlorination⁶ in a mixture of 10 ml of acetic acid and 0.5 ml of water 330 mg of product were obtained by vacuum evaporation of the reaction mixture and working up of the syrup as under a). A sample for analysis (needles) melted under loss of water in the 80–108°C range. The anhydrous product has m.p. 105°C according to literature⁶. For $C_{10}H_6Cl_2O_4 \cdot 0.5 H_2O$ found 44.41% C, 2.47% H. For the determination of water the substance was dried over P_4O_{10} at 60°C. After 1.5 hours of drying the weight loss corresponded to the loss of crystal water: 3.32%; calculated 3.36% H_2O . The sample melted within the 100–106°C range, with previous sintering at 95°C; on further drying it further lost weight. Even when the temperature was increased to 110°C dehydration took place only slowly, and the sample turned yellow. After a weight-loss corresponding to complete dehydration the sample continued to lose weight. The substance prepared according to procedure a) behaved on drying in the same manner.

The substances from both procedures were identical on thin-layer chromatography and according to their IR spectra. Chromatography was carried out in benzene–acetone 17:3 and the still wet chromatogram was sprayed with an alkalinized solution of sodium dithionate and heated at 100°C. The substances appeared as orange spots of R_F 0.36–0.40. IR spectrum (1800 to 700 cm^{-1} region): 1748 sh, 1730 s, 1712 s, 1640 b, 1590 s, 1574 sh, 1467 w, 1400 sh, 1385 sh, 1365 sh, 1326 m, 1290 m, 1260 s, 1227 m, 1171 s, 1147 w, 1096 m, 1057 m, 1025 w, 956 m, 905 w, 871 m, 854 m, 826 s, 791 m, 774 w, 754 m, 720 s, 705 w cm^{-1} .

Reaction with 1,2-phenylenediamine: A solution of 0.78 g of the product from procedure a) in 4 ml of acetic acid was mixed with a solution of 0.35 g of 1,2-phenylenediamine in 2 ml of acetic acid and the precipitate formed was filtered off under suction and washed with water. It was crystallized from 90% (v/v) acetic acid under addition of chlorine. Yield 0.82 g of a product identical according to IR spectrum and chromatography with compound *IIIa*.

Chlorination of Compounds *I* and *Ila* with Sulfuryl Chloride

a) 500 mg of compound *I* were dissolved in a boiling mixture of 35 ml of acetic acid and 10 ml of sulfuryl chloride. After vacuum evaporation on a water bath (at 25 Torr) the residue was

crystallized from 90% (v/v) acetic acid containing chlorine. Yield 580 mg of a substance which was identical with *IIIa*, chromatographically and spectrally (IR).

b) Similarly as under a), from 300 mg of compound *IIa*, 40 ml of acetic acid and 5 ml of sulfuryl chloride, 290 mg of a substance were obtained which was identical with substance *IIIa* according to IR spectra and chromatographic data.

Reaction of 5-Hydroxy-6-chlorobenzo[*a*]phenazine (*IIa*) with PCl_5 in Phosphorus Oxychloride

With the exception of the separation of the reaction product the procedure described in the literature⁸ was reproduced. A suspension of 950 mg of compound *IIa* in 3.0 ml of phosphorus oxychloride was heated at 80°C and additioned with 900 mg of PCl_5 . After 2 hours' refluxing the mixture was cooled, the precipitate filtered off under suction on a fritted glass filter, then digested with totally 100 ml of acetonitrile. 350 mg of a light-yellow substance remained undissolved. On dilution of the filtrate with 400 ml of water 500 mg of a reddish coloured fraction precipitated. The amount of both fractions is dependent on the volume of acetonitrile used. The volume is not indicated in the original paper.

Thin-layer chromatography (using samples for comparison) indicated in both fractions the presence of 5,6-dichlorobenzo[*a*]phenazine², dichloro derivative *IIIa*, and in the reddish fraction also the unreacted *IIa*. Both fractions were combined and chromatographed in benzene on a 5 × 4 cm column. After washing out of the yellowish zone (a mixture of 5,6-dichloro derivative and *IIIa*) the red zone of compound *IIa* was eluted from the column with ethanol. Yield 550 mg of the mixture and 150 mg of *IIa*. 200 mg of the mixture were chromatographed on a 15 × 4 cm column with tetrachloromethane affording 95 mg of dichloro derivative *IIIa* and 90 mg of 5,6-dichlorobenzo[*a*]phenazine, m.p. 204–205°C (lit.^{2,8} gives m.p. 202°C and 201°C, respectively). In a repeated experiment a twice distilled phosphorus oxychloride was employed, and 500 mg of compound *IIa* gave 300 mg of one fraction (after digestion with 20 ml of acetonitrile), and 150 mg of another fraction (after dilution with water). Spectrophotometry indicated that the first fraction represents a mixture of dichloro derivative *IIIa* and 5,6-dichlorobenzo[*a*]phenazine in a 5 : 1 ratio.

Reduction of Dihalo Derivatives *IIIa* and *IIIb*

a) A solution of 120 mg of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ in 2 ml of conc. hydrochloric acid was added to a solution of 100 mg of compound *IIIa* in 20 ml of acetic acid at 40°C and the mixture was diluted with 100 ml of water. The precipitate was filtered off under suction, washed with water and dried at 110°C. Yield 80 mg of product which was crystallized from ethanol–benzene 2 : 1, affording 60 mg of chromatographically pure *IIa*.

b) A solution of 1.0 g of compound *IIIb* in 100 ml of chloroform was heated to 40°C and 4 ml of phenylhydrazine were added to it dropwise over 4 minutes at the given temperature. After half-an-hour's standing the precipitate was filtered off under suction, washed with a small amount of ethanol and then ether. Yield 0.73 g of product (dried at 110°C). After crystallization from ethanol–benzene 0.55 g of chromatographically pure substance *IIB* were obtained.

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