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DIRECT AMINATION OF 2-METHYL-7-CHLOROCERAMIDONINE WITH AMMONIA OR SODAMIDE

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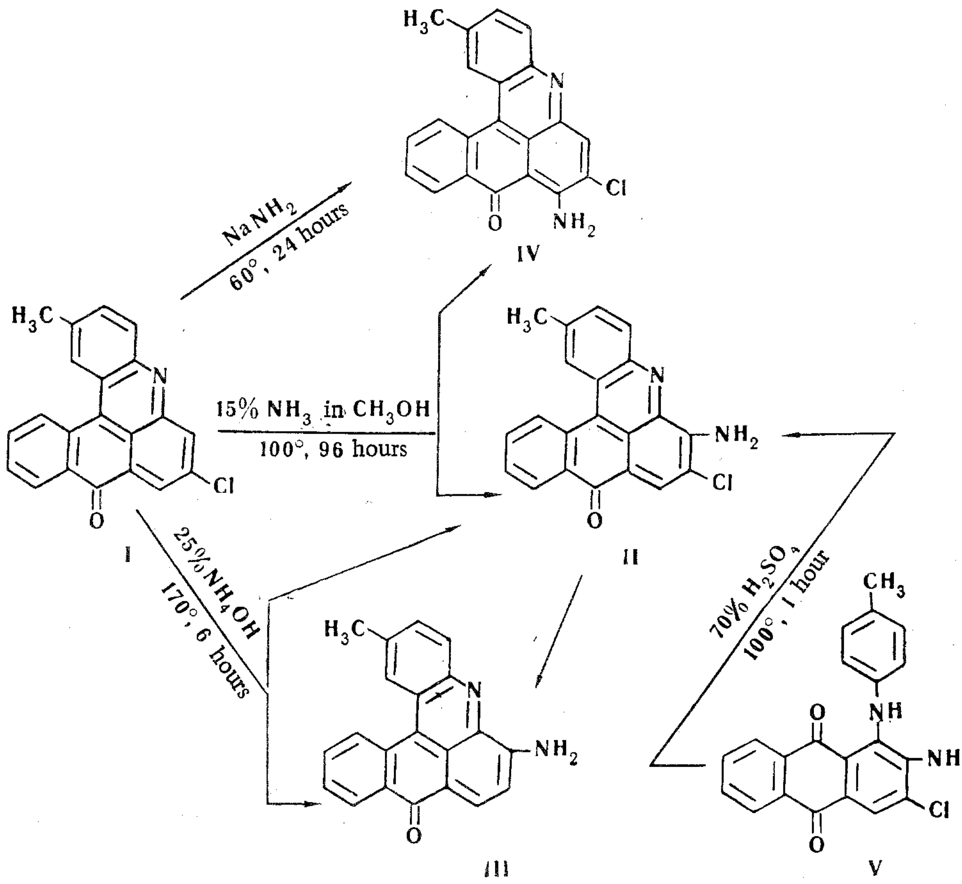
Treatment of 2-methyl-7-chloroceramidonine with aqueous ammonia gives 2-methyl-6-amino-7-chloroceramidonine, while treatment with sodamide gives 2-methyl-7-chloro-8-aminoceramidonine.

Continuing research on the direct amination of ceramidonines [1], we have investigated the reaction of 2-methyl-7-chloroceramidonine (I) with ammonia and sodamide. I was aminated by 25% aqueous ammonia at 170° C in the presence of copper acetate. Six hours' reaction gave 2-methyl-6-amino-7-chloroceramidonine (II) (29%), and 2-methyl-6-aminoceramidonine (III) (11%). Evidently direct amination of I is accompanied by dehalogenation of the resultant 2-methyl-6-amino-7-chloroceramidonine. Thus increasing the time of reaction of I with ammonia to 8 hr, increased the content of dehalogenation product III over twofold. It is known [2, 3] that some halogenated anthraquinones in reactions involving exchange between halogen and groups in aromatic and aliphatic amines, give dehalogenation products along with the corresponding amino derivatives. Nothing of the kind is observed when ammonia is allowed to act on halogenated anthraquinones.



Amination of I by treatment with methanolic ammonia gives both 2-methyl-6-amino-7-chloroceramidonine (12%), and 2-methyl-7-chloro-8-aminoceramidonine (IV) (2%). The action of sodamide on I in dimethylaniline gives only IV (15%) and its hydrolysis product, 2-methyl-7-chloro-8-hydroxyceramidonine (19%). Thus treatment of 2-methyl-7-chloroceramidonine with ammonia leads to an amino group entering at position 6, treatment with methanolic ammonia leads to its entering at positions 6 and 8, while treatment with sodamide results in its entering at position 8 only.

It is of interest to note that, as in the runs with aqueous ammonia, treatment of ceramidonines with aromatic amines gives mainly 6-amino-ceramidonines, while treatment with aliphatic amines gives 8-aminoceramidonines [1]. Apparently increased nucleophilicity of the reagent in amination of ceramidonines changes the orientation of the entering amino group from position 6 to position 8.

Experimental

Reaction with 2-methyl-7-chloroceramidonine (I). a) With aqueous ammonia. A mixture of 0.5 g (1.5 mmole) I, 0.25 g $Cu(OAc)_2$, and 10 ml 25% NH_4OH was heated for 6 hr at 170° C in a steel bomb with a glass liner. The precipitate was filtered off, washed with water, and dried. It was chromatographed on Al_2O_3, and two fractions obtained. The first gave 0.15 g (29%) 2-methyl-6-amino-7-chloroceramidonine (II), reddish-violet needles, mp 233°–235° C (ex MeOH). Undepressed mixed mp with authentic II. The IR spectra of the two materials were identical. The second fraction gave 0.05 g (11%) 2-methyl-6-aminoceramidonine (III), as violet needles, mp 268°–270° C (ex chlorobenzene). The literature gives [4] mp 258°–260° C. Absorption spectrum in EtOH: λ_{max}, mμ (lg ε): 232 (4.51), 292 (4.71), 382 (3.91), 536 (4.16), 556 (4.16). Found: C 81.02, 80.55; H 4.52, 4.54; N 8.76, 8.70%. Calculated for $C_{21}H_{14}N_2O$: C 81.27; H 4.55; N 9.02%. When the reaction time was increased to 8 hr, 0.10 g (19%) II and 0.11 g (24%) III were obtained.

b) With methanolic ammonia. 0.5 g (1.5 mmole) I and 30 ml 15% methanolic NH_3 were heated together in a sealed tube on a water bath for 96 hr. Chromatography on Al_2O_3 (benzene) gave 0.06 g (12%) II, and about 0.01 g (2%) 2-methyl-7-chloro-8-aminoceramidonine (IV), orange needles, mp 228°–230° C, undepressed mixed mp with IV [5], IR spectra of the two materials identical.

c) With sodamide. A suspension of 0.15 g (4 mmole) $NaNH_2$ (prepared as described in [6]) in liquid ammonia was stirred, and 30 ml dry dimethylaniline added carefully. After the dimethylaniline had melted, 1 g (3 mmole) I and 30 ml dimethylaniline were added. The mixture was stirred for 24 hr at 60° C. Then the products were poured into 10% HCl, the precipitate formed filtered off, washed with water, and dried. The solid was then dissolved in $CHCl_3$, and chromatographed on paper.* The top reddish-orange zone was separated, and extracted with MeOH, to give 0.15 g (15%) IV, mp 228°–232° C. The yellow zone was extracted with benzene to give 0.2 g (19%) yellowish-brown material in the form of needles, mp 252°–260° C (ex benzene). Undepressed mixed mp with 2-methyl-7-chloro-8-hydroxyceramidonine [5]. The IR spectra were identical too.

Retro-synthesis of 2-methyl-6-amino-7-chloroceramidonine (II). A mixture of 30 g (0.09 mole) 1-Br-2-NH_2-3-Cl-anthraquinone, 150 g (0.14 mole) p-toluidine, 15 g (0.15 mole) fused KOAc, and 1.2 g $Cu(OAc)_2$ was heated for 8 hr at 160° C. The reaction products were cooled to 100° C, poured into HCl (1:1), the precipitate filtered off, washed with water, and dried, to give 32 g (97%) 1-(p-toluidino)-2-amino-3-chloroanthraquinone (V), mp 153°–160° C. After purifying on an Al_2O_3 column ($CHCl_3$), it had mp 169° C (ex chlorobenzene). Absorption spectrum in EtOH, λ_{max}, mμ (lg ε): 254 (4.46), 284 (4.54), 516 (3.86). Found: Cl 9.98, 9.98; N 7.61, 7.41%. Calculated for $C_{21}H_{15}ClN_2O_2$: Cl 9.80; N 7.72%.

9.5 g (0.026 mole) V in 114 ml 70% H_2SO_4 was stirred for 1 hr at 100° C. Yield 8.79 g (96%) 2-Me-6-NH_2-7-Cl-ceramidonine, mp 224°–230° C, needles, mp 235° C (ex MeOH). Absorption spectrum in EtOH, λ_{max}, mμ, (lg ε); 228 (4.46), 237 (4.45), 291 (4.73), 395 (3.76), 528–542 (4.11). Found: Cl 10.28, 9.90; N 8.16, 8.02%. Calculated for $C_{21}H_{13}ClN_2O$: Cl 10.29; N 8.13%.

The absorption spectra (200–700 mμ) were observed with SF-4 and SF-5 spectrophotometers, in 95% EtOH, concentration 0.5×10^{-4} mole/l, layer thickness 0.5 and 2 cm. IR spectra (3600–2600 cm^{-1} and 1800–400 cm^{-1}) were observed with a UR-10 spectrophotometer, NaCl prism, tabletted with KBr using a concentration of 4 mg compound per 800 mg KBr.

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*The B grade chromatography paper, made by the Leningrad No. 2 Factory, size 240 × 120, was used for the preparative separation. It was impregnated with 10% α-bromonaphthalene in MeOH. The separation was carried out in a chromatography cell, charged with 80% AcOH saturated with α-bromonaphthalene.