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The ring closure of *N,N'*-bis[2-(dialkoxy)ethyl]-*p*-xylene- α,α' -diamine dihydrochloride in fuming sulfuric acid has been investigated and the cyclization products have been identified as the linear pyrido[3,4-*g*]isoquinoline as well as the previously reported angular 3,8-phenanthroline.

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In connection with previous reports on the synthesis of 4-phenyl-1,2,3,4-tetrahydroisoquinolines (1,2), it was demonstrated in these laboratories that the ring closure of *N,N'*-bis(1-hydroxy-1-phenyl-2-propyl)-*p*-xylene- α,α' -diamine dihydrochloride (**1**) with polyphosphoric acid (PPA) gave the linear octahydropyrido[3,4-*g*]isoquinoline (**2**).

In contrast to this observation, Ruggli and Schetty reported in 1940 that cyclization of *N,N'*-bis[2-(diethoxy)ethyl]-*p*-xylene- α,α' -diamine dihydrochloride (**3**) in fuming sulfuric acid afforded 3,8-phenanthroline (**4**) (4). No evidence supporting the phenanthroline structural assignment was cited nor was any mention made of the linear pyrido[3,4-*g*]isoquinoline (**5**), the other possible cyclization product of **3** (4).

In view of our experience with the cyclization of **1** (3), it was our contention that closure of **3** similarly could have afforded the linear compound **5**. Thus, the purpose of this communication is to report the results of a reinvestigation of this cyclization.

Initially, cyclization of the ethyl acetal **3** was repeated using precisely the same procedure reported by Ruggli and Schetty (4). In our hands, the isolated product melted at 170-171° whereas the melting point of the cyclization

product described in the 1940 work was 225°. The infrared and nuclear magnetic resonance spectra as well as the elemental analysis of the product isolated in these laboratories were consistent with a cyclized material but did not permit a distinction between the angular compound **4** and the linear product **5**.

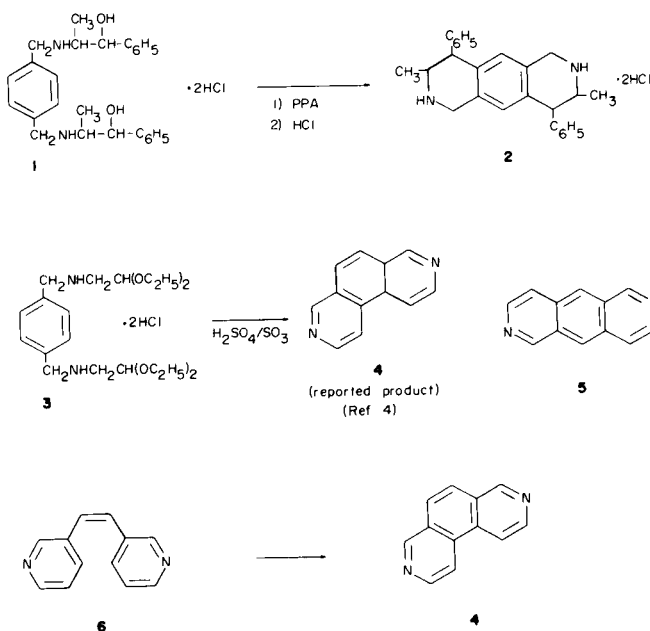
Furthermore, Perkampus and Kassebeer recently reported the unequivocal synthesis of the angular product **4** by photocyclization of the 1,2-dipyridylethylene **6** (5). The melting point of this product, 139-141°, differed considerably from both that reported by Ruggli and Schetty (225°) and that observed for the product obtained when the German work was repeated in these laboratories (170-171°). The nuclear magnetic resonance spectra for Perkampus and Kassebeer's angular compound was consistent for structure **4** but differed considerably from that of our cyclization product.

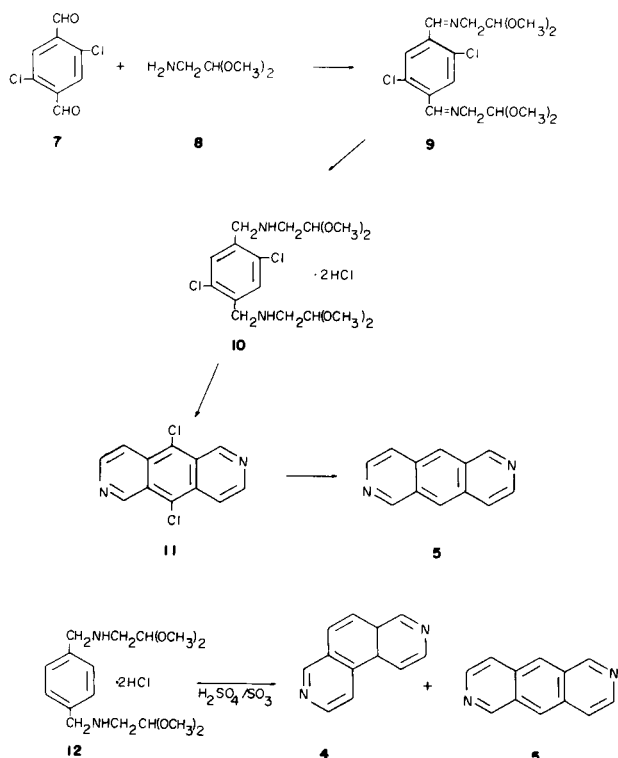
Thus, the recent work of Perkampus and Kassebeer casts further doubt on Ruggli and Schetty's contention that cyclization of **3** gave the angular compound **4**.

To demonstrate our original hypothesis that cyclization of **3** gave rise to pyrido[3,4-*g*]isoquinoline (**5**), this product was synthesized unequivocally in a four-step sequence originating with the previously reported 2,5-dichloroterephthalic dicarboxaldehyde (**7**) (6). Treatment of **7** with the aminoacetal **8** followed by sodium borohydride reduction of the intermediate Schiff base **9** gave **10** which was cyclized to 5,10-dichloropyrido[3,4-*g*]isoquinoline (**11**) with fuming sulfuric acid. Catalytic hydrogenolysis of **11** using palladium-on-carbon in diglyme in the presence of sodium acetate gave linear compound **5**, the infrared spectrum of which was identical to that of our product derived from **3**.

Subsequently, the cyclization of the methyl acetal **12** in fuming sulfuric acid was investigated. Extraction of the basified reaction mixture with ether gave a crude product which upon fractional recrystallization afforded the angular compound **4**, the melting point and nuclear magnetic resonance spectrum of which were in good agreement with those reported by Perkampus and Kassebeer (5). Subsequent extraction of the alkaline mixture with chloroform afforded the linear compound **5**.

When the alkaline mixture resulting from the cyclization of **12** was extracted directly with chloroform, there was obtained an 8.4% yield of product-mixture comprised





of 37% of **5** and 63% of **4** based on nuclear magnetic resonance spectral data.

Thus, this type of cyclization gives rise to both 3,8-phenanthroline **4** and pyrido[3,4-*g*]isoquinoline **5** rather than only the former product as previously described by Ruggli and Schetty (4).

EXPERIMENTAL

The nmr spectra were taken on a Bruker WP-80 instrument and were compared with TMS as an internal standard. Infrared spectra were determined as Nujol mulls on a Perkin-Elmer 137B spectrophotometer and melting points were taken on a Mel-Temp block and are uncorrected.

N,N'-Bis[2-(diethoxy)ethyl]-*p*-xylene- α,α' -diamine Dihydrochloride (3).

The compound was prepared by the method of Ruggli and Schetty (4). An analytical sample, mp 180° dec, was obtained by recrystallization from methanol; ir: μ 3.75-3.80 (N^+H_2), 6.30 (C=C), 8.86, 9.13-9.35 (acetal).

Anal. Calcd. for $\text{C}_{20}\text{H}_{36}\text{N}_2\text{O}_4 \cdot 2\text{HCl}$: C, 54.41; H, 8.68; N, 6.35. Found: C, 54.39; H, 8.52; N, 6.24.

Cyclization of *N,N'*-Bis[2-(diethoxy)ethyl]-*p*-xylene- α,α' -diamine Dihydrochloride (3) by the Procedure of Ruggli and Schetty (4).

Fuming sulfuric acid, 97 ml (30-33% SO_3), was cooled to 0° and 18.5 g (0.039 mole) of **3** was added over 5 minutes at 0°. The mixture was stirred rapidly and the reaction temperature rose to 20° over one hour. The mixture was allowed to stand at room temperature for 25 hours and then poured onto 1 kg of ice over 5 minutes at minus 10° to 0°. The dark brown solution was neutralized at 10-25° with 50% sodium hydroxide and then made strongly alkaline by the addition of 100 g sodium hydroxide.

The entire mixture was continuously extracted with ether for 2 hours and then extracted with fresh ether to give the crude product.

Recrystallization from heptane gave 0.60 g (8.7%) (literature yield: 6.5%) of the product, mp 158-167°.

Further recrystallization from petroleum ether gave an analytical sample of **5**, mp 170-171°; nmr (deuteriochloroform): δ 7.78 (d, $J = 3$ Hz, 2, 3-H, 8-H), 8.26 (s, 2, 5-H, 10-H), 8.55 (d, $J = 3$ Hz, 2, 4-H, 9-H), 9.53 (s, 2, 1-H, 6-H); ir: μ 6.24 (C=C).

Anal. Calcd. for $\text{C}_{12}\text{H}_8\text{N}_2$: C, 79.98; H, 4.48; N, 15.55. Found: C, 79.82; H, 4.35; N, 15.33.

An analytical sample, mp 289-291°, of the dipicrate of the above product was obtained by recrystallization from ethanol. Literature mp of picrate (**4**) was 235°.

Anal. Calcd. for $\text{C}_{12}\text{H}_8\text{N}_2 \cdot 2\text{C}_6\text{H}_3\text{N}_3\text{O}_7$: C, 45.15; H, 2.21; N, 17.55. Found: C, 44.99; H, 2.32; N, 17.42.

N,N'-Bis[2-(dimethoxy)ethyl]-1,4-dichlorobenzene-1,4-bis(methanimine) (9).

A solution of **7** (**6**) (94 g, 0.463 mole) in 850 ml of toluene was stirred and refluxed for one hour using a Dean-Stark trap to remove water. The reaction mixture was then treated with 105 g of **8** and refluxed for 20 hours, collecting 17.5 ml of water (theory: 16.7 ml) via a Dean Stark trap.

The reaction mixture was then filtered and concentrated to dryness under reduced pressure to give 169 g (97%) of a yellow-orange oil which crystallized, mp 54-60°.

2,5-Dichloro-*N,N'*-bis[2-(dimethoxy)ethyl]-*p*-xylene- α,α' -diamine Dihydrochloride (10).

A 169 g (0.448 mole) portion of **9** in 1.2 liters of methanol was treated with 39.8 g (1.06 mole) of sodium borohydride at 10-15°. The reaction mixture was stirred at 10-15° for 2 hours, at ambient temperature for 4 hours, and then concentrated to dryness under reduced pressure. The residue was partitioned between 1 liter of chloroform and 1 liter of water. The chloroform extract was dried over magnesium sulfate, filtered, and concentrated to dryness under reduced pressure to give 164 g of the crude free base. The free base was taken up in 400 ml of absolute ethanol, acidified with ethanolic hydrogen chloride, cooled, and filtered. The tan solid was air dried and dried to a constant weight at 60°, yield, 143 g (70%).

An analytical sample, mp >400° dec, was obtained by recrystallization from methanol; nmr (DMSO- d_6): δ 3.12 (d, 4, $\text{CH}_2\text{CH}(\text{OR})_2$), 3.41 (s, 12, OCH_3), 4.31 (s, 4, ArCH_2NH), 4.93 (t, 2, $\text{CH}_2\text{CH}(\text{OR})_2$), 8.10 (s, 2, aromatic C-H), 10.13 (broad s, exchangeable, 4, N^+H_2); ir: μ 3.70-3.90 (N^+H_2), 6.40 (C=C), 8.90, 9.10, and 9.32 (acetal).

Anal. Calcd. for $\text{C}_{16}\text{H}_{26}\text{Cl}_2\text{N}_2\text{O}_4 \cdot 2\text{HCl}$: C, 42.31; H, 6.21; N, 6.17. Found: C, 42.23; H, 6.21; N, 6.21.

5,10-Dichloropyrido[3,4-*g*]isoquinoline (11).

A 122 g (0.268 mole) portion of **10** was added portionwise to 700 ml of fuming H_2SO_4 (20% SO_3) at 30-50°. The reaction mixture was then stirred at 90-95° for 24 hours, poured into 9.6 liters of ice water and basified at 25-35° with 1.7 liters of saturated potassium hydroxide solution. The alkaline solution was then filtered to give 1100 g of a mixture of the product plus inorganic salts. The solid was washed with 6500 ml of water, filtered, and air dried to a constant weight to give 70 g of a green-brown solid.

The crude product was extracted with 2 liters of hot toluene. The extract was filtered, cooled, and again filtered to give 17 g (25%) of a yellow-brown solid. The filtrate was concentrated to a volume of 200 ml, refrigerated, and filtered to give 12 g (18%) of a red-brown solid.

The combined products (**29** g) were recrystallized from 375 ml of DMF to give 9.0 g (14%) of a dark green-brown solid, mp 256-261° dec.

An analytical sample, mp 262-267° dec, was obtained by recrystallization from heptane; nmr (deuterium chloride): δ 7.53 (s, 2, 1-H, 6-H), 9.60 (d, 2, $J = 7$ Hz, 3-H, 8-H), 9.65 (d, 2, $J = 7$ Hz, 4-H, 9-H); ir: μ 6.24 (C=C).

Anal. Calcd. for $\text{C}_{12}\text{H}_6\text{Cl}_2\text{N}_2$: C, 57.85; H, 2.43; N, 11.25. Found: C, 57.60; H, 2.53; N, 11.16.

Hydrogenolysis of **11**. Pyrido[3,4-*g*]isoquinoline (5).

A mixture of 1.00 g (0.004 mole) of **11**, 1.64 g (0.02 mole) of sodium acetate, 0.50 g 5% palladium-on-carbon (50% moisture) and 150 ml diglyme (2-methoxyethyl ether) was shaken with hydrogen on a Parr apparatus for 24 hours; hydrogen uptake: 11.6 ; theoretical 8.0 .

The catalyst was filtered and washed with 2 × 25 ml of diglyme. The filtrate and washings were concentrated to dryness and the residue was boiled with 100 ml chloroform. The solution was decolorized, filtered, and concentrated to dryness in vacuo. Recrystallization from heptane gave 0.05 g (7.3%) of a crystalline solid, the infrared spectrum of which was identical to that of the product obtained cyclization of **3**.

N,N'-Bis[2-(dimethoxy)ethyl]-*p*-xylene- α,α' -diamine Dihydrochloride (**12**).

This compound was prepared using the method described above for **3**. An analytical sample melted at 187-195° dec.

Anal. Calcd. for $C_{16}H_{28}N_2O_4 \cdot 2HCl$: C, 49.87; H, 7.88; N, 7.27. Found: C, 50.04; H, 7.85; N, 7.42.

Cyclization of *N,N'*-Bis[2-(dimethoxy)ethyl]-*p*-xylene- α,α' -diamine Dihydrochloride (**12**) to **4** and **5**.

To 75 ml of fuming sulfuric acid (25% SO_3) was added over 10 minutes 10.55 g (0.027) of **12**, the reaction temperature being maintained to 35-40° with a water bath. The mixture was stirred at ambient temperature for 20 hours and poured into 1300 g of iced water. After the pH of the solution was adjusted to 13 with solid potassium hydroxide at 30-60°, the mixture was stirred with seven 350 ml portions of ether for one hour each. The ether extracts were dried (magnesium sulfate) and concentrated to dryness to give the crude product which was boiled with 400 ml of heptane for 3 hours. Cooling for 3 days at room temperature gave 0.35 g of a crude solid which was discarded. Concentration of the heptane filtrate to 250 ml gave, upon standing at room temperature for 18 hours, 0.32 g of a crude solid which was discarded. Further concentration of the heptane filtrate to a volume of 60 ml gave 0.36 g of crude product, recrystallization of which from 5 ml of toluene gave pure **4**, mp 145-148°, lit (5) mp 139-141°; nmr (deuteriochloroform): δ 7.92 (s, 2, 5-H, 6-H); 8.38 (d, J = 3 Hz, 2, 1-H, 10-H); 8.83 (d, J = 3 Hz, 2, 2-H, 9-H); 9.35 (s, 2, 4-H, 7-H); lit (5) (deuteriochloroform): δ signals at 7.82, 8.25, 8.80, 9.17; ir: μ 6.32 (C = N).

Anal. Calcd. for $C_{12}H_8N_2$: C, 79.98; H, 4.48; N, 15.52. Found: C, 79.90; H, 4.43; N, 15.42.

The alkaline aqueous solution resulting from the ether extract was stirred with five 400 ml portions of chloroform for 4 hours each. The combined extracts were dried (magnesium sulfate) and concentrated to dryness in vacuo. The residue was heated with 175 ml of heptane for 3 hours. After the solution was allowed to stand at room temperature for 3 days, a small amount of amorphous material was filtered and discarded. Upon concentration of the filtrate to 45 ml, 0.10 g of **5** was obtained. The ir and nmr spectra of this product were identical to those of the product isolated by cyclization of **3**.

Cyclization of **12** to a Mixture of **4** and **5**.

Treatment of 130 g (0.337 mole) of **12** in 682 ml fuming sulfuric acid (20% SO_3) for 24 hours, pouring the mixture into 7 kg of ice, adjusting the pH to 13 with 3 liters of 50% potassium hydroxide, filtration to remove potassium sulfate and extraction with 4 × 2.5 liters of chloroform gave 12 g of a brown solid. Extraction of the solid with 4 × 1 liter of boiling heptane and concentration of the heptane solution to 2 liters gave 5.1 g (8.4%) of a yellow solid, mp 110-117°. The nmr spectrum of the product was a composite of the spectra of **4** and **5** and indicated the 4:5 ratio as 63:37.

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