[Contribution from the Department of Chemistry, University of Rochester]

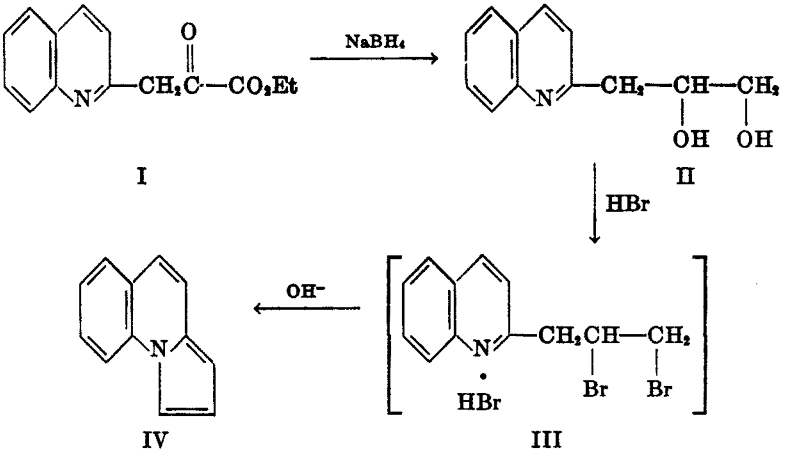
A SYNTHESIS OF 5,6-BENZOPYRROCOLINE[1]

EDWARD M. ROBERTS, MARSHALL GATES, and V. BOEKELHEIDE

Received June 14, 1955

In an investigation directed toward the synthesis of aromatic heterocycles of unusual structure, we had need of 5,6-benzopyrrocoline as an intermediate. The most general method of preparing pyrrocolines is the Chichibabin reation in which an α-picoline derivative is treated with an α-haloketone under conditions designed to effect cyclization (1). However, as has been noted previously by Borrows, Holland, and Kenyon (2), the reaction of quinaldine with either α-chloroacetone or phenacyl bromide gives merely the corresponding quinaldine hydrohalide. It was necessary, therefore, to devise a new approach for the synthesis of 5,6-benzopyrrocoline and the successful scheme that has been developed in this work may possibly be of general usefulness.

As reported by Wislicenus and Kleisinger (3), quinaldine undergoes condensation readily with ethyl oxalate to give ethyl 2-quinolylpyruvate (I) in good yield. When ethyl 2-quinolylpyruvate was treated with sodium borohydride in methanol, it gave the unexpected, but desired, product, 1-(2-quinolyl)-2,3-propanediol (II), in 52% yield. Treatment of this diol with hydrobromic acid followed by steam-distillation from alkali gave 5,6-benzopyrrocoline (IV) directly in 85% yield. Presumably the dibromo derivative (III) is an intermediate in this conversion.

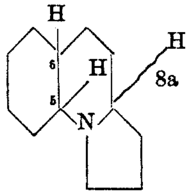


5,6-Benzopyrrocoline was obtained as white crystals, m.p. 108–109°, which, as would be expected for a pyrrocoline derivative, showed a light blue fluorescence and gave a deep blue color in the Ehrlich test. That ring closure had occurred in the transition from III to IV was further established through hydrogenation experiments. Reduction of IV using Adams' catalyst in the presence of

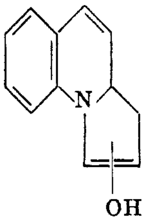
---

[1] Supported by the Office of Ordnance Research, Contract No. D.A.-30-115-O.R.D.-421.

acid led to complete saturation of the molecule and gave a dodecahydro derivative (V). Since the infrared spectrum of this dodecahydro derivative does not show abosrption in the region (2.5–3.4μ) normally assigned to the nitrogen-hydrogen stretching frequency, both IV and V must be tertiary amines.



V

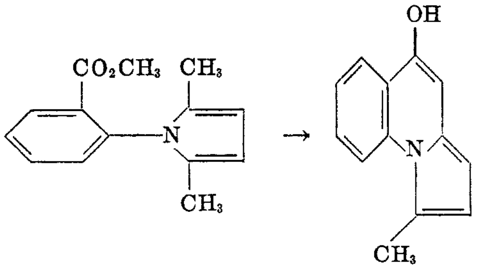


VI

The behavior of ethyl 2-quinolylpyruvate toward metallic hydrides appears to be somewhat unusual. As previously indicated, the use of sodium borohydride, which normally does not attack esters, led to complete reduction to give 1-(2-quinolyl)2,3-propanediol (II). On the other hand the use of lithium aluminum hydride, which might be expected to give II, yielded an unstable amphoteric compound whose composition corresponds to the empirical formula $C_{12}H_9NO$. Although the structure of this material has not been established, it would appear likely that it is a result of a base-catalyzed cyclization reaction followed by loss of water in which either a 2- or 3-hydroxy-5,6-benzopyrrocoline (VI) has been produced. The unstable and amphoteric nature of the product, its spectral properties and positive behavior in the ferric chloride test for enols, as well as the preparation of a series of derivatives are consistent with this hypothesis.

The relatively short and straight-forward manner in which 5,6-benzopyrrocoline is afforded by the present scheme suggests that this approach might be useful for preparing pyrrocolines in other instances as well. In contrast to most pyrrocoline syntheses the present one does not require substituent groups in the five-membered ring.

In the preliminary investigations directed toward 5,6-benzopyrrocoline, a number of alternate routes were explored as well. In one attempt 2,5-dimethyl-1-(2-carbomethoxyphenyl)pyrrole (VII) was prepared and was treated with strong base. It was hoped that a cyclization might be effected to yield 3-methyl-7-hydroxy-5,6-benzopyrrocoline (VIII) but this was not realized.



VII VIII

EXPERIMENTAL[2]

1-(2-Quinolyl)-2,3-propanediol (II). A solution of 3.0 g. of sodium borohydride in 150 ml. of methanol was added dropwise with stirring to a solution of 20.0 g. of the potassium enolate of ethyl 2-quinolylpyruvate (3) in 50 ml. of methanol. Although the yellow color of the solution quickly disappeared, the solution was boiled under reflux for three hours to ensure complete reduction. The solvent then was removed under reduced pressure and the residue was treated with 50 ml. of water followed by 25 ml. of a 40% sodium hydroxide solution. The resulting solution was extracted with chloroform, and the chloroform extract was dried and concentrated to give 7.5 g. (52%) of crystals, m.p. 109–112°. Recrystallization of this material from benzene gave white crystals, m.p. 115–116°. The infrared spectrum of these crystals showed no absorption in the carbonyl region.

Anal. Calc'd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45.

Found: C, 70.77; H, 6.73.

The *picrate* of *II* formed readily in ethanol and was obtained as yellow needles, m.p. 162–163°.

Anal. Calc'd for $C_{18}H_{16}N_4O_9$: C, 50.00; H, 3.73.

Found: C, 50.11; H, 4.01.

5,6-Benzopyrrocoline (IV). A solution of 250 mg. of 1-(2-quinolyl)-2,3-propanediol (II) in 5 ml. of a 47% hydrobromic acid solution was boiled under reflux for 7 hours. At the end of this time the solution was cooled and solid sodium carbonate was added slowly with cooling to neutralize the acid. When the solution was alkaline, it was subjected to steam-distillation, the 5,6-benzopyrrocoline separating from the steam-distillate as fluorescent white crystals. These were removed by extraction with ether and the crystalline residue, after concentration of the ethereal solution, was recrystallized from an ethanol-water mixture to give 175 mg. (85%) of white crystals, m.p. 108–108.5°. 5,6-Benzopyrrocoline gives a dark blue color with *p*-dimethylaminobenzaldehyde in the Ehrlich test. It is weakly basic and will dissolve in 10% hydrochloric acid from which it can be recovered unchanged on neutralization. The ultraviolet absorption spectrum of 5,6-benzopyrrocoline shows maxima at 227 (log ϵ, 4.51) 243 (log ϵ, 430), 250 (log ϵ, 4.36), 264 (log ϵ, 3.98), 276 (log ϵ, 3.90), 325–365 mμ (broad peak, log ϵ, 3.74) with corresponding minima at 238 (log ϵ, 4.25), 246 (log ϵ, 4.27), 260 (log ϵ, 3.96), 272 (log ϵ, 3.84), and 291 mμ (log ϵ, 2.95).

Anal. Calc'd for $C_{12}H_9N$: C, 86.20; H, 5.42.

Found: C, 85.97; H, 5.68.

Dodecahydro-5,6-benzopyrrocoline (V). A solution of 1.0 g. of 5,6-benzopyrrocoline and 50 mg. of prereduced Adams' catalyst in 100 ml. of ethanol was subjected to hydrogenation at atmospheric pressure and room temperature. One mole of hydrogen was absorbed very rapidly and then hydrogen uptake ceased. Addition of 10 drops of 6 *N* hydrochloric effected a resumption of hydrogen absorption and the reduction proceeded to completion. The catalyst and solvent were removed, and the residue was dissolved in water, made basic, and extracted with ether. After the ethereal solution had been dried, it was concentrated and the residual oil was distilled using a short path still. The distillate was collected in four fractions over a temperature range for the heating bath from 45 to 70° at 1 mm. The analytical sample was taken from the third fraction and its infrared spectrum lacked absorption peaks in the 2.5–3.4 μ region, indicating the absence of an —N—H group.

Anal. Calc'd for $C_{12}H_{21}N$: C, 80.38; H, 11.80.

Found: C, 80.76; H, 11.93.

It would be expected that, if hydrogenation occurred in a stepwise but *cis* fashion, two diastereoisomers of VI would result depending on whether the hydrogen atom at 8a is on the same side or opposite to the bridgehead hydrogens at positions 5 and 6. When the oil obtained above was converted to the corresponding picrate derivative, two different compounds resulted as would be expected for the two diastereoisomeric picrates. From the first fractions of the distillate a picrate was obtained which, although a mixture, was puri-

---

[2] Analyses by Miss V. Williams and Miss A. Smith.

fied by repeated crystallization from ethanol to give homogeneous yellow crystals, m.p. 146–147°.

Anal. Calc'd for $C_{18}H_{24}N_4O_7$: C, 52.93; H, 5.92.
Found: C, 53.24; H, 5.43.

From the last fraction a picrate was obtained which again after repeated crystallization from ethanol gave homogeneous yellow crystals, m.p. 169–170°.

Anal. Calc'd for $C_{18}H_{24}N_4O_7$: C, 52.93; H, 5.92.
Found: C, 52.45; H, 6.22.

Lithium aluminum hydride reduction of ethyl 2-quinolylpyruvate. To a solution of 12.5 g. of ethyl 2-quinolylpyruvate (3) in 200 ml. of purified tetrahydrofuran there was added a solution of 2.2 g. of lithium aluminum hydride in 50 ml. of tetrahydrofuran. After the mixture had boiled under reflux for two hours, it was decomposed by the addition of moist ether. This was followed by the addition of 200 ml. of 10% hydrochloric acid. The mixture was extracted with ether to remove any non-basic material and then was made neutral by the addition of Rochelle salts and alkali. Extraction of the neutral solution followed by concentration of the ether extracts gave 3.2 g. (34%) of a brown solid. This, after crystallization from an ethanol-water mixture, yielded yellow needles, m.p. 66–68°. This product (presumably 2- or 3-hydroxy-5,6-benzopyrrocoline, VI) appeared to contain water of crystallization since on prolonged drying *in vacuo* over phosphorus pentoxide it lost water and was converted to a brown solid, m.p. 95–97°. Recrystallization of this brown solid from an ethanol-water mixture regenerated the original yellow needles, m.p. 66–68°.

The yellow needles gave a brown color with ferric chloride solution and a positive Tollens test. Although the establishment of the empirical formula of this compound was complicated by its strong tendency to crystallize with molecules of solvent, the formation of a monoacetate derivative as well as anhydrous picrate and perchloride salts is in agreement with the provisional structure VI.

Anal. Calc'd for $C_{12}H_9NO \cdot 2H_2O$: C, 65.74; H, 5.98.
Found (yellow needles, m.p. 66–68°): C, 66.00; H, 6.15.

Anal. Calc'd for $C_{12}H_9NO \cdot H_2O$: C, 71.62; H, 5.51.
Found (brown solid, m.p. 95–97°): C, 72.05; H, 5.80.

The *picrate* of VI, prepared from either the yellow needles, m.p. 66–68° or the brown solid, m.p. 95–97°, was obtained after recrystallization from ethanol as orange crystals, m.p. 141–142°.

Anal. Calc'd for $C_{18}H_{12}N_4O_8$: C, 52.43; H, 2.93.
Found: C, 52.03; H, 3.67.

The *perchlorate* of VI was obtained after recrystallization from ethanol as red needles, m.p. 145–146°. Treatment of the perchlorate derivative with base regenerated the yellow needles, m.p. 66–68°.

Anal. Calc'd for $C_{12}H_{10}ClNO_5$: C, 47.77; H, 4.01; N, 4.64.
Found: C, 47.81; H, 3.93; N, 5.05.

A *monoacetate* of VI was prepared by heating 500 mg. of the yellow needles, m.p. 66–68°, with 10 ml. of acetic anhydride. After removal of the excess acetic anhydride under reduced pressure, the residue was recrystallized from ethanol to give 608 mg. (95%) of white crystals, m.p. 110–111°.

Anal. Calc'd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39.
Found: C, 69.22; H, 5.72.

2,5-Dimethyl-1-(2-carbomethoxyphenyl)pyrrole (VII). A solution of 5.0 g. of acetonylacetone, 6.6 g. of methyl anthranilate, and 5 ml. of acetic acid in 20 ml. of benzene was boiled under reflux for 3 hours. At the end of this time the reaction mixture was distilled and the forerun was discarded. There was obtained 7.0 g. (69%) of a light yellow oil; b.p. 116–120° at 5 mm., n_D^{20} 1.5518. This product was insoluble in dilute acid and gave positive pine splinter and Ehrlich tests for the pyrrole nucleus.

Anal. Calc'd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.60; N, 6.11.
Found: C, 73.67; H, 6.65; N, 6.02.

When a 2.0 g. sample of VII was dissolved in ethanol and was subjected to hydrolysis by heating it with a 10% ethanolic solution of potassium hydroxide, a solid crystallized out upon cooling the solution. This proved to be the potassium salt of 2,5-dimethyl-1-(2-carboxyphenyl)pyrrole and was obtained after crystallization from a methanol-ethyl acetate mixture as colorless crystals, m.p. 273–274°.

Anal. Calc'd for $C_{13}H_{12}KNO_2$: C, 61.63; H, 4.77; K, 15.43.
Found: C, 61.75; H, 4.74; K, 14.74.

2,5-Dimethyl-1-(2-carboxamidophenyl)pyrrole. An attempt to effect the cyclization of VII to give VIII was made by heating a solution of 25 ml. of toluene containing 8.0 g. of 2,5-dimethyl-1-(2-carbomethoxyphenyl)pyrrole (VII) and 4.0 g. of sodium amide (4) under reflux for 3 hours. At the end of this time ice and hydrochloric acid were added to decompose the excess sodium amide; the toluene layer was removed and concentrated. This gave a dark residual oil which solidified on stirring with ether to give 5.2 g. of a yellow solid, m.p. 106–110°. Repeated crystallization of this material from an ethanol-water mixture gave 2.0 g. of colorless crystals, m.p. 129–130°. As indicated below the composition of these crystals is in agreement with that expected for the corresponding amide.

An attempt to effect cyclization of VII to VIII using similar conditions but substituting sodium hydride for sodium amide was unsuccessful.

Anal. Calc'd for $C_{13}H_{14}N_2O$: C, 72.90; H, 6.54; N, 13.08.
Found: C, 73.14; H, 6.78; N, 13.07.

SUMMARY

A synthesis of 5,6-benzopyrrocoline is described. The method developed differs from the usual pyrrocoline syntheses and may possibly have general usefulness.

ROCHESTER 3, NEW YORK

REFERENCES

(1) BORROWS AND HOLLAND, *Chem. Revs.*, **42**, 611 (1948).
(2) BORROWS, HOLLAND, AND KENYON, *J. Chem. Soc.*, 1069 (1946).
(3) WISLICENUS AND KLEISINGER, *Ber.*, **42**, 1140 (1909).
(4) VAUGHN, VOGT, AND NIEUWLAND, *J. Am. Chem. Soc.*, **56**, 2120 (1934).