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SYNTHETIC APPLICATION OF LITHIATION REACTIONS—IV*

NOVEL SYNTHESIS OF LINEAR FUROQUINOLINE ALKALOIDS AND A SYNTHESIS OF EDULITINE†

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Abstract—A new synthesis of the linear furoquinoline ring system is described and its applicability to obtain some of the linear furoquinoline alkaloids illustrated. A synthesis of edulitine has also been achieved.

FOUR different routes are available for the synthesis of the alkaloids of the linear furoquinoline group.[1-4] A common feature is that the carbon chain at the 3-position of the quinoline molecule, required for the formation of the furan ring, is incorporated as the quinoline ring is built. This is necessary because such a carbon chain cannot be introduced later exclusively on the quinoline ring at 3-position by electrophilic substitution reactions as the molecule is more reactive in the benzene than in the pyridine ring.

A new and entirely different approach to the synthesis of the linear furoquinoline alkaloids is now described. In this, on a preformed quinoline ring, the necessary side chain at the 3-position was introduced, and subsequently modified into a furan ring. We first describe the synthesis of the parent linear furoquinoline, and later apply the synthesis to furoquinoline alkaloids.

Synthesis of 2,3-*dihydro furo* [2,3-b] *quinoline and its* 2-*methyl derivative.* 2-Ethoxyquinoline lithiates at the 3-position.[5] These organometallic compounds are highly nucleophilic in character and the one derived from 2-ethoxyquinoline was treated with ethylene oxide. The 3-hydroxyethyl derivative obtained, on treatment with HBr furnished 2,3-dihydrofuro [2,3-b] quinoline (IV) $C_{11}H_9ON$, m.p. 122–123°. In another experiment the organometallic intermediate was treated with alkyl bromide. The crude alkyl derivative without purification, was refluxed with HBr to yield the 2-Me derivative VI, $C_{12}H_{11}ON$, m.p. 87°.

Synthesis of linear furoquinoline alkaloids; *dictamnine* XII ($R_1 = R_2 = H$), *pteleine* XII ($R_1 = —OMe$, $R_2 = H$) *and dihydro γ-fagarine* IX ($R_1 = H$, $R_2 = —OMe$). The above synthesis of the linear furoquinoline ring system was next extended to obtain the following alkaloids i.e. dictamnine, pteleine and dihydro γ-fagarine.[6] The starting compounds were 2,4-dimethoxy, 2,4,6-trimethoxy and 2,4-8-trimethoxyquinolines respectively. Of these the dimethoxyquinoline is known.[7] The trimethoxy-

* Part III: N. S. Narasimhan and M. V. Paradkar, *Ind. J. Chem.* 7, 1004 (1969).

† For preliminary communications, see *Chem. Ind.* 831 (1967); 515 (1968)

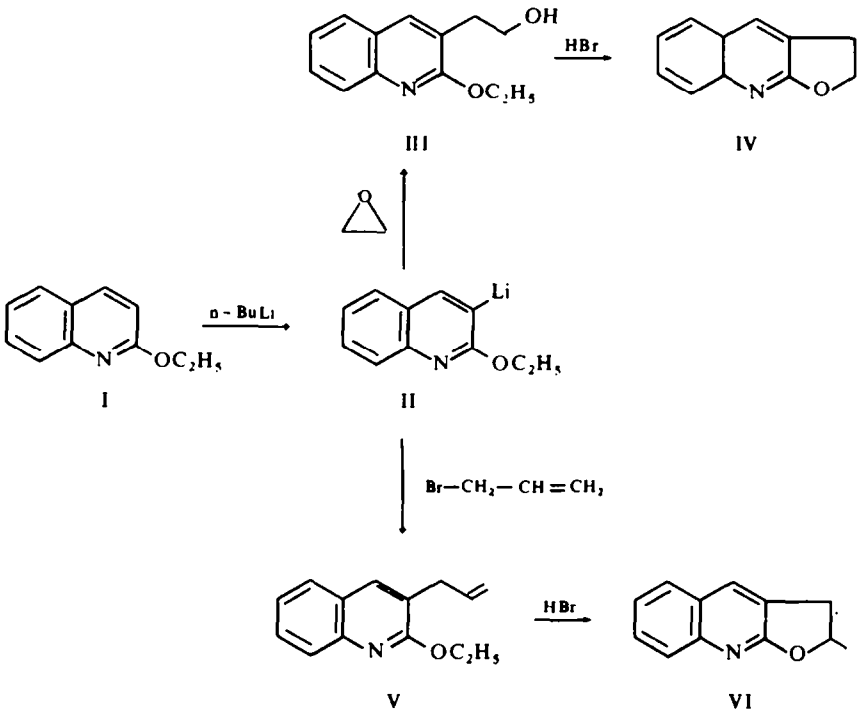

FIG. 1.

quinolines were obtained by treatment of the corresponding 2,4-dichloro 6 (or 8) methoxyquinoline with NaOMe. The 2,4-dichloro-8-methoxyquinoline reported[9] has a m.p. 92°, while our specimen, which has been adequately characterised melts at 137°.

In the next stage, the methoxyquinolines were lithiated with n-BuLi and the methalation mixture treated with ethylene oxide to give the 3-hydroxyethyl derivatives (VIII). The furan ring was then constructed by hydrolysis of VIII with HCl. It was observed that, under mild conditions, the 2-OMe group was hydrolysed selectively, to the hydroxy compound, which then cyclised to the dihydro derivative of the linear isomer IX. In one instance, i.e. the mild hydrolysis of VIII (R_1 = —OMe, R_2 = H), the uncyclised compound X (R_1 = —OMe, R_2 = H) was also isolated. Under more vigorous conditions, both the methoxyls at 2- and 4-positions were hydrolysed, and cyclisation then occurred with the 4-OH group to give the dihydro derivative of the angular isomer XI.[2]

The dihydro derivatives of dictamnine[3] and pteleine[9] have been dehydrogenated to the parent alkaloids.

In the above syntheses, which the yield of the 3-hydroxyethyl derivative (III) from 2-ethoxyquinoline was poor (4%) the yield of the corresponding compound from

* Prof. Y. Kuwayama in a private communication informed us that he has dehydrogenated dihydroteleine to pteleine.

the di- and tri-methoxyquinolines was considerably better, being 66, 28, 15% (78, 68, 30% after taking into account recovery of the starting material). This was presumably due to the greater acidity of the 3H in the quinolines having alkoxyl groups both at 2- and 4-positions than the one having only one alkoxyl group at the 2-position. This results in greater metalation at the 3-position in the relevant di- and tri-methoxyquinolines and improved yields of the 3-hydroxyethyl derivatives. In all the above

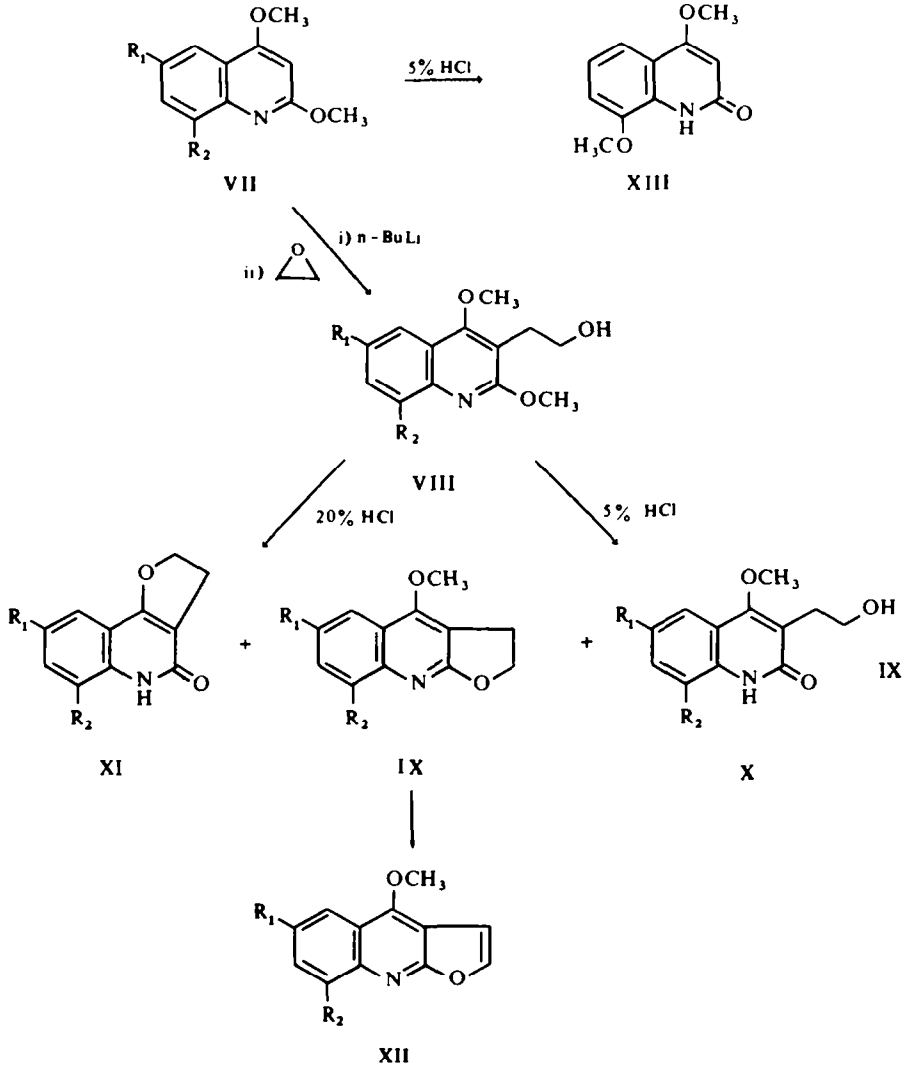

FIG. 2.

syntheses no compound corresponding to metalation at any other positions could be isolated and, therefore, the metalation is fairly selective.

Synthesis of edulitine. Edulitine XIII. $C_{11}H_{11}O_3N$, m.p. 235–236°, the alkaloid from *Casimiroa edulis* Lalve et Lex, has the structure XIII.[10] This was synthesised

by the mild hydrolysis (5% HCl) of 2,4,8-trimethoxyquinoline which had been obtained as an intermediate in the synthesis of dihydro-γ-fagarine.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were measured as nujol mulls and chemical shifts are expressed in ppm downfield from TMS as an internal standard.

2,3-*Dihydro-furo*[2,3-b]*quinoline* (IV). A soln of 2-ethoxyquinoline (8·65 g) in ether (50 ml) was cooled to 0° and treated with n-BuLi (from 1·1 g Li and 8·6 g n-BuBr) in ether. The resulting reddish violet coln was stirred for 1 hr. A cooled soln of ethylene oxide (4 ml) in ether (15 ml) was added and the mixture stirred for 4 hr, left overnight and hydrolysed with water (50 ml). Working up the organic layer gave a dark red coloured liquid (10 g) which was dissolved in HBr (47%, 40 ml) and the clear soln refluxed for 5 hr. On cooling 2-hydroxyquinoline (5 g) separated out. The acid layer was rendered alkaline with $KHCO_3$ and extracted with $CHCl_3$. Removal of solvent gave a semi solid (1·8 g) which on chromatography over basic alumina in benzene followed by crystallisation from hexane furnished IV (0·3 g), m.p. 122–123° (lit. m.p.[11] 122–123°); ν_{max}, 1639, 1587 cm^{-1}; NMR ($CDCl_3$), 3·27 δ (2H t, J = 8 c/s, —C<u>H</u>$_2$—CH_2—O—); 4·62 δ (2H t, J = 8 c/s, —CH_2—C<u>H</u>$_2$—O—); 7–8 δ (5H m, aromatic H). (Found: C, 76·91; H, 5·38. $C_{11}H_9ON$ requires: C, 77·17; H, 5·30%).

2-*Methyl*-2,3-*dihydro-furo*[2,3-b]*quinoline* (VI). Alkylbromide (4·86 g) in ether (20 ml) was added to the metalation mixture of 2-ethoxyquinoline (obtained from 7 g I, 0·88 g Li and 6·85 g n-BuBr) under vigorous stirring. The resulting soln was stirred for 4 hr at room temp, left overnight and poured on crushed ice (100 g). Evaporation of the organic layer gave an amber coloured liquid (8·5 g) which was dissolved in HBr (47%, 21 ml) and refluxed for 6 hr. Usual workup gave 2-hydroxyquinoline (2·5 g) and another product (1·6 g) from acidic filtrate after basification. Chromatography of the latter over basic alumina in benzene gave a white solid from benzene eluates. Crystallisation from ether followed by sublimation *in vacuo* (bath temp 120–125°/2 mm) gave VI (0·31 g), m.p. 87°; ν_{max}, 1626, 1582 cm^{-1}; NMR ($CDCl_3$), 1·49 δ (3H d, J = 7 c/s, —CH_3); 2·5–3·6 δ (2H m, —CH_2—); 4·88 δ (1H m, —CH); 7–8 δ (5H m, aromatic H). (Found: C, 78·20; H, 6·27; N, 7·24. $C_{12}H_{11}ON$ requires: C, 77·81; H, 5·99; N, 7·56%).

2,4-*Dimethoxy*-3-(2-*hydroxyethyl*)*quinoline* VIII (R_1 = R_2 = H). A soln of 2,4-dimethoxyquinoline (8 g) in ether (100 ml) was cooled to 0° and treated with n-BuLi in ether (from 0·93 g Li and 7·3 g n-BuBr). The resulting soln was stirred for 1 hr and treated with ethylene oxide (7 ml) in ether (25 ml). The mixture was stirred for 4 hr, left overnight and hydrolysed with water (50 ml). The residue, obtained from organic layer, on crystallisation from hexane yielded VIII (6·5 g), m.p. 74°; ν_{max}, 3175, 1626, 1605 cm^{-1}; NMR ($CDCl_3$), 2·09 δ (1H S, —OH), 3·01 δ (2H t, J = 7 c/s, benzilic —C<u>H</u>$_2$), 3·85 δ (2H t, partly hidden under methoxyl signal, J = 7 c/s, —CH_2—O—), 3·59 δ (3H S, —OCH_3), 4·07 δ (3H S, —OCH_3), 7·16–8 δ (4H m, aromatic H). (Found: C, 66·88; H, 6·35. $C_{13}H_{15}O_3N$ requires: C, 66·93; H, 6·48%).

From the mother liquor 2,4-dimethoxyquinoline was recovered (1·2 g) after chromatography over basic alumina in benzene.

Dihydrodictamnine IX (R_1 = R_2 = H). The alcohol from the above experiment (0·5 g) was dissolved in HCl (20%, 10 ml) and the clear soln refluxed for ½ hr. The solid, that separated on cooling, was washed with water and crystallised from MeOH to give XI (R_1 = R_2 = H, 0·23 g), m.p. 280–282° (lit. m.p.[2] 280–282°); (Found: C, 70·74; H, 5·16; N, 7·86. $C_{11}H_9O_2N$ requires: C, 70·58; H, 4·85; 7·48%).

The filtrate on neutralisation gave a solid which on crystallisation from hexane furnished IX (0·042 g), m.p. 103–104° (lit. m.p.[3] 103–104° mixed m.p. undepressed), identical in every respect (UV, IR, NMR) with an authentic sample. (Found: C, 71·22; H, 5·65. $C_{12}H_{11}O_2N$ requires: C, 71·62; H, 5·52%).

Dictamnine XII (R_1 = R_2 = H). Dihydrodictamnine (30 mg) was dehydrogenated to dictamnine (15 mg) according to the procedure of Cooke and Haynes.[3]

2,4-6-*Trimethoxyquinoline* VII (R_1 = —OMe, R_2 = H). 2,4-Dichloro-6-methoxyquinoline (3 g) was added to NaOMe (from 2 g Na and 30 ml MeOH), refluxed for 20 hr, cooled and poured in cold water (100 ml). The ppt on crystallisation from hexane followed by sublimation *in vacuo* (bath temp 75–85°/0·4 mm) afforded VII (1·8 g), m.p. 79°; ν_{max}, 1600, 1583, 1245, 1222, 1200 cm^{-1}. (Found: C, 65·54; H, 5·71; N, 6·48. $C_{12}H_{13}O_3N$ requires: C, 65·74; H, 5·98; N, 6·39%).

3(2-*Hydroxyethyl*)-2,4,6-*trimethoxyquinoline* VIII (R_1 = —OMe, R_2 = H). A soln of 2,4,6-trimethoxyquinoline (4·4 g) in ether (100 ml) was cooled to 0° and treated with n-BuLi in ether (from 0·5 g Li and 3·9 g n-BuBr). The red coloured soln was stirred for 3 hr and left overnight at room temp. The resulting brown soln was cooled to −5°, a soln of ethylene oxide (5 ml) in ether (15 ml) added, the mixture stirred

for 3 hr and treated with water (30 ml). The residue (4·9 g), obtained after removal of solvent on chromatography over alumina gave the starting compound i.e. 2,4,6-trimethoxyquinoline (2·6 g) from benzene eluates. Benzene-alcohol (99:1) elution gave a solid which on crystallisation from benzene:hexane provided 3(2-hydroxyethyl)-2,4,6-trimethoxyquinoline (1·46 g), m.p. 107°; ν_{max} 3120 cm^{-1}. (Found: C, 64·18; H, 6·68; N, 5·09. $C_{14}H_{17}O_4N$ requires: C, 63·86; H, 6·51; N, 5·32%).

Dihydropteleine IX (R_1 = —OMe, R_2 = H). The alcohol VIII (0·3 g) was dissolved in HCl (20%, 9 ml) and the clear soln refluxed for ½ hr. Usual workup gave the angular compound XI (R_1 = —OMe, R_2 = H, 0·19 g), m.p. 276–278°; ν_{max} 1656, 1600, 1580 cm^{-1}; (Found: C, 66·58; H, 5·34. $C_{12}H_{11}O_3N$ requires: C, 66·36; H, 5·10%) and another compound (0·070 g) from the filtrate after basification. Chromatography of the latter over alumina in benzene gave a white solid from benzene eluates, which on crystallisation afforded dihydropteleine (0·030 g), m.p. 156–157° (lit. m.p.[12] 156–157°), mixed m.p. with an authentic sample undepressed; ν_{max} 1613, 1575, 1227 cm^{-1}; NMR ($CDCl_3$), 3·55 δ (2H t, J = 8 c/s, benzylic —CH_2—), 4·57 δ (2H t, J = 8 c/s, —$\underline{CH_2}$—O—), 3·88 and 4·16 δ (3H each s, —OMe), 7·68 δ (C_8H q, J = 8·5 and 1·5 c/s), 7·2 δ (C_7H q, J = 8·5 and 3 c/s), 7·3 δ (C_5H m, coupling pattern masked). (Found: C, 67·24; H, 5·9; N, 6·15. $C_{13}H_{13}O_3N$ requires: C, 67·52; H, 5·67; N, 6·06%).

4,6-*Dimethoxy-3(2-hydroxyethyl)-2-quinoline* X (R_1 = —OMe, R_2 = H). A soln of VIII (0·2 g) and HCl (5%, 6 ml) was refluxed for 1 hr, cooled, rendered alkaline with $KHCO_3$ and extracted with $CHCl_3$. Evaporation of the solvent yielded a solid (0·180 g). Chromatographic separation over alumina gave dihydropteleine (0·070 g) from benzene. Benzene:alcohol (95:5) elution, followed by crystallisation from alcohol gave XI (0·070 g) m.p. 183°; ν_{max} 3145, 1661, 1612, 1608, 1053 cm^{-1}. (Found: C, 62·91; H, 6·17; N, 5·65. $C_{13}H_{15}O_4N$ requires: C, 62·64; H, 6·07; N, 5·62%).

2,4-*Dichloro-8-methoxyquinoline*. A mixture of 2,4-dihydroxy-8-methoxyquinoline (10 g) and $POCl_3$ (100 ml) was refluxed for 16 hr, cooled, poured under vigorous stirring over crushed ice (2 kg) and left overnight. The ppt obtained after basification with 5N NaOH was filtered off, washed with water and sublimed (bath temp 150–160°/0·4 mm) to give 2,4-dichloro-8-methoxyquinoline (9·5 g), m.p. 137° (lit. m.p.[8] 92°), ν_{max} 1605, 1282, 1264, 752 cm^{-1}. (Found: C, 52·77; H, 3·37; N, 5·89; Cl, 31·14. $C_{10}H_7ONCl_2$ requires: C, 52·64; H, 3·07; N, 6·14; Cl, 31·15%).

2,4,8-*Trimethoxyquinoline* VII (R_1 = H, R_2 = —OMe). This was prepared from 2,4-dichloro-8-methoxyquinoline (5 g) and NaOMe (from 3·5 g Na and 100 ml MeOH). The products on chromatography over alumina in benzene followed by sublimation (bath temp 125–135°/0·3 mm) furnished VII (3·6 g), m.p. 152°, ν_{max} 1613, 1595, 1265, 1209, 1167 cm^{-1}. (Found: C, 65·92; H, 6·20; N, 6·62. $C_{12}H_{13}O_3N$ requires: C, 65·74; H, 5·98; N, 6·39%).

3(2-*Hydroxyethyl*)-2,4,8-*trimethoxyquinoline* VIII (R_1 = H, R_2 = —OMe). A soln of n-BuLi in ether (from 0·60 g Li in 50 ml ether and 4·8 g n-BuBr in 20 ml ether) was added to a cooled soln of 2,4,8-trimethoxyquinoline (4·4 g) in THF (100 ml) at 0°. The colour changed through yellow-red-purple and finally dark violet. The mixture was stirred for 3 hr and left overnight at room temp. The resulting mixture was cooled to −5° and treated with a soln of ethylene oxide (5 ml) in ether (15 ml). The colour changed from violet-reddish white and finally a white ppt appeared at the end of 2·5 hr. After hydrolysis with water a residue was obtained (5 g) from the organic layer. Separation on alumina column gave 2,4,8-trimethoxyquinoline (2·2 g) from the benzene fraction. Further elution with $CHCl_3$–benzene (50:50) gave another solid which on crystallisation from benzene:hexane gave VIII (0·8 g), m.p. 120°. (Found: C, 63·90; H, 6·51; N, 5·50. $C_{14}H_{17}O_4N$ requires: C, 63·86; H, 6·51; N, 5·32%).

Dihydro-γ-fargarine IX (R_1 = H, R_2 = —OMe). A soln of VIII (R_1 = H, R_2 = —OMe, 0·2 g) in HCl (5%, 6 ml) was refluxed for 1 hr, yielding after following the usual workup a solid (0·190 g). Separation by chromatography on alumina yielded from benzene:$CHCl_3$ (95:5) a solid which on sublimation (bath temp 175–180°/0·4 mm) furnished dihydro-γ-fagrine (0·075 g), m.p. 168° (lit. m.p.[2] 168–170°), having identical UV, IR and NMR values as reported. (Found: C, 67·14; H, 6·01; N, 6·35. $C_{13}H_{13}O_3N$ requires: C, 67·52; H, 5·67; N, 6·06%). Further elution with $CHCl_3$ gave another solid (0·085 g) which on crystallisation from EtOH afforded XI (R_1 = H, R_2 = —OMe) m.p. 216° (lit. m.p.[2] 219–220°). (Found: C, 66·68; H, 5·28; N, 6·64. $C_{12}H_{11}O_3N$ requires: C, 66·35; H, 5·10; N, 6·45%).

Edulitine XIII. A soln of 2,4,8-trimethoxyquinoline (0·20 g) in HCl (5%, 6 ml) was refluxed for 1 hr, cooled, basified and extracted with $CHCl_3$. Evaporation of the solvent gave a solid (0·190 g) which was chromatographed over alumina. The benzene fraction yielded the starting material (0·090 g) while benzene:$CHCl_3$ (90:10) gave another solid (0·090 g). The latter on crystallisation from EtOAc furnished XIII, m.p. 234° (lit. m.p.[13] 235–236°); ν_{max} 1645, 1620, 1590 cm^{-1}; NMR ($CDCl_3$ + CD_3SOCD_3): 3·98 δ (6H S, —OCH_3), 5·98 δ (C_3H s), 7·5 δ (C_5H q, J = 7·5 and 3 c/s), 7·16 δ (C_6H apparent triplet, J = 7·5

c/s), 7·08 δ (C_7H q, J = 7.5 and 3 c/s). (Found: C, 64·06; H, 5·41; N, 6·44. $C_{11}H_{11}O_3N$ requires: C, 64·38; H, 5·40; N, 6·83%).

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