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STUDIES IN THE ALLO- AND ISOALLOXAZINE SERIES. XII*. NEW SYNTHESIS OF 7-CHLOROALLOXAZINE

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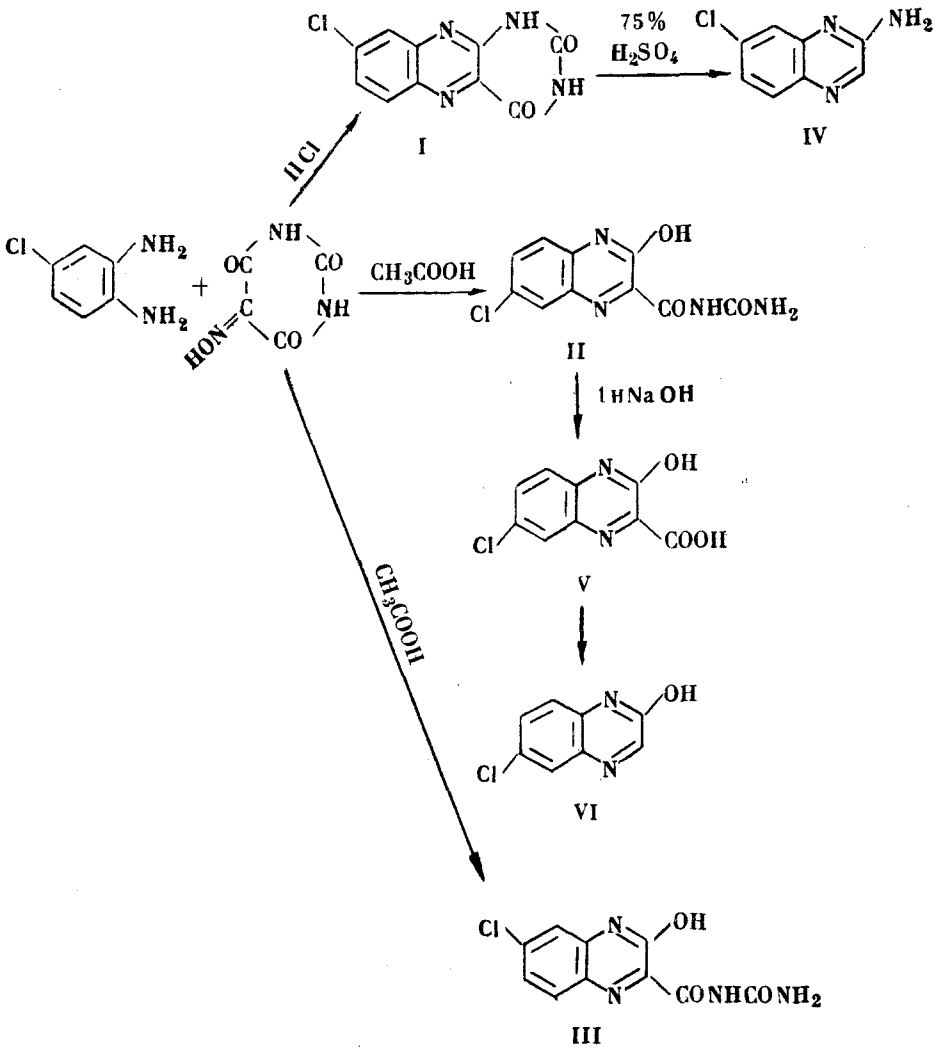
A new synthesis of 7-chloroalloxazine is effected by condensing 4-chloro-o-phenylenediamine with violuric acid in 3 N HCl. The same starting materials when condensed together in 50% acetic acid give 6-chloro-2-hydroxyquinoxaline-3-carboxylic acid ureide.

7-Chloroalloxazine, which has diuretic properties [2], was first synthesized by condensing 4-chloro-o-phenylenediamine with alloxan [3, 4].

It was of interest to extend to 7-chloroalloxazine (I) a method of synthesizing allo- and isoalloxazines by condensing aromatic o-diamines with violuric acid [5]. The reaction is unambiguous and, depending on the acidity of the medium, yields the alloxazine or hydroxyquinoxaline carboxylic acid ureide.

A 60% yield of I is obtained by condensing 4-chloro-o-phenylene-diamine with violuric acid in a strongly acid medium (3 N hydrochloric acid). However, condensation in dilute acetic acid gives, along with 7-chloroalloxazine (yield 10%), 6-chloro-2-hydroxyquinoxaline-3-carboxylic acid II (yield 30%), and not the corresponding 7-chloro acid (III). Evidently this can be explained by a change in nucleophilicity of two nitrogen atoms of the amino groups of 4-chloro-o-phenylenediamine in condensation with violuric acid, depending on the acidity of the medium.

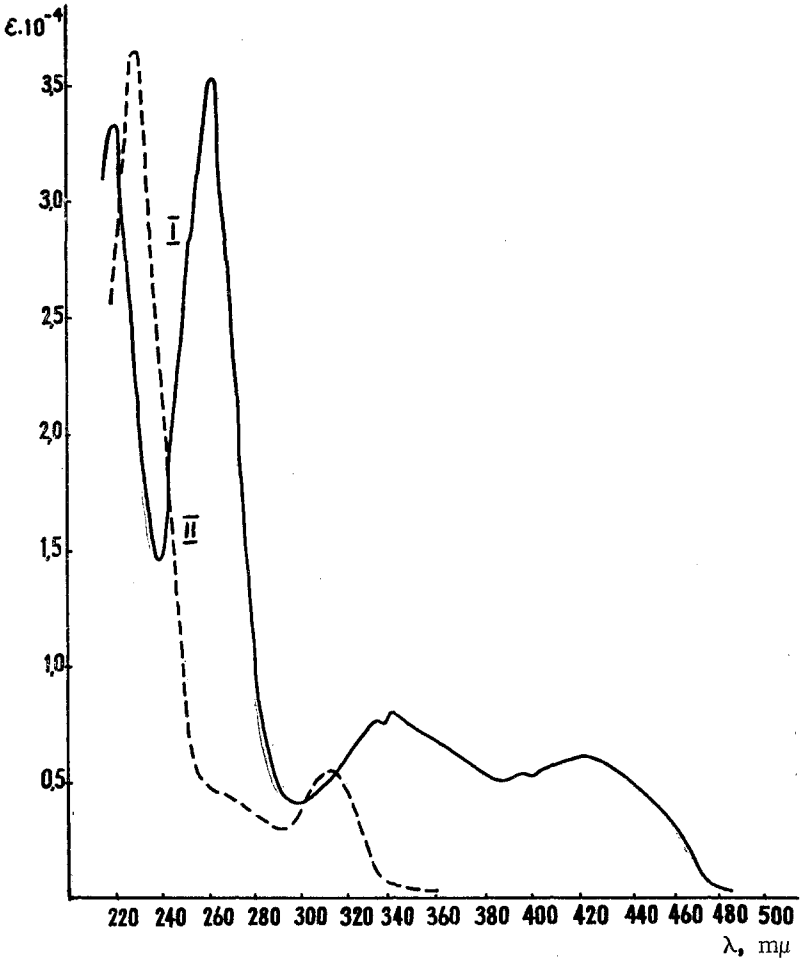


*For Part XI see [1].

The structure of I is demonstrated by breaking it down into 7-chloro-2-aminoalloxazine (IV) on heating in sulfuric acid and that of 6-chloro-2-hydroxyquinoxaline-3-carboxylic acid ureide (II) by breaking it down into 6-chloro-2-hydroxyquinoxaline-3-carboxylic acid (V) on heating with 1 N NaOH with subsequent decarboxylation to 6-chloro-2-hydroxyquinoxaline (VI) and comparison of the properties of compounds IV and VI with the data of [4, 6]. The absorption spectra of I and II are shown in the figure.

EXPERIMENTAL

7-Chloroalloxazine (I). A mixture of 1.57 g violuric acid and 1.64 g 4-chloro-o-phenylenediamine is boiled for 4 hr in 40 ml 3 N hydrochloric acid. The reaction mixture is cooled to room temperature and 1.5 g (60%) yellow precipitate filtered off and washed with boiling water and alcohol (2 × 20 ml). The lemon-yellow needles (from glacial acetic acid) do not melt below 360°. According to the literature [3] m.p. > 360°. The precipitate is chromatographed on M-grade paper (ascending front) using n-butanol-pyridine-water (6:4:3). The spot has R_f = 0.80 (pale blue fluorescence); according to the literature, [4] R_f = 0.81. The absorption spectrum in 0.1 N sodium hydroxide is: λ_{max} mμ 220 (ε 3.32×10^4), 262 (ε 3.52×10^4), 335 (ε 0.65×10^4), 340 (ε 0.79×10^4), 398 (ε 0.53×10^4), 425 (ε 0.60×10^4), in agreement with



Absorption spectra (in 0.1 N NaOH)
I, 7-Chloroalloxazine; II, 6-Chloro-2-hydroxyquinoxaline-3-carboxylic acid ureide

the data in the literature [4]. The absorption spectrum in alcohol is: λ_{max} mμ 219 (ε 3.48×10^4), 245 (ε 2.84×10^4), 333 (ε 0.64×10^4), 365 (ε 0.69×10^4), 374 (ε 0.78×10^4). Found: C 48.04, 48.27; H 2.39, 2.26; Cl 14.04, 13.95%. Calculated for $C_{10}H_5ClN_4O_2$: C 48.31; H 2.03; Cl 14.26%.

6-Chloro-2-hydroxyquinoxaline-3-carboxylic acid ureide (II). A mixture of 1.57 g violuric acid, 1.64 g 4-chloro-o-phenylenediamine and 30 ml 50% acetic acid is refluxed for 5 hr. 0.80 g (30.0%) ureide II is filtered off from the cooled reaction mixture; it contains I as impurity (~10%). Light yellow needles (from 50% acetic acid) m.p. 248-250° (decomp.). The literature [4] gives m.p. 249-251° (decomp.). In n-butanol-pyridine-water (6:4:3) R_f = 0.67 (yellowish-green fluorescence). The literature [4] gives R_f = 0.65. Absorption spectrum in 0.1 N sodium hydroxide: λ_{max} 230 mμ (ε 3.66×10^4) and 315 mμ (ε 0.54×10^4), agreeing with the literature data [4]. Absorption spectrum in alcohol: λ_{max} mμ 225 (ε 3.69×10^4), 307 (ε 0.82×10^4), 368 (ε 0.19×10^4). Found: C 44.98, 44.97; H 3.00, 3.08; Cl 13.81, 13.70%; calculated for $C_{10}H_7ClN_4O_3$: C 45.04; H 2.65; Cl 13.30%.

To estimate the 7-chloroalloxazine impurity a sample of ureide was chromatographed using the same system, with

blanks. The chromatogram spots were eluted with alcohol and analyzed quantitatively by fluorometry.

7-Chloro-2-aminoquinoxaline (IV). 3.0 g I is heated at 200-205° for 1 hr in 20 ml 75% sulfuric acid and, after cooling, the reaction mixture is poured onto crushed ice. The brownish-green precipitate is filtered off, 1.4 g (unchanged 7-chloroalloxazine). 10% sodium hydroxide solution is added to the mother liquor to bring it to pH 10, and the precipitate, 0.4 g (20%), is filtered off and purified by vacuum sublimation at 150-160° (10 mm). Lemon-yellow crystals melt at 194-196°. The literature gives m.p. 185-190° [6], 199-200° [4]. Found: C 53.43, 53.36; H 3.40, 3.65; Cl 20.04, 20.13%; calculated for $C_8H_6ClN_3$: C 53.50; H 3.37; Cl 19.74%.

6-Chloro-2-hydroxyquinoxaline (VI). 1.0 g of the ureide II and 20 ml 1 N NaOH are refluxed together for 3 hr. The reaction mixture is then acidified with hydrochloric acid (until acid to Congo red), and 0.6 g acid is filtered off. The filtrate is boiled with 5 ml nitrobenzene for 10-15 min. After cooling, 0.2 g precipitate are separated off and purified by vacuum sublimation at 160-170° (10 mm). Lemon-yellow crystals melt at 301-302°. According to the literature [4] m.p. 300-303°. Found: C 53.38, 53.42; H 2.85, 3.01; Cl 19.21, 19.52%. Calculated for $C_8H_5ClN_2O$: C 53.20; H 2.79; Cl 19.52%.

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