SYNTHESIS OF 8-(1-AMINOETHYL)QUINOLINE

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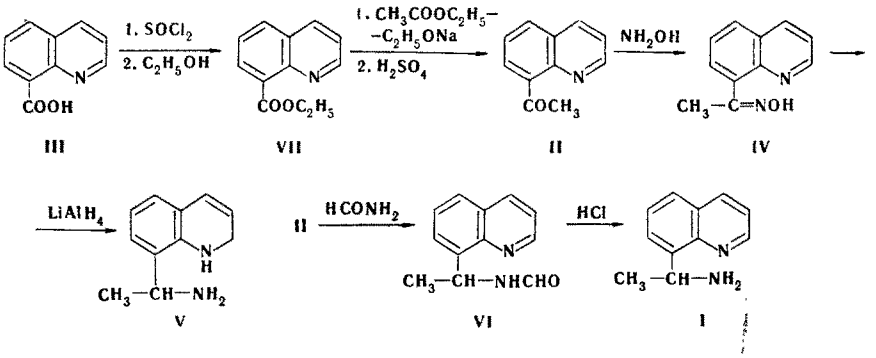
UDC 547.831.6.07

8-(1-Aminoethyl)quinoline, which has antimonoaminooxidase activity, was synthesized by the Leuckart reaction. Reduction of 8-acetylquinoline oxime with lithium aluminum hydride gives 8-(1-aminoethyl)-1,2-dihydroquinoline.

α-Aminoethyl-substituted quinolines are of definite interest in connection with their potential biological activity (for example, as substances that inhibit the activity of the enzyme monoaminooxidase). Only 2-, 3-, and 4-(1-aminoethyl)quinolines are known [1, 2]; quinolines with α-aminoethyl-substituted benzene rings have not been described.

We carried out the synthesis of 8-(1-aminoethyl)quinoline (I) via the following scheme:



The key compound — 8-acetylquinoline (II) — was obtained by the method in [3] with certain modifications: in particular, we made a more precise determination of the conditions for carrying out the Skraup reaction in the preparation of quinoline-8-carboxylic acid (III), namely, the optimum reaction temperature and time are 160-170°C and 5 h. 8-Acetylquinoline was obtained in poor yield because of the formation of considerable amounts of acid III during the hydrolysis of the product of Claisen condensation (β-keto ester). Changes in the hydrolysis conditions did not lead to an increase in the yield of desired ketone II.

8-Acetylquinoline oxime (IV) was reduced with lithium aluminum hydride for conversion to amine I. Lithium aluminum hydride has been used for the reduction of various functional groups in quinoline derivatives [4], although reduction of the quinoline ring is possible in this case [5]. In fact, a mixture of substances containing only traces of I was obtained as a result of the reaction of oxime IV with lithium aluminum hydride in ether. The chief reaction product was 8-(1-aminoethyl)-1,2-dihydroquinoline (V), which was obtained as a yellow oil that rapidly darkened in air (it also gave a monopicrate and a monohydrochloride). The spectral characteristics of V make it possible to assign the indicated structure to it: the UV spectrum of V in ethanol is similar to the spectra of simple 1,2-dihydroquinolines [6] (λ_{max} 204, 254, and 365 nm). A comparison of the PMR spectra of V and 1-methyl-1,2-dihy-

Institute of Biological and Medicinal Chemistry, Academy of Medical Sciences of the USSR, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 514-516, April, 1975. Original article submitted March 6, 1974.

droquinoline [7] makes it possible to observe an obvious similarity in them.

We were able to obtain amine I in low yield via the Leuckart reaction. The formyl derivative of 8-(1-aminoethyl)quinoline (VI) was obtained by heating 8-acetylquinoline with formamide at 170-180°. The reaction is accompanied by considerable resinification. Formyl derivative VI was purified by chromatography on aluminum oxide or by extraction with hot water in the presence of activated charcoal and was hydrolyzed to amine I with hydrochloric acid. Its structure was confirmed by its PMR and IR spectra. The UV spectrum of amine I practically coincides with the spectrum of 8-(N,N-dimethylaminomethyl)quinoline [4], which we took as a model compound. According to preliminary data, 8-(1-aminoethyl)quinoline inhibits in vitro (in concentrations up to 10^{-6} M) the activity of monoaminooxidase from rat liver during oxidative deamination of tyramine and serotonin.

EXPERIMENTAL METHOD

The UV spectra of $0.4\text{-}0.8\cdot10^{-4}$ M solutions of the compounds in 95% ethanol were recorded with a CF-4R spectrophotometer. The IR spectra of liquid films of the compounds were obtained with a Perkin-Elmer 257 spectrometer. The PMR spectra of CCl_4 solutions (2%) were measured with a JEOL 3H spectrometer (60 MHz) with tetramethylsilane as the internal standard. Thin-layer chromatography (TLC) was carried out on Silufol UV-254 plates in petroleum ether—ethyl acetate (1:1) with development in UV light. Preparative chromatography was carried out with a column filled with activity III (Brockmann classification) Al_2O_3.

Quinoline-8-carboxylic Acid (III). A mixture of 102 g (0.75 mole) of anthranilic acid, 0.75 g (0.45 mole) of o-nitrobenzoic acid, 250 g of anhydrous glycerol, and 150 ml of concentrated sulfuric acid was heated gradually with stirring on an oil bath. At 160° (bath temperature) a vigorous reaction with frothing began; frothing was reduced by the addition of octyl alcohol. The mixture was then heated with stirring at 160-170° (bath temperature) for another 5 h, after which it was cooled and poured over ice. The resulting solution was treated with ammonia to bring the pH up to 3-4, and the mixture was decanted away from the resin and extracted with chloroform. The solvent was then evaporated to give 68 g (53%) of crude acid III with mp 179-182°, which was in agreement with the literature melting point [3].

Ethyl Quinoline-8-carboxylate (VII). A mixture of 86 g of crude acid III and 284 ml of thionyl chloride was refluxed for 1 h, after which the excess thionyl chloride was removed by vacuum distillation at 60°. The residue was heated for 30 min with 160 ml of absolute ethanol, after which the unchanged ethanol was removed by vacuum distillation. The residue was neutralized to pH 6-7 with aqueous $NaHCO_3$ solution, and the product was extracted with chloroform. The solvent was removed by distillation, and the residue was fractioned at 125-130° (0.05 mm) to give 61.2 g (60%) of VII with mp 43-44°, which was in agreement with the literature melting point [3].

8-Acetylquinoline (II). Dry toluene (130 ml), 54.5 g (0.27 mole) of ester VII, and 34 ml (0.34 mole) of ethyl acetate were added to dry sodium ethoxide obtained from 8.5 g (0.37 g-atom) of sodium and 100 ml of absolute ethanol, and the mixture was stirred and refluxed for 5 h. Fifteen minutes after refluxing had begun, a precipitate (the sodium derivative of the β-keto ester) formed. After the refluxing period, the reaction mixture was cooled, and the precipitate was removed by filtration to give the sodium derivative in 70% yield. The precipitated sodium derivative was heated with 455 ml of 20% sulfuric acid at 95° for 3 h, after which the mixture was cooled, made alkaline to pH 8-9, and extracted with ether. The yield of 8-acetylquinoline, with bp 114-116° (0.7 mm) and mp 42-43.5° (in agreement with the values in [3]), was 22 g (47%). In individual experiments, the yields of II ranged from 34-42% and even lower. Acid III was isolated in 10% yield from the sulfuric acid mother liquor after separation of the ketone by partial neutralization. Other variants of the hydrolysis of the β-keto ester (refluxing for 2 h with 5% hydrochloric acid or heating with 20% sodium hydroxide) did not give higher yields of ketone II.

8-Acetylquinoline Oxime (IV). A mixture of 8.0 g (0.115 mole) of hydroxylamine hydrochloride, 16.5 g (0.095 mole) of II, and 6.5 g (0.115 mole) of potassium hydroxide in 195 ml of 50% ethanol was refluxed for 2 h, after which it was diluted to three times its original volume with water, and the precipitated IV was removed by filtration to give 8.4 g (47%) of a product with mp 137° (from aqueous ethanol) (in agreement with the value in [8]).

Reduction of 8-Acetylquinoline Oxime. A solution of 4.48 g (0.024 mole) of oxime IV in 70 ml of absolute ether was added with stirring to 1.27 g (0.033 mole) of lithium aluminum hydride in 70 ml of absolute ether, and the mixture was refluxed with stirring for 3 h. It was then cooled and acidified to pH 2 with dilute sulfuric acid, the ether layer was separated, and the aqueous layer was made alkaline to pH 10 and extracted with ether. The extracts were combined, and the substance (2.62 g of an oil) obtained by workup of them was applied to a column (28 by 3 cm) filled with Al_2O_3 and eluted with petroleum ether—ethyl acetate (1:1). The principal fraction (V) obtained was 0.75 g (18%) of a yellow oil with R_f 0.83. IR spectrum of V: 3400, 3300 (NH_2); 2950, 2845 (CH_3) cm^{-1}. PMR spectrum, δ, ppm: 1.45 (d, CH_3, J = 6Hz), 1.6 (s, NH_2), 3.2-3.9 (m, —CH—, NH, 2H), 6.0-6.5 (m, 3H), 6.7 (d, 4H, J = 6Hz), and 7.0-7.7 (m, aromatic protons). The monopicrate was obtained in ethanol as red prisms with mp 169-170° (from ethanol). Found %: C 50.2; H 4.1; N 17.2. $C_{11}H_{14}N_2 \cdot C_6H_3N_3O_7$. Calculated %: C 50.1; H 4.2; N 17.4. Compound V reacted with excess hydrochloric acid to give a monohydrochloride, which crystallized only on prolonged standing (for about a month) to give dark-red plates with mp 159-162° (from acetone). Found %: N 13.1; Cl 16.4. $C_{11}H_{14}N_2 \cdot HCl$. Calculated %: 13.3; Cl 16.8. The spots of unidentified compounds with R_f 0.43 and 0.71 were observed on the thin-layer chromatogram of the reaction mixture obtained from the combined ether extract in addition to V and unchanged oxime IV (R_f 0.21) and traces of amine I (R_f 0.03).

8-(1-Aminoethyl)quinoline (I). Freshly distilled formamide (18 ml) was added to 5 g of ketone II, and the mixture was refluxed for 2 h at 170-180°. The mixture was then worked up by one of the following methods. A) The formamide was removed by vacuum distillation, the residue was dissolved in chloroform, and the solution was applied to a column filled with Al_2O_3 and eluted with petroleum ether—ethyl acetate (1:1). B) The reaction mixture was diluted with water and extracted with chloroform. The extract was evaporated, water was added to the residue, and the aqueous mixture was refluxed for 1 h. The supernatant solution was decanted away from the resin, activated charcoal was added, and the mixture was refluxed for 1.5 h. It was then filtered, and the filtrate was evaporated. The yield of formyl derivative VI, with mp 110° (from water or benzene—petroleum ether), was 0.6 g (10.5%). Found %: C 72.1; H 6.3; N 13.8. $C_{12}H_{12}N_2O$. Calculated %: C 71.9; H 6.0; N 13.9. A total of 20 ml of 18% hydrochloric acid was added to 600 mg of formyl derivative VI, and the mixture was refluxed for 2.5 h. The resulting solution was evaporated to dryness to give 0.53 g (71%) of the dihydrochloride of I with mp 260-261° (from ethanol). Found %: C 53.9; H 5.6; Cl 28.5; N 11.1. $C_{11}H_{12}N_2 \cdot 2HCl$. Calculated %: C 53.9; H 5.7; Cl 28.9; N 11.4.

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