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Synthesis Of Dehydro- And Oxohomoproaporphine Alkaloids

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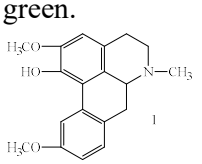
In the last decade, from a large number of plants - producers of aporphine alkaloids and analogues, their dehydro derivatives containing double bonds and hydroxy groups in various positions have been isolated [1] and their quaternary bases were also synthesized.

Cava and others [2] iodine oxidation of non-phenolic aporphins converted them into 6a,7-dehydro and 7-oxoaporphins, while iodine oxidation of phenolic aporphins led to completely different compounds [3]. Thus, in the oxidation of isotebaine (1) with iodine, compound 2 was isolated in green.



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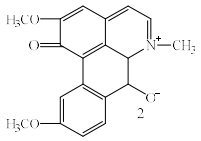
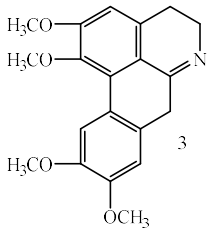


2

Previously, only two alkaloids of the dehydronoraporphin (6,6a-didehydronoraporphine) series were known in the literature - dehydronorglaucine (3) and dehydronorlauredin (4) [4].



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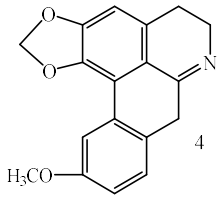

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In recent years, from plants of the family. Annonaceae isolated a number of 6,6a-dehydronoraporphins, but containing substituents in the C-7 position in the Oxidation with iodine in the presence of sodium acetate from Kesselringin gives regecoline in 86% yield. However, due to the low solubility in chloroform and the presence of sodium acetate, it can be isolated only by obtaining the acetyl derivative (8). Regecolin can be obtained from the latter after hydrolysis to 12-demethylregecolin (9) and its methanolysis reaction.

A small admixture of regelion in regecoline was also converted into regecoline by reduction with zinc dust [5].

Oxidation with iodine in the presence of sodium acetate from Kesselringin (6) gives regecoline in 86% yield. However, due to the low solubility in chloroform and the presence of sodium acetate, it can be isolated only by obtaining the acetyl derivative (8). Regecolin can be obtained from the latter after hydrolysis to 12-demethylregecolin (9) and its methanolysis reaction.

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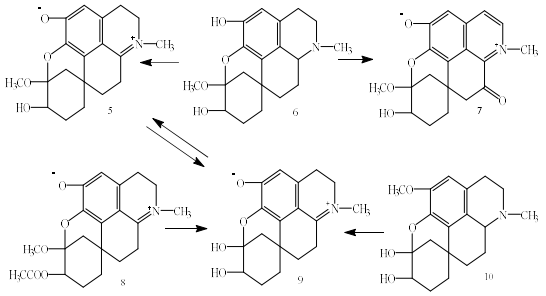
Synthesis of regecolin and regelinone

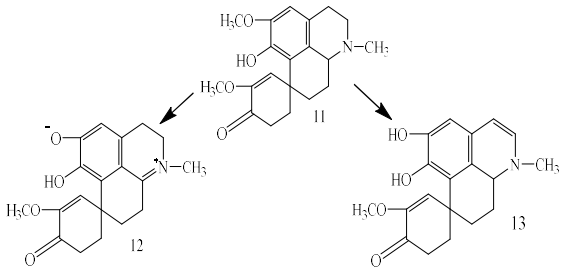


When oxidized with iodine, Kesselringin without the participation of anhydrous sodium acetate catalyst was able to quantitatively convert it into regecoline and directly obtain in crystalline form after distillation of the solvent.

Oxidation of regelamine (10) with iodine both in the presence of sodium acetate and without it leads to a mixture of substances, the main of which is 12-demethylregecolin (9) isolated and studied, a similar oxidation of luteidine (11) leads to isolation from the mixture two new compounds, which, according to the spectral data, have structures 12 and 13 [6].

It should be noted that the elimination of the methyl group from the C-2 position of the benzene ring during oxidation with iodine was also observed by some authors in aporphine alkaloids. It should be noted that the oxidation of both phenolic and non-phenolic homoproporphins with iodine gives quaternary dehydro derivatives with a double bond at 6.6a, while aporphins form 6a,7-dehydro derivatives [2].

The oxidation reaction of luteidine with iodine



In addition to oxidation with iodine, regecolin and regelinone were also obtained from Kesselringin by a photochemical reaction. By irradiating an aqueous solution of Kesselringin with sunlight after displacing air with nitrogen, regecoline was obtained. When air is displaced from the solution by oxygen and irradiated, Kesselringin forms a mixture of reaction products containing a significant amount of regelinone (7), Yield 26% [7].

Synthesized regecolin and regelinone both by the oxidation reaction of Kesselringin with iodine and by irradiation with sunlight were identified with their natural samples. The products of luteidine oxidation (12 and 13) could not be unambiguously identified.

Merobustine has the composition $C_{21}H_{25}O_5N$, m.p. 241-242 ° and / α / D^+ 76 °, In its UV spectrum there are absorption maxima at 260 and 290 nm, in the IR spectrum - absorption bands of hydroxyl groups. (3470-3420 cm^{-1}). The mass spectrum of the base shows ion peaks with m/z371 (M^+), 356 $(M-15)^+$, 354 $(M-17)^+$ (100%), 340 $(M-31)^+$. The PMR spectrum shows signals of two aromatic protons isolated from each other at 6.67 and 6.43 ppm (1HX2, cc, H-3 and H-9), three O-methyl groups at 3.85-3.83 ppm (9H) three-proton singlet of the N-methyl group (3H,s, 2.40 ppm).

Synthesis of dehydro derivatives of homoproporphin bases

Oxidation of Kesselringin with iodine (partial synthesis of regecolin, 5). a) 0.66 g of

Kesselringin was dissolved in 30 ml of dried and freshly distilled dioxane, and 0.65 g of freshly melted sodium acetate was added to the solution. Bring the solution to a boil for 4 hours. 0.33 g of iodine in 26 ml of dioxane was added dropwise until the reaction solution turned dark orange (excess iodine).

Thin-layer chromatography revealed that the reaction product, regecoline (Rf 0.39), contains impurities of kesselringin (Rf 0.90) and regelinone (Rf 0.52, chloroform-methanol-acetone-benzene-25% aqueous ammonia system 10:8 :6.5:3:5).

The solvent was distilled off and the remaining substance was dissolved in 85 ml of water, the aqueous solution was extracted with chloroform until the kesselringin was completely removed. 2 ml of acetic acid and 0.5 g of zinc dust were added to the aqueous solution and left with alternating shaking for 6 hours. at room temperature until complete recovery of the impurity of regelinone in regecolin. The solution was evaporated to dryness in a vacuum, the remaining substance was dissolved in 5 ml of freshly distilled acetic anhydride and 2-3 drops of concentrated sulfuric acid were added. After complete conversion of regecoline to 22-acetylrehecoline (8), the excess of the reagent was removed by adding methanol and evaporating. The residue was dissolved in water and the reaction product was extracted with chloroform.

The isolated acetylregecoline was identified by the Rf value (0.62) and spectral data with the previously obtained sample [8]. Yield 0.64 g (86%).

NMR spectrum ($CDCl_3$, ppm): 6.55 (1H,s, H-3), 4.96 (H-22), 3.44 (3H,s, ^{+}N-CH_3), 3, 30 (3N,s, al. OCH_3), 2.00 (3H,s, $COCH_3$).

b. A solution of 1 g of Kesselringin in 50 ml of dioxane was brought to a boil by heating on a sand bath, and a solution of 0.5 g of iodine in 40 ml of dioxane was added dropwise to the boiling solution. When the color of the reaction solution changed (darkened), 5 ml of iodine solution (0.06 g of iodine) remained in excess.

Chromatographic analysis showed that Kesselringin was quantitatively dehydrogenated to regecoline. The solvent was distilled off in vacuo and the remaining material was crystallized from acetone. Selected 0.92 g (92%) of the base with so pl. 311-312°.

Hydrolysis of II-acetylregecolin to 12-demethylregecolin (9).

0.30 g of acetylregecolin in 10 ml of 7% hydrochloric acid was heated at 100°C for two hours. The solution was evaporated in vacuum, the residue was dissolved in 3 ml of methanol and purified by passing through a small pad of alumina. 12-demethylregecolin was isolated, chromatographically identified with a genuine sample derived from regecolin.

Hydrolysis regecoline 12-demethylregecoline (9). A solution of 0.2 g of regecoline (Rf 0.41, system: chloroform-benzene-methanol-25% ammonia) and 5 ml of 5% hydrochloric acid is heated at 100°C. 12-demethylregecoline is extracted from the mixture of acetone and methanol by evaporation of the solvent in a vacuum, and the product of hydrolysis is 11-acetylregecoline, which is identified by Rf (0.31). ПМР-спектр (в C_2D_5OD, м.д.): 6,60 (1H,c, H-3), 3,60 (3H,c, ^{+}N-CH_3).

Regalamine oxidation with iodine. After dissolving 0.10 g of regelamine in 4.5 ml of dioxane, 0.10 g of freshly melted sodium acetate was added. Next, 0.08 g of iodine and 6.2 ml of dioxane were added to the boiling solution over 2 hours.

After distilling off the dioxane, the dry residue was taken up with acetone and a mixture of acetone and methanol (95:5). The reaction product on the chromatogram appeared as two spots, with Rf 0.19 and 0.31 (main substance), Regelamine has Rf 0.75. Part of the main substance was isolated by treating the mixture with acetone. NMR-spectrum (C_2D_5OD, ppm): 6,63 (1H,c, H-3), 3,56 (3H,c, ^{+}N-CH_3).

According to the value of Rf and the PMR spectrum, the reaction product corresponds to the structure of 12-demethylregecolin.

Oxidation of luteidine (11) by iodine. After dissolving 0.15 g of base in 8 ml of dioxane, 0.15 g of freshly melted sodium acetate was added. Next, 0.12 g of iodine in 6 ml of dioxane was added to the boiling solution over 2 hours.

Using different solubility of the reaction products in dioxane, acetone and a mixture of acetone and methanol and chromatography on alumina, it was possible to isolate 3 compounds with Rf 0.41; 0.47 (minor) and 0.64 (luteidine with Rf 0.52) according to system 4.

The NMR spectra of two compounds with Rf 0.41 and 0.64 (in C_2D_5OD) were studied;

Compound 12, Rf 0.41 (ppm): 6.50 (1H, s, H-3), 3.58 (3H, s, ^{+}N-CH_3) and 3.52 (3H, s, ol. OCH_3).

Compound 13, Rf 0.64 (ppm): 5.76; 5.83 and 5.88 (H-13, H-4, H-5), 3.55(3H, s, ol. OCH_3), 2.40 (3H,s, N-CH_3).

b. After dissolving 0.10 g of luteidine in 5 ml of dioxane with heating, slowly, dropwise, was added to the boiling solution on a sand bath over 2 hours. solution of 0.08 g of iodine in 6 ml of dioxane.

After the completion of the addition of the iodine solution, the reaction mixture continued to boil for another 30 min. The solution was cooled, the precipitate formed was separated, and dioxane was distilled off in a vacuum. Spent chromatographic analysis of the sediment and the residue from the mother liquor (system 4).

Sediment composition: compounds with Rf 0.32; 0.46 and 0.62.

The composition of the mother liquor: compounds with Rf 0.46 and 0.62.

It was not possible to separate the mixture into individual compounds

Photochemical reactions of Kesselringin

Dehydrogenation of kesselringin (6) to regecolin (5). After dissolving 1.0 g of Kesselringin in 10 ml of methanol in a quartz round bottom flask, the volume of the solution was brought up to 500 ml by adding chilled, freshly boiled and filtered distilled water. Next, gaseous nitrogen was passed through the solution for 15 minutes and the solution was irradiated with sunlight for 36 days in a stoppered form. The progress of the reaction was monitored by thin-layer chromatography on silica gel (chloroform-methanol-acetone-benzene-25% aqueous ammonia system, 10:8:6.5:3:5). After the completion of the reaction, the solution was extracted five times with chloroform to remove traces of unreacted Kesselringin. After distillation of water in vacuum to a small volume (50 ml), the solution was again extracted seven times with chloroform. The resulting extracts contain a mixture of Kesselringin and Regecolin. Then the aqueous solution was evaporated to dryness and the remaining substance was treated with acetone. A light orange crystalline substance was isolated, identified by the Rf value; melting point and spectral data with regecolin. Yield 0.76 g (76%)

Photooxidation of Kesselringin to Regelinone (7). To a solution of 1.0 g of Kesselringin in 10 ml of methanol was added 490 ml of freshly boiled and filtered distilled water, after which oxygen was passed through the solution for 15 min. The oxygen-saturated solution of Kesselringin was exposed to sunlight for 30 days, during which it turned from almost colorless to bright orange.

The isolation of the reaction product was carried out as described above.

Chromatographic analysis of the reaction product revealed regelinone (the main compound), rogecoline, kesselringin, and some unidentified minor compounds.

By chromatography on a column of alumina (20 g), eluting first with acetone, then with mixtures of acetone and methanol (99:1, 98:2, 97:3, 95:5, 90:10), 0.26 g was isolated from the last eluates an individual compound identified by regelinone by chromatographic mobility.

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