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THE CONVERSION OF LILOLINE DERIVATIVES TO QUINOLINIUM SALTS USING CYANOGEN BROMIDE

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In a recent publication (1) the chemistry of β -erythroidine and its derivatives was summarized and interpretations were advanced to explain the degradative evidence at hand. One of the most important degradation products of this alkaloid is apo- β -erythroidine for which structure I was proposed. Since it would be highly desirable to obtain synthetic evidence regarding the correctness of the proposed structures, we have initiated studies directed toward this end and the present paper records some of our preliminary results.



The immediate goal in the present study was the synthesis of desoxyapo- β erythroidinol, a degradation product closely related to apo- β -erythroidine (2). This molecule has been assigned structure II and its synthesis appeared more feasible than that of I. In considering possible approaches to the synthesis of II, we were attracted by the fact that the ring system contained in II is homologous with that of liloline (1,8-ethano-1,2-dihydroquinoline) (VI, where $R_1 = R_2 = H$). Since Bamberger and Sternitzski (3) have shown that the formation of substituted 2-lilolones(1,8-ethano-2-quinolones) can readily be accomplished by the Knorr quinoline synthesis, the important steps to a synthesis of II by this route would be the reduction of the amide function of an appropriately substituted 2-lilolone and expansion of the resulting six-membered heterocyclic ring to a seven-membered one.

Analogies are available in the literature to indicate the likelihood of success for both these steps. The reduction of 1-isoquinolones with lithium aluminum hydride to give 1,2-dihydroisoquinoline derivatives has been reported by several authors (4, 5). Likewise, von Braun and Aust (6) have reported that the reaction of N-methyl-2-*n*-propyl-1,2-dihydroquinoline (III) with cyanogen bromide results in ring cleavage and gives IV. Thus, the von Braun cyanogen bromide reaction appeared to offer a feasible approach for the expansion of sixmembered rings of this type.



The compounds investigated in this reaction sequence are shown in Scheme I. The substituted 2-lilolones, Va and Vb, were readily prepared from indoline and the appropriately substituted acetoacetic esters. Their reduction with lithium aluminum hydride to the corresponding liloline derivatives, VIa and VIb, proceeded smoothly and in good yield. The liloline derivatives, when removed from solution, proved to be rather unstable and their characterization was accomplished through the formation of quaternary ammonium derivatives.

When solutions of VIa or VIb were treated with cyanogen bromide in an attempt to obtain the type of cleavage reported by von Braun and Aust (6), there were produced water-soluble, crystalline solids having none of the properties to be expected for a cyanamide such as IV. That the products were actually quinolinium bromides (VIIa and VIIb) was shown in several ways. Their composition agreed with that required for the quinolinium salts and the presence of ionic bromine in these samples was readily demonstrated. The presence of two easily reducible double bonds in the heterocyclic ring was shown by the fact that VIIb



on reduction over Adams catalyst absorbed two moles of hydrogen and gave a tertiary amine having the correct composition for VIII. As final evidence for the quinolinium structures, it was shown that oxidation of VIIa with alkaline ferricyanide solution gave the corresponding 2-lilolone (Va).

It is evident therefore that the reaction of these liloline derivatives with cyanogen bromide resulted in oxidation rather than the type of cleavage that is usually experienced in the von Braun reaction. This apparently is the first time that this type of oxidation has been observed (7), although it would seem probable that this is a general reaction for partially hydrogenated heterocycles. Certainly, in view of our results, the assumptions which von Braun and Aust made in assigning structure IV to their product cannot be accepted without further investigation.

Snyder and his associates (8, 9) have shown that treatment of quaternary allylic ammonium salts with cyanide ion is a useful method for preparing allylic nitriles. It was of interest to see whether this reaction could be applied to a cyclic allylic amine of the type present in the lilolines. When IXa and IXb were treated with sodium argentocyanide under the conditions used by Snyder, the only products isolated were the corresponding quaternary ammonium argentocyanides (Xa and Xb). These derivatives were unexpectedly stable and, because of their desirable physical properties, they were useful for characterization of the lilolines. In one attempt to effect reaction under more vigorous conditions, the crystalline methargentocyanide Xb was dry distilled. However, the only volatile product produced was the corresponding liloline (VIb).



EXPERIMENTAL¹

3,4-Dimethyl-2-lilolone (Va). A mixture of 17.8 g. of indoline² and 21.6 g. of ethyl α -methylacetoacetate was boiled under reflux for one hour and then 75% of the expected quantity of ethanol, resulting from amide formation, was removed by fractional distillation. The residual oil was cooled and added in 2-ml. portions to 20 ml. of conc'd sulfuric acid, keeping the temperature of the mixture below 110°. Finally, the cyclization reaction was completed by heating the mixture on a steam-bath for 15 minutes. The warm mixture was then poured into 150 ml. of ice-water and was neutralized with alkali. The organic layer was extracted with chloroform, dried, and the chloroform was removed.

¹ Analyses by Miss Claire King. All melting points are corrected.

² The most satisfactory method of preparing indoline proved to be the high pressure reduction of indole over Raney nickel at 150°. After fractional distillation to separate the octahydroindole, indoline $(n_{\rm p}^{20} \ 1.5882)$ was obtained in average yields of 60-70% when running the reaction on a two-molar scale.

Recrystallization of the residual solid from a benzene-hexane mixture gave 13.4 g. (45%) of white crystals, m.p. 151.5-153.5°.

Anal. Calc'd for C₁₃H₁₃NO: C, 78.36; H, 6.58.

Found: C, 78.57; H, 6.89.

4-Ethyl-3-methyl-2-lilolone (Vb). When 17.8 g. of indoline and 23.7 g. of ethyl 2-propionylpropionate were treated in the same manner as described for the preparation of 3,4-dimethyl-2-lilolone, there was obtained 23.4 g. (74%) of white crystals, m.p. 85.0-85.7°, after recrystallization from a chloroform-hexane mixture.

Anal. Calc'd for C₁₄H₁₅NO: C, 78.84; H, 7.09.

Found: C, 78.48; H, 7.09.

4-Methyl-2-lilolone. As a model for studying the formation of 2-lilolones, indoline was treated with ethyl acetoacetate in the same manner as above. This gave in 49% yield white crystals, m.p. 174.5-175.5°, after crystallization from a benzene-hexane mixture.

Anal. Cale'd for C₁₂H₁₁NO: C, 77.81; H, 5.99.

Found: C, 78.16; H, 6.13.

The hydrochloride of 4-methyl-2-lilolone was prepared using 20% aqueous hydrochloric acid and, after recrystallization from the same solvent, was obtained as white crystals. The hydrochloride dissociated fairly readily as indicated by its melting point behavior. A gas was evolved, the crystals became liquid, resolidified, and finally melted at 176-177°, the melting point of the free base.

Anal. Calc'd for C₁₂H₁₂ClNO: C, 65.01; H, 5.46.

Found: C, 65.36; H, 5.46.

3,4-Dimethylliloline (VIa). A solution of 4.35 g. of 3,4-dimethyl-2-lilolone in 150 ml. of dry benzene was added dropwise with stirring to a boiling solution containing 50 ml. of a 1.0 N ethereal solution of lithium aluminum hydride and 200 ml. of benzene. After the solution had boiled under reflux for 4 hours, 5 ml. of water was carefully added to decompose the excess lithium aluminum hydride. The inorganic salts were removed and were washed with 100 ml. of benzene. The combined benzene filtrate and washings was concentrated to 50 ml. and stored under nitrogen. This solution was then used for other reactions as needed. When attempts were made to isolate the 3,4-dimethylliloline in a pure state, serious deterioration of the sample occurred whereas benzene solutions of the base were sufficiently stable to permit storage.

The methiodide of 3,4-dimethylliloline (IXa) was prepared by treating 10 ml. of the stock solution of 3,4-dimethylliloline with 4 ml. of methyl iodide in 10 ml. of ethanol. This mixture was concentrated to a small volume and treated with 30 ml. of ethyl acetate. The solid, which separated, was recrystallized from a methanol-ethyl acetate mixture to give 1.1 g. (80%, based on 3,4-dimethyl-2-lilolone) of white crystals, m.p. 171-171.5°. These crystals were unstable and rapidly turned color on standing making it difficult to obtain an analytically pure sample.

Anal. Calc'd for C₁₄H₁₈IN : C, 51.39; H, 5.55.

Found: C, 50.87; H, 5.39.

1,3,4-Trimethyllilolinium argentocyanide (1,3,4-Trimethyl-1,8-ethano-1,2-dihydroquinolinium argentocyanide) (Xa). When 1.2 g. of the methiodide of 3,4-dimethylliloline (IXa) was heated with a solution of 1.4 g. of silver nitrate and 0.80 g. of sodium cyanide in 6 ml. of water, a heavy oil separated. This was extracted with chloroform, dried, and the chloroform extract was concentrated. The resulting solid, obtained in good yield, was recrystallized from an alcohol-ether mixture to give white crystals, m.p. 149-151°.

Anal. Calc'd for C₁₆H₁₈AgN₃: C, 53.35; H, 5.04; Ag, 29.95.

Found: C, 53.05; H, 5.30; Ag, 30.25.

4-Ethyl-3-methylliloline (VIb). This was prepared from 4-ethyl-3-methyl-2-lilolone in the same manner described previously for the preparation of 3,4-dimethylliloline (VIa). It also proved to be unstable and was not isolated in the pure state but, instead, was kept available as a stock solution in benzene.

The methiodide of 4-ethyl-3-methylliloline (IXb) was also prepared in the same manner

as that described for the preparation of IX. It was obtained after recrystallization from an ethanol-ether mixture as white crystals, m.p. 167–168°. The yield of methiodide, based on 4-ethyl-3-methyl-2-lilolone as starting material, was 83%.

Anal. Calc'd for C₁₅H₂₀IN: C, 52.79; H, 5.91.

Found: C, 52.04; H, 6.11.

1,3-Dimethyl-4-ethyllilolinium argentocyanide (1,3-Dimethyl-4-ethyl-1,8-ethano-1,2dihydroquinolinium argentocyanide) (Xb). A sample of 1.2 g. of the methiodide of 4-ethyl-3-methylliloline was treated with a solution of 1.36 g. of silver nitrate and 0.80 g. of sodium cyanide in 6 ml. of water and the resulting mixture was heated on a steam bath for onehalf hour. The heavy oil, which separated, was extracted with chloroform, dried, and the chloroform extract was concentrated. The resulting solid, obtained in high yield, was recrystallized from chloroform to give white crystals m.p. 138-140°.

Anal. Calc'd for C₁₇H₂₀AgN₃: C, 54.56; H, 5.39.

Found: C, 54.30; H, 5.49.

In an attempt to effect displacement of the allylic amine by cyanide ion, a 350-mg. sample of 1,3-dimethyl-4-ethyllilolinium argentocyanide was heated in a molecular still at 150-200° at 1 mm. pressure. The light yellow oil, which distilled, was treated directly with methyl iodide. The resulting solid, after recrystallization from an ethanol-ether mixture, gave 81 mg. (36%) of white crystals, m.p. 163-165°, alone or mixed with an authentic sample of the methiodide of 4-ethyl-3-methylliloline.

3,4-Dimethyl-1,8-ethanoquinolinium bromide (VIIa). To a solution of 3,4-dimethylliloline (prepared as above from 5.0 g. of 3,4-dimethyl-2-lilolone) in 100 ml. of benzene, there was added a solution of 4.0 g. of cyanogen bromide in 10 ml. of benzene. When the resulting mixture was heated on a steam-bath, a heavy oil soon separated and crystallized. After the mixture had been heated for one-half hour, the solid was separated and was recrystallized from an ethanol-ethyl acetate mixture. This gave 4.4 g. (66%, based on 3,4dimethyl-2-lilolone) of white crystals, m.p. 280-285° dec.

Anal. Calc'd for C₁₃H₁₄BrN: C, 59.09, H, 5.34.

Found: C, 58.45; H, 5.55.

4-Ethyl-3-methyl-1,8-ethanoquinolinium bromide (VIIb). When a benzene solution of 4-ethyl-3-methyllioline (prepared from 5.0 g. of 4-ethyl-3-methyl-2-lilolone) was treated with cyanogen bromide in the same manner as described above for the preparation of 3,4dimethyl-1,8-ethanoquinolinium bromide, there was obtained 4.5 g. (69%, based on 4-ethyl-3-methyl-2-lilolone) of white crystals, m.p. 234-236°, after recrystallization from an ethanolethyl acetate mixture.

Anal. Cale'd for C14H15BrN: C, 60.44; H, 5.80.

Found: C, 60.63; H, 6.07.

Hydrogenation of 4-ethyl-3-methyl-1,8-ethanoquinolinium bromide. A solution of 1.0 g. of 4-ethyl-3-methyl-1,8-ethanoquinolinium bromide (VIIb) in 10 ml. of methanol was subjected to hydrogenation over an Adams catalyst at room temperature and atmospheric pressure. Absorption of hydrogen occurred over a 4-hr. period and, when complete, corresponded to absorption of two moles of hydrogen per mole of reactant. After removal of solvent and catalyst, the hydrobromide of VIII was obtained as a gum. This was taken up in water, made alkaline with sodium carbonate, and extracted with chloroform. After removal of the chloroform, the residue was distilled using a molecular still to give 1.0 g. of a colorless oil, b.p. 150° (pot temperature) at 5 mm.

Anal. Calc'd for C₁₄H₁₉N: C, 83.53; H, 9.51.

Found: C, 83.38; H, 9.75.

Alkaline ferricyanide oxidation of 3,4-dimethyl-1,8-ethanoquinolinium bromide. To a solution of 120 mg. of 3,4-dimethyl-1,8-ethanoquinolinium bromide and 330 mg. of potassium ferricyanide in 10 ml. of water, there was added 10 ml. of benzene followed by the dropwise addition with shaking of 2 ml. of an aqueous 10% sodium hydroxide solution. The benzene layer was then removed, washed with water, and concentrated. The solid residue was crystallized from a benzene-hexane mixture to give crystals melting at 149-

152°. A sample of these crystals when mixed with authentic 3,4-dimethyl-2-lilolone showed no depression of melting point.

SUMMARY

The preparation of several substituted lilolines has been accomplished and their possible utility in a synthesis of degradation products of apo- β -erythroidine has been investigated. It has been shown that the reaction of these liloline derivatives with cyanogen bromide does not lead to ring cleavage but, instead, results in oxidation to the corresponding quinolinium bromides.

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