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NOVEL SYNTHESES OF THE METHOXY ISOQUINOLINES AND ISOCOUMARINS

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A recent publication by Hauser and coworkers (1) on the lithiation of a few ring substituted N-N dimethyl benzyl amines prompts us to publish our own results in this field. We have been studying (2) the lithiation of the parent compound and its methoxy derivatives, to obtain the corresponding isoquinolines. Our results briefly are as follows.

Ortho, meta and para methoxy N-N-dimethyl benzylamines were lithiated with n-butyl lithium in ether. In the first instance, to fix up the position of lithiation, the metalation mixture was treated with benzophenone. In the case of the ortho compound, the reaction took a complex course and no useful result was obtained. However in the case of the meta and para compounds the corresponding benzhydrols $C_{23}H_{25}O_2N$*, I- m.p. 106° (lit. m.p. 104-104.5°(1)) and II - m.p. 130° (lit. m.p. 129-129.5°(1)) were obtained in good yields, indicating that lithiation occured ortho to the dimethyl amino methyl side chain. In order to obtain the isoquinolines then, the metalation mixture, in the above cases, was treated with ethylene oxide. Further work up,according to the procedure of Narasimhan and Ranade (2) then furnished the

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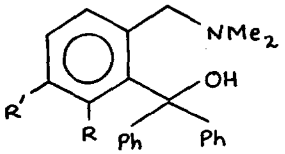
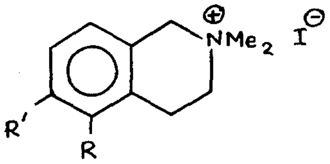
* The compounds reported in this communication have satisfactory elemental analysis and spectral (I.R. and N.M.R.) data.

N-N dimethyl tetrahydro isoquinolinium iodides $C_{12}H_{18}ONI$, III - m.p. 234-235° (lit. m.p. 229° (3a) and 239° (3b)) and IV - m.p. 180° (lit. m.p. 174° (4)).



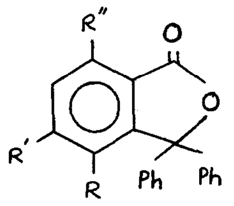
I R = OMe, R' = H
II R = H R' = OMe



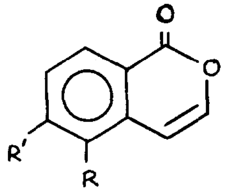
III R = OMe,R' = H
IV R = H, R' = OMe

It may be mentioned that the former (III) is indeed not readily available by the acid catalysed methods.

In a related work i.e. syntheses of methoxy isocoumarins, we have also studied the lithiation of ortho, meta and para methoxy N-methyl benzamides. Hauser and coworkers (5) have observed that in the lithiation of N-methyl benzamide, metalation proceeded at the ortho position. In our compounds there were two groups, methoxy and amide, which were both capable of controlling the position of lithiation. In the first instance, to fix up the position of lithiation, the metalation mixture was treated with benzophenone. In the case of the meta and para methoxy compounds, the lactones $C_{21}H_{16}O_3$, V - m.p. 226° and VI - m.p. 154° (which were obviously formed through the corresponding benzhydrols) were obtained consistently in good yields. In the case of the ortho methoxy compound, complications were encountered, although the lactone $C_{21}H_{16}O_3$, VII - m.p. 171° was obtained, in a few experiments, in comparatively poor yield. The results however clearly indicated that in the meta and para methoxy N-methyl benzamides, the metalation was occurring predominantly at the ortho position with respect to the amide group. In order to get the methoxy isocoumarins then, the corresponding metalation mixture, from the lithiation of meta and para methoxy compounds, was treated with ethylene oxide. Working up the reaction mixture, 5 - methoxy dihydro isocoumarin $C_{10}H_{10}O_3$, m.p. 82°, and 6-methoxy dihydro isocoumarin $C_{10}H_{10}O_3$, m.p. 68° (lit. m.p. 68° (6)), were obtained in good yields. Bromination with N-bromosuccinimide, followed by dehydrohalogenation with triethylamine furnished the methoxy isocoumarins $C_{10}H_8O_3$, VIII - m.p. 107-108° and IX - m.p. 95-96° (lit. m.p. 98° (6).



V R = OMe, R' = R" = H
VI R'= OMe, R = R" = H
VII R"= OMe, R = R' = H



VIII R = OMe,R' = H
IX R'= OMe, R = H

Again it may be noted that 5 - methoxy isocoumarin (VIII) is not available by the usual procedures and has indeed been obtained for the first time.

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