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SYNTHETIC APPLICATION OF LITHIATION REACTIONS—XIV
NOVEL SYNTHESIS OF 7,8-DIMETHOXY PHENANTHRIDINE

N. S. NARASIMHAN* and P. S. CHANDRACHOOD
Department of Chemistry, University of Poona, Pune 411 007, India

and

N. R. SHETE
Department of Chemistry, S. P. College, Pune 411 030, India

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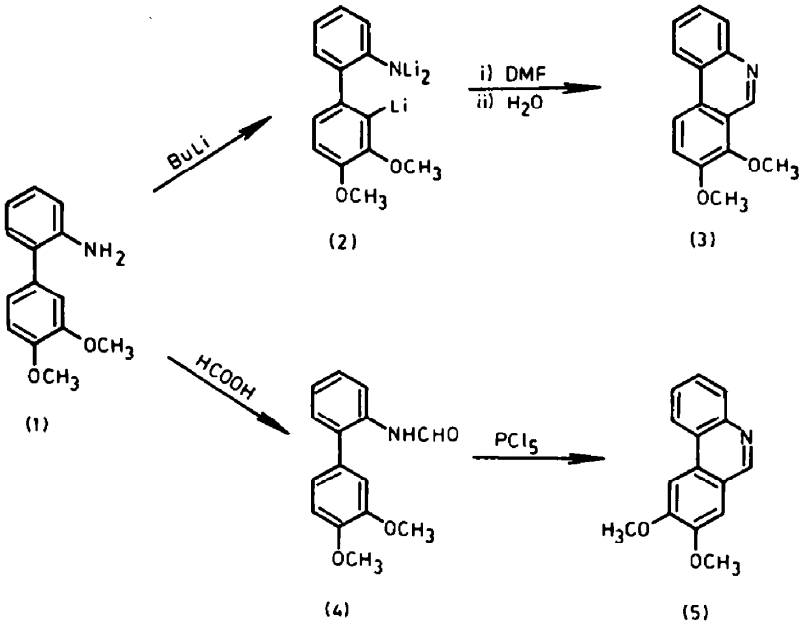
Abstract—The difficultly accessible 7,8-dimethoxy phenanthridine has been synthesised by organolithiation reaction in simple steps and in good yield.

In an earlier paper[1] it was shown that 2-aminobiphenyl was lithiated by BuLi in ether solution at 2′ position. The organolithium compound was further reacted with carbondioxide to furnish phenanthridone, which was reduced with LAH to phenanthridine. We have now achieved a direct synthesis of the phenanthridine by treatment of the organolithium compound with DMF instead of carbondioxide. The reactions represent sequence **1**→**6**→**3** and **1**→**2**→**3** in Schemes 1 and 2 where the OMe groups are replaced by H.

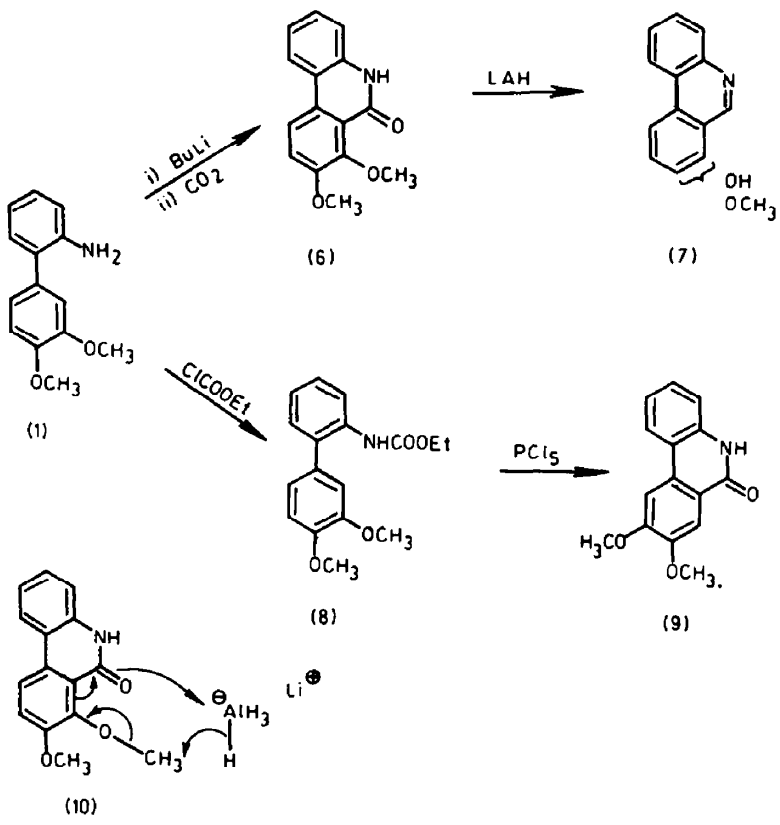
The new phenanthridine synthesis was expected to lead readily to the synthesis of the difficultly accessible 7,8-dimethoxyphenanthridine (**3**) from the readily synthesised 2-amino-3′, 4′-dimethoxybiphenyl (**1**). Thus lithiation of 2-amino-3′, 4′-dimethoxybiphenyl, in analogy with the lithiation of 2-aminobiphenyl, would proceed at 2′ or 6′ position. Further, since the OMe group at 3′ position, by inductive effect would render the 2′ H more acidic than 6′ H, lithiation was expected to proceed at 2′ position, in agreement with the trends in aromatic lithiation reactions.[2] This was indeed realised and 7,8-dimethoxy phenanthridine was obtained by treatment of 2-amino-3′, 4′-dimethoxybiphenyl with BuLi, followed by DMF as shown in Scheme 1.

The structure of the dimethoxy phenanthridine was established by Nuclear Overhauser Effect experiments, which indicated the steric proximity of the H_6 (i.e. of the –CH=N group) with a OMe group. Further the isomeric 8, 9-dimethoxy phenanthridine (**5**) was synthesised (Scheme 1) by converting 2-amino-3′, 4′-dimethoxy biphenyl into the N-formyl derivative (**4**) and cyclising with PCl_5 when the aromatic cyclodehydration occured at the electrophilically more reactive 6′ position. The two compounds were completely different.

In another experiment the organolithium compound was treated with carbon dioxide, when the 7, 8-



Scheme 1.



Scheme 2.

dimethoxy phenanthridone (**6**) was obtained. N-Ethoxy carbonyl derivative **8** of the amine **1** on acid catalysed cyclisation, on the other hand, gave the isomeric 8, 9-dimethoxy phenanthridone **9** (Scheme 2) corresponding to cyclisation at the electrophilically more active 6′ position. Attempts to reduce the 7, 8-dimethoxyphenanthridone by LAH gave a phenanthridine **7** in which, concurrently, one of the OMe groups had also been demethylated. Although it is not known exactly which of the OMe groups is demethylated, on mechanistic grounds **10** it would appear to be the one closer to the amide CO group.

The above experiments bring out the complementary character of the lithiation and acid catalysed reactions for the synthesis of methoxyl substituted phenanthridines.

EXPERIMENTAL

^{1}H NMR spectra were recorded on Perkin-Elmer R-32 90 MHz instrument using TMS as an internal standard. IR spectra were recorded on Perkin–Elmer 337 instrument. UV spectra were recorded on Shimadzu UV 300 instrument. Unless otherwise stated the solvents for NMR, IR and UV are $CDCl_3$, Nujol and MeOH.

(1) *Lithiation of 2-aminobiphenyl and treatment with DMF*

A soln of n-BuLi (0.07 mole, prepared from 1.0 g Li and 9.6 g n-BuBr) in ether (80 ml) was added to a well stirred soln of 2-aminobiphenyl (2.8 g, 0.017 mol) in ether (20 ml) at a moderate rate (in 10 min) at room temp. The mixture became dark green, changed to dark brown and finally to brown with yellow fluorescence (all in 10 mins). It was stirred for 48 hr, when it became reddish brown, and treated with a soln of DMF (5.10 g, 0.07 mol) in ether (10 ml) and, after stirring for 1 more hr decomposed with water (15 ml). The aqueous layer was extracted with ether (3 × 20 ml) and combined with the original. The ether extract was extracted with dil HCl (3 × 20 ml), the acidic extract basified with 2 N NaOH and extracted with ether (2 × 20 ml). Drying over $NaSO_4$ and removal of solvent gave a solid, which on crystallisation from petether furnished phenanthridine (1.83 g, 62%, 92% after taking recovery into consideration), m.p. 104° (lit.[1] m.p. 104°C). Found: C, 87.01; H, 4.96; N, 7.96, $C_{13}H_9N$ Requires; C, 87.12; H, 5.06; N, 7.82% ν_{max} 1630, 1590, 1575, 1460, 1248, 892, 772, 750, 747, 720 cm^{-1}; λ_{max} 214(sh) nm (log ϵ 3.55), 241 nm (log ϵ 3.87), 267 (s) nm (log ϵ 3.12), 286 nm (log ϵ 2.86), 297 nm (log ϵ 2.76); NMR (CCl_4) δ 7.43-8.6 (m, H-8, aromatic protons), 9.11 (s, H-1, -N=CH).

The non basic part of the mixture on hydrolysis with alcoholic HCl and usual work up gave the starting 2-aminobiphenyl (0.85 g, 30%) and some more phenanthridine (0.06 g, 2%).

(2) *Lithiation of 2-amino-3′, 4′-dimethoxybiphenyl and treatment with DMF*

2-Amino-3′, 4′-dimethoxybiphenyl (1.14 g, 0.005 mol) was lithiated with n-BuLi (0.05 mol) as above. A white ppt started appearing, which changed to pale brown and light yellow (all in 15 min). The mixture was stirred for 48 hr, when the ppt became yellow. It was treated with a soln of DMF (0.05 mol) in ether (10 ml). Workup, as above, gave a solid (0.75 g), which was chromatographed on silica gel (20 g) in benzene to yield 7, 8-dimethoxy phenanthridine (0.7 g, 58%, 100% after taking recovery into consideration), m.p. 121° from pet-ether Lit.[3] m.p. 121–122°. (Found: C, 75.12; H, 5.29; N, 5.68 $C_{15}H_{13}NO_2$ Requires: C, 75.30; H, 5.48; N, 5.85%); ν_{max} 1600, 1575, 1525, 1450, 1270, 1065, 995, 765 cm^{-1}. λ_{max} 207.5 nm (log ϵ 3.70), 235 nm (log ϵ 3.56), 260.5 nm (log ϵ 3.77), 307 nm (log ϵ 2.87), 359 nm (log ϵ 2.73). δ 3.99 (s, H-3, $-OCH_3$), 4.08 (s, H-3, $-OCH_3$), 7.48 (d, H-1, J = 9 Hz, H_9), 7.53–8.50 (m, H-5, aromatic protons), 9.58 (s, H-1, -N=CH-). nOe: 9% enhancement was observed for the proton at δ 9.58, when the OMe signal at δ 4.08 was irradiated.

The non basic part of the mixture, on hydrolysis with alcoholic HCl and chromatography of the product over silica gel (15 g) in

benzene, gave in the earlier fractions (500 ml) the starting 2-amino-3', 4'-dimethoxy biphenyl (0.45 g, 40%) and later some more 7, 8-dimethoxyphenanthridine (0.024 g, 2%).

(3) *Lithiation of 2-amino-3', 4'-dimethoxybiphenyl and treatment with carbondioxide*

A soln of n-BuLi (0.07 mol) in ether (75 ml) was added at room temp to a stirred soln of 2-amino-3', 4'-dimethoxy biphenyl (2.2 g, 0.01 mol) in THF (30 ml) during 20 min. The colour of the mixture was green at first, then changed to pale green (15 min) and finally to yellow (30 hr). The mixture was stirred for 30 hr, and poured into a slurry of solid CO_2 in dry ether. After stirring for some time, ether was removed and the residue acidified with HClaq and extracted repeatedly with $CHCl_3$. The $CHCl_3$ extract was washed with water. Drying and removal of solvent afforded a brownish semisolid. The semisolid was dissolved in small amount of $CHCl_3$ and transferred to a column of neutral alumina in benzene. Elution with benzene furnished the starting compound (0.5 g, 23%). Subsequent elution with $CHCl_3$ yielded the **6** (1.1 g, 88% after taking recovery into consideration), m.p. 269°. (Found: C, 70.58; H, 5.13; N, 5.49; $C_{15}H_{13}NO_3$ Requires: C, 70.52; H, 4.81; N, 5.39%); ν_{max} 1660, 3300 cm^{-1}; λ_{max} 264 nm (log ϵ 3.74), 308 nm (log ϵ 4.05), 337 nm (log ϵ 4.12), 353 nm (log ϵ 3.98). NMR spectrum could not be determined as the compound was insoluble in $CDCl_3$ and DMSO.

The acid extract after basification with NaOH gave the starting base (0.6 g). The total base recovered thus was (1.1 g).

(4) *Reduction of 7, 8-dimethoxy phenanthridone with LAH*

7, 8-Dimethoxy phenanthridone (0.2 g) was added to a well stirred suspension of LAH (0.08 g) in ether (100 ml). The mixture was refluxed for 60 hr, cooled and decomposed with water (10 ml). Usual work up yielded **7** (0.12 g, 84%), m.p. 74° from pet-ether (Found: C, 74.51; H, 4.81; N, 6.20; $C_{14}H_{11}NO_2$ Requires: C, 74.65; H, 4.92; N, 6.22%); IR: no bands in the region C=O, OH, NH_2. λ_{max} 260 nm (log ϵ 4.42), 349 nm (log ϵ 4.50), 357 nm (log ϵ 4.51). δ 7.16–7.83 (m, H-4, H_2, H_3, H_9, OH), 8.17 (m, H-2, H_4 and H_1), 8.46 d, H-1, J=8 Hz, H_{10}), 9.17 (s, H-1, H_6).

The neutral part furnished the unreacted phenanthridone (0.042 g).

(5) *Synthesis of 8, 9-dimethoxy phenanthridine*

(i) *N-Formly-2-amino-3', 4'-dimethoxy biphenyl.* 2-Amino-3', 4'-dimethoxybiphenyl (1.0 g) was refluxed with formic acid, (90%, 10 ml) and fused NaOAc (0.5 g) for 3 hr to yield **4** (0.9 g, 83%), m.p. 164° from pet-ether–EtOAc (Found: C, 69.85; H, 5.50; N, 5.25; $C_{15}H_{15}NO_3$ Requires: C, 70.02; H, 5.88; N, 5.44%); ν_{max} 3350, 1660 cm^{-1}.

(ii) *Cyclisation of the N-formylderivative* (**4**). PCl_5 (1.0 g) was added to an ice-cooled soln of the N-formyl derivative (0.5 g) in $CHCl_3$(50 ml). After keeping for 48 hr, the solvent was removed and the mixture decomposed with ice-water. Extraction with ether, drying over Na_2SO_4 and removal of solvent gave the starting compound (0.13 g).

The aqueous layer was basified with N NaOH and extracted with $CHCl_3$. The $CHCl_3$ extract, on drying and removal of solvent gave a compound which was chromatographed over alumina in benzene to give **5** (0.30 g, 64%), m.p. 164° from pet-ether–EtOAc, lit.[3] m.p. 169°. (Found: C, 75.13; H, 5.76; N, 5.70; $C_{15}H_{13}NO_2$ Requires: C, 75.30; H, 5.48; N, 5.85%); IR: no bands in the region C=O, OH, NH_2. λ_{max} 255 nm (log ϵ 4.93), 332 nm (log ϵ 4.59), 348 nm (log ϵ 4.52); δ 3.93 (s, 4.3, OCH_3), 3.98 (s, H-3, OCH_3), 7.17 (s, H-1, H_7), 7.6 (s, H-1, H_{10}), 7.6 to 7.9 (m, H-2, H_2 and H_3), 8.17 (m, H-2, H_1 and H_4), 9.0 (s, H-1, H_6).

(6) *Synthesis of 8, 9-dimethoxyphenanthridone*

(i) *N-Ethoxycarbonyl-2-amino-3', 4'-dimethoxybiphenyl.* To a stirred mixture of 2-amino-3', 4'-dimethoxybiphenyl (0.5 g) in $CHCl_3$ (3 ml) and Na_2CO_3aq (10%, 5 ml), a soln of ethyl chloroformate (2 ml) in $CHCl_3$ (2 ml) was added gradually. The mixture was stirred for 3 hr and decomposed with water. The $CHCl_3$ layer was washed with HCl and water, dried over Na_2SO_4 and evaporated to yield **8** (0.48 g, 70%), m.p. 110° from pet-ether-EtOAc. (Found: C, 68.10; H, 6.10; $C_{17}H_{19}NO_4$ Requires: C, 67.76; H, 6.36%): ν_{max} 1750, 3350 cm^{-1}.

(ii) *Cyclisation of the N-ethoxycarbonyl derivative.* The N-ethoxy carbonyl derivative (0.5 g) was cyclised as before, to give **9** (0.3 g, 60%), m.p. 296° from EtOH. (Found: C, 70.42; H, 5.21; N, 5.30% $C_{15}H_{13}NO_3$ Requires: C, 70.58; H, 5.13; N, 5.49%); ν_{max} 1660, 3300 cm^{-1}. λ_{max} 250 nm (log ϵ 4.48), 265 nm (log ϵ 4.15), 307 nm (log ϵ 3.83), 320 nm (log ϵ 3.80), 336 nm (log ϵ 3.76). NMR spectrum could not be determined as the compound was insoluble in $CDCl_3$ and DMSO.

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