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SYNTHESIS OF REGECOLINE

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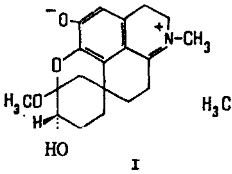
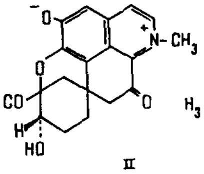
An improved synthesis of the quaternary homoproaporphine alkaloid regecoline from the main alkaloid of Colchicum kesselringii Rgl. – kesselringine – has been carried out by two methods: by photochemical conversion (yield 77%) and by iodine oxidation (yield 86%). It has been shown that the iodine oxidation of homoproaporphines of the kesselringine type leads to C_{6a}-dehydro derivatives.

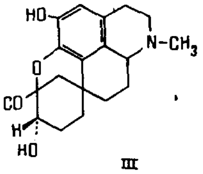
Regecoline (I), isolated from the epigeal parts of the plant Colchicum kesselringii Rgl. is the first representative of the quaternary dehydrohomoproaporphine alkaloids with a spirocyclohexane ring [1]. The dehydrohomoproaporphine bases [1, 2] belong to the minor alkaloids of this plant, and their chemical and pharmacological properties have been little investigated. We have studied possible routes for their synthesis from structurally close compounds. In [1], we described the passage to regecoline from regelinone (I) – a 7-oxotetrahydrohomoproaporphine, and also a minor, alkaloid. Its synthesis from the main alkaloid of the plant – kesselringine (III) [3, 4] – by oxidation with iodine or with hydrogen peroxide led to a mixture of regecoline and unknown substances.



I



II



III

In the present communication we consider an improved synthesis of regecoline from kesselringine effected by two methods. A good yield was obtained both by the irradiation of kesselringine in solution with sunlight, and also by oxidation with iodine in dioxane solution. As is known, the oxidation of aporphines by iodine leads to 6a,7-didehydroaporphines [5]. On oxidation under similar conditions, however, kesselringine forms a 6a-dehydro derivative that is a quaternary base with a betaine nature, i.e., regecoline.

The regecoline obtained by the oxidation of kesselringine with iodine contained the initial base and regelinone as impurities. It was successfully isolated in the individual

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state in the form of the acetyl derivative after the elimination of the impurities. Acetylregecoline can be reconverted into regecoline by hydrolysis with hydrochloric acid to 12-demethylregicoline with subsequent methanolysis by a known method [4].

EXPERIMENTAL

1. In a round-bottomed quartz flask, 1 g of kesselringine was dissolved in 10 ml of methanol, and the volume of the solution was made up to 500 ml by the addition of cold freshly boiled and filtered distilled water. Then gaseous nitrogen was passed through the solution for 15 min and the solution in the sealed flask was irradiated with sunlight for 36 days. The course of the reaction was monitored by thin-layer chromatography in silica gel (5/40 μ with 13% of gypsum in the chloroform—methanol—acetone—benzene—25% ammonia (10:8:6.5:3:5) system). After the end of the reaction, the solution was extracted five times with chloroform to eliminate traces of unchanged kesselringine. The water was distilled off in vacuum to small volume (∿50 ml) and the solution was again extracted, seven times, with chloroform. The chloroform extracts so obtained contained a mixture of kesselringine and regecoline. Then the aqueous solution was evaporated to dryness and the residual substance was treated with acetone. A light orange crystalline substance separated out which was identified by its R_f value, melting point, and spectral characteristics as regecoline [2]. Yield 0.76 g (77%).

2. A solution of 0.66 g of kesselringine in 30 ml of dried and redistilled dioxane was treated with 0.65 g of freshly fused sodium acetate. The solution was brought to the boil, and over 4 h a solution of 0.33 g of iodine in 26 ml of dioxane was added dropwise, the solution finally acquiring a dark orange color. Thin-layer chromatography of the reaction solution showed that the reaction product — regecoline (R_f 0.39) — contained kesselringine (R_f 0.90) and regelinone (R_f 0.52) as impurities.

The solvent was distilled off, and the residual substance was dissolved in 85 ml of water, the solution then being extracted with chloroform until the kesselrine has been completely eliminated. After this, 2 ml of acetic acid and 0.5 g of zinc dust were added to the aqueous solution and it was left with occasional shaking at room temperature for 6 h, when the regelinone impurity had been completely reduced to regecoline. The solution was evaporated in vacuum to dryness, the residual substance was dissolved in 5 ml of freshly redistilled acetic anhydride, and 2-3 drops of concentrated sulfuric acid was added. After the formation of the acetyl derivatives of regecoline, the excess of reagent was eliminated by the addition of methanol and evaporation. The residue was dissolved in water, and the solution was extracted with chloroform. Acetylregecoline with R_f 0.62 was isolated. In its spectral characteristics it was identical with a sample obtained previously [2]. Yield 0.64 g (86%).

SUMMARY

An improved synthesis of the quaternary homoproaporphine alkaloid regecoline from kesselringine has been carried out by two methods — photochemical conversion and oxidation with iodine in dioxane.

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