SYNTHESIS OF 9-METHOXY-1,6-DIAZAPHENALENE

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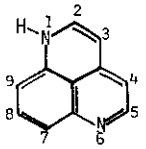
Abstract -- A new entry into the 1,6-diazaphenalene ring system via carbonylation of the anion derived from 4-methyl-5-amino-6-methoxyquinoline 6 is described. This method permits the preparation of 1,6-diazaphenalene derivatives not easily accessible through substitution reactions on the parent heterocycle.

Recently we reported the synthesis of the new heterocycle 1,6-diazaphenalene 1.[1] Interest in this molecule stems from the desire to utilize it as a template for the construction of potential antimalarials related to the 8-aminoquinolines. Since the placement of a methoxy group at C-6 of the 8-aminoquinolines yields compounds many times more active than the unsubstituted derivatives,[2] we sought to prepare the 9-methoxy derivative of 1,6-diazaphenalene 2 with the hope of obtaining enhanced antimalarial activity.



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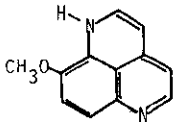

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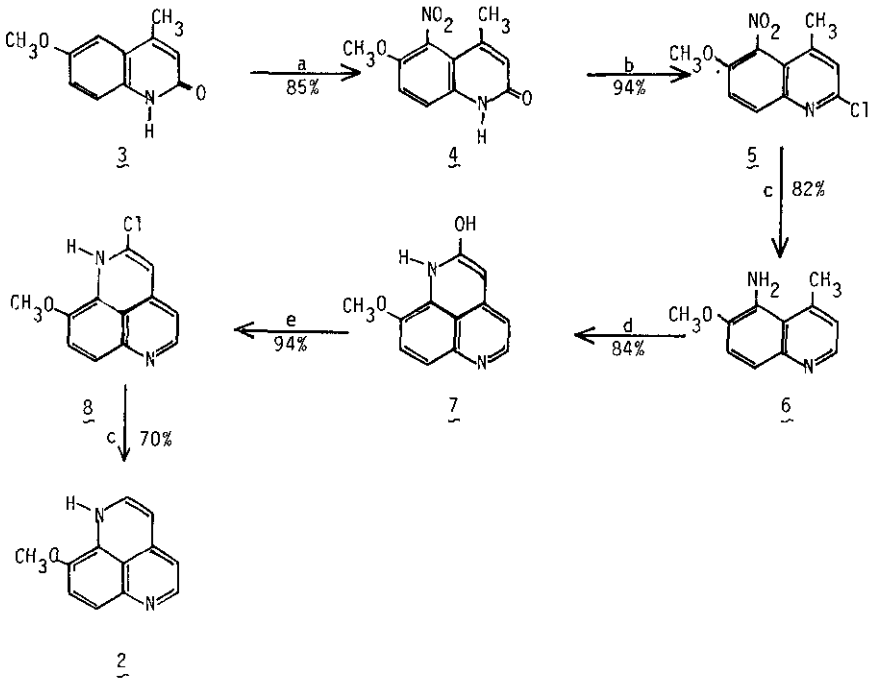
Although the diazaphenalene 1 undergoes electrophilic substitution primarily at the 3- and 7-positions,[3] the inherent difficulties associated with the direct incorporation of a methoxyl function into an aromatic ring prompted the search for an alternate route to substituted 1,6-diazaphenalenes. It seemed particularly attractive to prepare 2 from a suitably substituted quinoline derivative due to the extensive literature available, as regards the chemistry of these heterocycles. The synthesis of the nitroquinoline 4 has been described,[4] and this compound appeared to be an excellent intermediate since the methoxy group and nitrogen functions are in the necessary juxtaposition. The acidic methyl group at the 4-position, moreover, could be employed for one-carbon homologation, followed by cyclization to form the desired tricyclic system.

Results of this approach are outlined in the following Scheme:



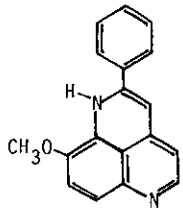
a KNO$_3$, H$_2$SO$_4$, b POCl$_3$, c H$_2$NNH$_2$, Pd/C, EtOH, d 2LDA, CO$_2$, e POCl$_3$.

Nitration of 2-hydroxy-6-methoxylepidine 3,[5] according to the published procedure, ("nitrous vapours") was successful on a small scale, but was unsuitable for the preparation of large quantities of 4. It was found that nitration of 3 with potassium nitrate/sulfuric acid, a procedure which has been effective for the nitration of several similar quinoline derivatives,[6] could be carried out efficiently at the 100 gram level. The nitroquinoline 4 was readily converted into the 2-chloro derivative 5[7] on treatment with phosphorous oxychloride. Hydrogenolysis of the chlorine atom with concomitant reduction of the nitro group was best performed with palladium on carbon, and hydrazine in refluxing ethanol.[8] This gave the aminoquinoline 6 in good yield.[9] Construction of the third ring was considered the key step in the synthetic plan, and was accomplished by generation of the dianion of 6 with two equivalents of LDA[10] followed by carbonylation. From this sequence the tricyclic lactam 7 was isolated in good yield.[11] This material was converted into the 2-chloro-1,6-diazaphenalene 8 with hot phosphorous oxychloride.[12] Removal of the chlorine atom was again performed using palladium

on carbon/hydrazine in refluxing ethanol to provide 9-methoxyl-6-diazaphenalene 2.[13]

The properties of 2 are similar to those reported for the parent heterocycle 1 (polar molecule, low solubility in common organic solvents) with the exception of the proton nmr spectrum. Prototropic shift of the N-H proton in 1 to the pyridine nitrogen results in generation of a molecule of identical structure to the parent, thus imparting a pseudo plane of symmetry to 1 and simplifying the nmr spectrum (only four C-H signals).[1] Incorporation of the methoxy group into 2, however, results in a loss of symmetry for this compound; one observes an nmr spectrum consisting of six doublets, as would be expected.

The successful construction of the tricyclic system of 2 *via* the dianion of 6 prompted an examination of the reactivity of this species toward other electrophiles. In this regard, 6 was stirred with two equivalents of LDA, followed by addition of ethyl benzoate to furnish the 2-phenyl derivative 9[14], while the corresponding reaction of the dianion with carbon disulfide gave the thiol derivative 10[15]. The yields of these reactions were 41% and 64%, respectively, and have not been maximized.



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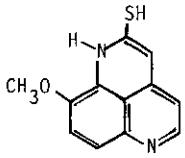

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In conclusion, this method *via* the dianion of 6 provides access to a host of substituted 1,6-diazaphenalenes not easily accessible through simple electrophilic substitution reactions on the parent heterocycle. Further work with regard to the chemistry of these 1,6-diazaphenalenes, as well as the scope of the reaction of the dianion with electrophiles is in progress, and will be reported in due course.

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7. 5: mp 134-136 °C; ir (KBr) 1620, 1530, 1260, and 1100 cm^{-1}; nmr ($CDCl_3$) δ 2.48 (s, 3H), 4.00 (s, 3H), 7.18 (s, 1H), 7.47 (d, 1H, J=8Hz), 7.98 (d, 1H, J=8Hz); mass spectrum (C.I., CH_4), 253, (M+1, 100).

8. W. L. Mosby, Chem. Ind., 1959, 1348.

9. 6: mp 98-100 °C, ir(KBr) 3420, 3340, 1620, 1250 cm^{-1}; nmr ($CDCl_3$) δ 2.99 (s, 3H), 3.98 (s, 3H), 4.55 (s, 2H), 6.97 (d, 1H, J=6Hz), 7.40 (d, 1H, J=8Hz), 7.58 (d, 1H, J=8Hz), 8.57 (d, 1H, J=6Hz); mass spectrum (C.I., CH_4) 189, (M+1, 100).

10. The procedure used was that of Uskokovic for the generation of 6-methoxylepidyllithium; J. Gutzwiller and M. R. Uskokovic, J. Am. Chem. Soc., 100, 1978, 576.

11. 7: mp 253-255 °C, ir(KBr) 3230, 1640, 1580, 1250 cm^{-1}; nmr (DMSO-d_6) δ 3.88 (s, 3H), 5.32 (s, 1H), 5.62 (d, 1H, J=7Hz), 6.55 (d, 1H, J=8Hz), 7.01 (d, 1H, J=7Hz), 7.10 (d, 1H, J=8Hz); mass spectrum (C.I., CH_4) 215 (M+1, 100).

12. 8: mp 228-232 °C, ir(KBr) 3240, 1620, 1540, 1280, 1250, 1120 cm^{-1}; nmr (DMSO-d_6), δ 3.82 (s, 3H), 5.70 (d, 1H, J=7Hz), 6.25 (s, 1H), 6.61 (d, 1H, J=8Hz), 7.04 (d, 1H, J=7Hz) 7.12 (d, 1H, J=8Hz); mass spectrum (C.I., CH_4) 233 (M+1, 100).

13. 2: mp 192-194 °C, ir (KBr) 1600, 1550, 1330, 1220 cm^{-1}; nmr (DMSO-d_6), δ 3.81 (s, 3H), 5.82 (d, 1H, J=6Hz), 5.97 (d, 1H, J=6Hz), 6.78 (d, 1H, J=8Hz), 7.18 (2d, 2H, superimposed), 7.65 (d, 1H, J=6Hz); mass spectrum (C.I., CH_4) 199 (M+1, 100).

14. 9: mp 184 °C, ir(KBr) 2900, 1600, 1530, 1430, 1340, 1270, 1220 cm^{-1}; nmr ($CDCl_3$), δ 3.92 (s, 3H), 6.08 (s, 1H), 6.16 (d, 1H, J=5 Hz), 7.10-7.80 (m, 7H), 7.92 (d, 1H, J=5 Hz); mass spectrum (C.I., CH_4) 275 (M+1, 100).

15. 10: mp 204-207°C, ir(KBr) 3200, 1630, 1600, 1550, 1100, 930 cm^{-1}; nmr (DMSO - d_6) δ 3.92 (s, 3H), 5.85 (d, 1H, J=6Hz), 6.13 (s, 1H), 6.86 (d, 1H, J=8 Hz), 7.30-7.60 (m, 2H); mass spectrum (C.I., NH_3) 231 (M+1, 100).

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