SYNTHESIS OF 3-METHYL ISOQUINOLINES

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This paper is concerned with a study of the limitations and usefulness of a novel method developed by Bruckner and co-workers (1) for the synthesis of 3-methyl isoquinolines. Bruckner and co-workers have applied the method only to propenylbenzenes derived from safrole and eugenol. The scheme of work in the present study is shown in Chart I. In the group of compounds employed, poor yields were obtained in the conversion of allylphenols to propenylphenols from which, in turn, pseudonitrosites were formed only in low yields. The study was therefore conducted with the O-methyl ethers (IV) of the allylphenols, which could be transformed in high yield to propenylanisoles (V) by treatment with alkali.

All the propenyl compounds used in this study have a methoxy group ortho to the propenyl side chain. There were marked variations in the yield of pseudonitrosites (Table I), depending on the position of the third substituent on the benzene ring. Thus 2-methoxy-3-methyl-, 2-methoxy-3-chloro-, and 2,3-dimethoxy-propenylbenzenes gave low yields of the pseudonitrosites in comparison with the excellent yields obtained with 2-methoxy-, 2-methoxy-5-methyl-, 2-methoxy-5-chloro-, and 2,5-dimethoxy-propenylbenzenes. The mechanism of addition of dinitrogen tetroxide to olefins has been clearly elucidated by the recent work of Levy and co-workers (2). It has been suggested that the additions are polar and involve the initial attack of the electrophilic nitrogen of the nitro group to the activated double bond. If the mechanism of addition of nitrogen trioxide is formulated as shown below, the formation of the pseudonitrosites should be facilitated by electron release to the β-carbon atom.

$$\begin{align*}
\text{H}_3\text{C} & \\
\text{X} & \\
\text{CH} & \\
\text{CH} & \\
\text{O} & \\
\text{N} & \\
\text{O} & \\
\end{align*}$$

It is possible that steric interference of the third substituent [X] with the methoxyl group inhibits electron release from the latter, slowing down the addition of nitrogen trioxide, with the result that alternate reactions like polymerization predominate.

The pseudonitrosites were smoothly transformed to the acetoxy nitro compounds (VII) by acetic anhydride and sulfuric acid. Except for α-(2-methoxy-5-chlorophenyl)-α-acetoxy-β-nitropropane (VIIc) and α-2-(1-methoxynaphthyl)
α-acetoxy-β-nitropropane all of the acetoxy nitro compounds encountered in this series were syrupy oils which could not be induced to crystallize and were used as such for the next stage. The acetoxy nitro compounds were reduced at a mercury cathode in satisfactory yields to α-aryl-β-acetylamino-3-propanols (VIII)
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and the latter cyclized to 1,3-dimethylisoquinolines by treatment with phosphorus oxychloride.

The product obtained by cyclization of $\alpha$-(2,5-dimethoxyphenyl)-$\beta$-acetylaminopropanol (VIIIId) displayed anomalous characteristics. Solutions of this substance in benzene, ether, or alcohol displayed a marked blue fluorescence when exposed to bright light. The hydrochloride was colored yellow and solutions of the base in mineral acid were deeply fluorescent. An independent synthesis according to the scheme shown below proved however that the product was indeed

\[ \text{Fig. 1. Ultraviolet Absorption Spectra. A. 1,3-Dimethyl-5,8-dimethoxyisoquinoline; B. 1,3-Dimethyl-5-methoxybenzo[g]isoquinoline.} \]

1,3-dimethyl-5,8-dimethoxyisoquinoline. This isoquinoline is an oil which takes up water on exposure to air with remarkable facility, forming a crystalline monohydrate, m.p. 70°. The ultraviolet absorption spectrum of 1,3-dimethyl-5,8-dimethoxyisoquinoline is recorded in Fig. 1.

\[ \begin{align*}
\text{CH}_3O & \quad \text{CH}_2 \quad \text{CHCH}_3 \quad \text{POCl}_3 \quad \text{Pd-C} \\
\text{CH}_3O & \quad \text{CH}_2 \quad \text{C}--\text{CH}_3
\end{align*} \]
The cyclization of α-2-(1-methoxynaphthyl)-β-acetylamino propanol yielded only 1,3-dimethyl-5-methoxybenz[g]isoquinoline. The structure assigned to this product is confirmed by the absorption spectrum which, as is to be expected (3), shows a striking similarity to that of anthracene (4). All the absorption maxima however occur at longer wave lengths than in the case of anthracene. In the absence of absorption data on the parent member of the series, benz[g]isoquinoline, it is not possible to say whether the shift of absorption maxima to longer wave lengths is caused merely by the substitution of an azomethine linkage for an ethylenic group in anthracene or by the further presence of methoxy and methyl groups in the compound under study.

The α-aryl-β-acetylamino propanols (VIII) were converted by hydrolysis with methanolic hydrochloric acid to the amine hydrochlorides of general formula X. These amines may be considered to be nuclear substituted derivatives of the therapeutically useful sympathomimetic amine Propadrine (5). One of these

| TABLE I |
| ALLYLANISOLE (IV), PROPENYLANISOLE (V), AND PSEUDONITROSITES OF THE LATTER (VI) |

<table>
<thead>
<tr>
<th></th>
<th>IV</th>
<th>R₁</th>
<th>R₂</th>
<th>B.P., °C./MM.</th>
<th>nₒ¹⁰</th>
<th>nₒ₀¹⁰</th>
<th>B.P., °C.</th>
<th>M.P., °C.</th>
<th>Yield, %</th>
<th>Calc'd</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>H</td>
<td>85/11</td>
<td>1.525</td>
<td>104/13</td>
<td>1.56</td>
<td>83</td>
<td>130</td>
<td>12.5</td>
<td>12.42</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>H</td>
<td>CH₃</td>
<td>106/14</td>
<td>1.525</td>
<td>118/16</td>
<td>1.547</td>
<td>58</td>
<td>132</td>
<td>11.76</td>
<td>11.89</td>
<td></td>
</tr>
<tr>
<td>c</td>
<td>H</td>
<td>CI</td>
<td>135/25</td>
<td>1.543</td>
<td>135/19</td>
<td>1.566</td>
<td>64</td>
<td>116</td>
<td>10.83</td>
<td>10.92</td>
<td></td>
</tr>
<tr>
<td>e</td>
<td>CH₃</td>
<td>H</td>
<td>98/16</td>
<td>1.518</td>
<td>95/14</td>
<td>1.533</td>
<td>20</td>
<td>124</td>
<td>11.76</td>
<td>11.87</td>
<td></td>
</tr>
<tr>
<td>f</td>
<td>Cl</td>
<td>H</td>
<td>95/16</td>
<td>1.536</td>
<td>108/11</td>
<td>1.552</td>
<td>21</td>
<td>120</td>
<td>10.83</td>
<td>10.88</td>
<td></td>
</tr>
<tr>
<td>g</td>
<td>OCH₃</td>
<td>H</td>
<td>120/13</td>
<td>1.525</td>
<td>130/13</td>
<td>1.552</td>
<td>21</td>
<td>126</td>
<td>11.03</td>
<td>10.78</td>
<td></td>
</tr>
</tbody>
</table>

* Previously reported (12).

amines, α-(2,5-dimethoxyphenyl)-β-aminopropanol has been prepared earlier by an alternate route (6). The hydrochloride and the diacetate of this compound have been reported to melt at 215° and 119–120° respectively. The amino propanol prepared by us yields a hydrochloride and a diacetate melting at 176° and 98–100° respectively. The differences are evidently due to the fact that the amino propanols prepared by different routes differ in configuration.

EXPERIMENTAL

Procedures for the preparation of 1,3-dimethyl-5,8-dimethoxyisoquinoline and 1,3-dimethyl-5-methoxybenz[g]isoquinoline are described. In other cases employing the same route similar procedures were followed and physical constants and analytical data for the intermediates and final products are recorded in the Tables.

1,3-Dimethyl-5,8-dimethoxyisoquinoline (IXd). 2,5-Dimethoxypropenylbenzene (Vd). This substance was obtained by treatment of 2,5-dimethoxyallylbenzene (7) with a solution of potassium hydroxide in ethylene glycol at 170–178°, until the product attained a constant refractive index. Three hours of heating was adequate for the purpose, b.p. 126°/13 mm.; nₒ²⁰ 1.586; yield, 85%.
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2,5-Dimethoxypropenylbenzene pseudonitrosite (VIId). Erratic results were obtained by following the Bruckner procedure (1) in the addition of nitrogen trioxide, when working with propenyl compounds in amounts of about 20 g. Consistent and reproducible results were obtained by conducting the experiments in several 1-g. batches.

A solution of 1 g. of the freshly distilled 2,5-dimethoxypropenylbenzene in 10 ml. of ether was treated with a solution of sodium nitrite (21 g.) in 8 ml. of water. Then 10 ml. of 4 N sulfuric acid was added dropwise during 20 minutes. The solution turned green and then yellow and a white crystalline solid separated. After leaving in the ice chest overnight, the precipitate was filtered, washed with ether, then water, and dried in air. Twenty such experiments run simultaneously yielded 18 g. of the pseudonitrosite, m.p. 130° (decomp.).

**TABLE II**

<table>
<thead>
<tr>
<th>VIII</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>M.P., °C.</th>
<th>RECRYSTALIZED FROM</th>
<th>YIELD, %</th>
<th>N</th>
<th>Calc'd</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>H</td>
<td>174</td>
<td>Toluene</td>
<td>76</td>
<td></td>
<td>6.28</td>
<td>6.21</td>
</tr>
<tr>
<td>b</td>
<td>H</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>135</td>
<td>Benzene</td>
<td>41</td>
<td></td>
<td>5.91</td>
<td>5.95</td>
</tr>
<tr>
<td>c</td>
<td>H</td>
<td>Cl</td>
<td>204</td>
<td>Alcohol</td>
<td>56</td>
<td></td>
<td>5.44</td>
<td>5.28</td>
</tr>
<tr>
<td>e</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>H</td>
<td>84</td>
<td>Benzene</td>
<td>49</td>
<td></td>
<td>5.91</td>
<td>5.87</td>
</tr>
<tr>
<td>f</td>
<td>Cl</td>
<td>H</td>
<td>95</td>
<td>Benzene</td>
<td>43</td>
<td></td>
<td>5.44</td>
<td>5.45</td>
</tr>
<tr>
<td>g</td>
<td>OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>H</td>
<td>Oil</td>
<td>—</td>
<td>63</td>
<td></td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**Acetylation** of the above compound with acetic anhydride in pyridine at room temperature yielded α-(2,5-dimethoxyphenyl)-a-acetoxy-β-acetylamino propane, melting at 98-100° after recrystallization from benzene.
1,8-Dimethyl-5,8-dimethoxyisoquinoline (IXd). A solution of 1 g. of the acetylamino compound in 10 ml. of dry toluene was treated with 3 ml. of phosphorus oxychloride and refluxed for 75 minutes, with exclusion of moisture. The solution was then poured into ice water and the excess phosphorus oxychloride was decomposed by gentle warming on a water-bath. A fluorescent, orange-yellow solution was obtained, which was cooled strongly in ice and basified with sodium hydroxide solution. The isoquinoline was extracted with ether and the ether extract was dried over potassium carbonate. Removal of the ether yielded 0.75 g. of a thick oil, which was dissolved in dry benzene and passed through a column of alumina (30 g.). On washing the column with benzene a yellow zone moved rapidly into the filtrate. This fraction of the eluate on removal of benzene yielded 0.65 g. of a pale yellow oil, which solidified on rubbing. Recrystallization from petroleum ether yielded pale yellow silky needles melting at 70°.

**TABLE III**

1,3-Dimethylisoquinolines (IX)

<table>
<thead>
<tr>
<th>IX</th>
<th>R₁</th>
<th>R₂</th>
<th>YIELD, %</th>
<th>HYDROCHLORIDE</th>
<th>PICROLONATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>a²</td>
<td>H</td>
<td>H</td>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>H</td>
<td>CH₃</td>
<td>49</td>
<td>174</td>
<td></td>
</tr>
<tr>
<td>c</td>
<td>H</td>
<td>Cl</td>
<td>41</td>
<td>217</td>
<td>220</td>
</tr>
<tr>
<td>e</td>
<td>CH₃</td>
<td>H</td>
<td>53</td>
<td>220</td>
<td>242</td>
</tr>
<tr>
<td>f</td>
<td>Cl</td>
<td>H</td>
<td>50</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td>g</td>
<td>OCH₃</td>
<td>H</td>
<td>57</td>
<td>212</td>
<td>238</td>
</tr>
</tbody>
</table>

² The free base crystallized from dilute alcohol melted at 124°. Calc'd for C₁₂H₁₃NO: N, 7.48. Found: N, 7.37. Other isoquinolines listed in this table were oils. ³ Yield based on hydrochlorides. ⁴ The hydrochlorides were all crystallized from an absolute alcohol-ether mixture. ⁵ The picrolonates were crystallized from alcohol. ⁶ The hydrochloride was extremely hygroscopic.

Alternate synthesis of 1,8-dimethyl-5,8-dimethoxyisoquinoline. β-2,5-dimethoxyphenylisopropylamine was prepared by a different route than that reported by Baltzly and Buck (8) in better over-all yield, starting from 2,5-dimethoxybenzaldehyde (9).
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α-Methyl-β-2,5-dimethoxyphenylacrylic acid. A mixture of 25 g. of 2,5-dimethoxybenzaldehyde, 20 g. of propionic anhydride, and 15 g. of freshly fused sodium propionate was heated for 48 hours at 140-150°. The mixture after cooling was treated with 300 ml. of 4 N sodium hydroxide solution, heated to boiling, cooled, and extracted with benzene to remove unchanged 2,5-dimethoxybenzaldehyde, and the stilbene. Neutralization of the alkaline solution yielded 20 g. of the acid which melted at 114° after one crystallization from dilute alcohol.

Anal. Calc'd for C₁₂H₁₄O₃: C, 64.86; H, 6.34.
Found: C, 64.52; H, 5.88.

α-Methyl-β-2,5-diethoxyphenylpropionic acid. This was obtained by reduction of the above acrylic acid with sodium amalgam in nearly quantitative yield. The product melted at 61-62°. (Cf. Ref. 8, m.p. 59.5°).

α-Methyl-β-2,5-dimethoxyphenylpropionamide. Baltzly and Buck (8) have made this by passing dry ammonia gas into the molten acid. The following procedure gives better results.

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>M.P., °C.</th>
<th>N</th>
<th>M.P., °C.</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Hydrochloride</td>
<td>Calc'd</td>
<td>Found</td>
<td>Calc'd</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>156</td>
<td>6.45</td>
<td>6.77</td>
<td>122</td>
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<tr>
<td>H</td>
<td>CH₃</td>
<td>182</td>
<td>6.05</td>
<td>5.72</td>
<td>166</td>
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<tr>
<td>H</td>
<td>Cl</td>
<td>186</td>
<td>5.56</td>
<td>5.25</td>
<td>208</td>
</tr>
<tr>
<td>H</td>
<td>OCH₃</td>
<td>174</td>
<td>5.66</td>
<td>5.44</td>
<td>177</td>
</tr>
<tr>
<td>CH₃</td>
<td>H</td>
<td>167</td>
<td>6.05</td>
<td>5.71</td>
<td>122</td>
</tr>
<tr>
<td>Cl</td>
<td>H</td>
<td>176</td>
<td>5.56</td>
<td>5.25</td>
<td>196</td>
</tr>
<tr>
<td>OCH₃</td>
<td>H</td>
<td>194</td>
<td>5.66</td>
<td>5.43</td>
<td>196</td>
</tr>
</tbody>
</table>

Crystallized from an absolute alcohol-ether mixture. Crystallized from alcohol.

A solution of 20 g. of the pure dry acid in 20 ml. of absolute benzene was treated with 15 ml. of purified thionyl chloride. The mixture was left for 12 hours and warmed briefly on the water-bath to complete the reaction. It was then added dropwise with good stirring to 275 ml. of ammonia liquor and 10 ml. of 50% sodium hydroxide solution well cooled in ice. After 30 minutes, the precipitated amide was filtered, well washed with water, and recrystallized from hot water, m.p. 101.5° (Cf. Ref. 8, m.p. 99°); yield, 15 g.

β-8,5-Dimethoxyphenylisopropylamine was prepared after Baltzly and Buck (8) by the action of sodium hypochlorite on the amide in dioxane solution (sodium hypobromite caused halogenation of the ring), b.p. 140°/3 mm. Hydrochloride, m.p. 118°; yield, 80%.

The acetyl derivative prepared in the usual way melted at 111° after recrystallization from dilute alcohol.


1,3-Dimethyl-5,8-dimethoxy-3,4-dihydroisquinoline. From 1 g. of the acetyl derivative on cyclization with phosphorus oxychloride, there formed 0.6 g. of the dihydroisquinoline which was an oil. The picrolonate recrystallized from alcohol melted at 185-186°.
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Anal. Calc'd for C_{13}H_{13}NO_{2}: N, 14.6. Found: N, 14.8.
The hydrochloride, recrystallized from absolute alcohol, melted at 177°.

1,8-Dimethyl-5,8-dimethoxyisoquinoline. A solution of 0.5 g. of the dihydroisoquinoline in 10 ml. of freshly distilled decalin was heated with 50 mg. of palladized charcoal (5% Pd) in a stream of dry carbon dioxide under reflux for 8 hours. After filtering from the catalyst, the decalin solution was extracted with two 25-ml. portions of 4 N HCl. The acid extract was freed from decalin by extraction with ether, cooled well, and basified. The isoquinoline was obtained by extraction with ether. Yield, 0.4 g. after purification by chromatography as previously, m.p. 70°. The hydrochloride and the picrolonates melted at the same temperatures as reported for the derivatives from the base prepared by the other method. Mixture melting points showed that the bases prepared by the different routes and their derivatives were identical.

2,4-DIMETHYL-5-(2',5'-DIMETHOXYPHENYL)OXAZOLE

2,4-Dimethoxypropiophenone was made according to Bruckner, et al. (10).

2,5-Dimethoxy-α-isonitrosopropiophenone. This has been reported in a patent (11), but only one form is reported whereas two forms are obtained by the following procedure:

A solution of 13 g. of 2,5-dimethoxypropiophenone in 100 ml. of dry ether was cooled in an ice-salt bath and treated with 9 g. of freshly distilled butyl nitrite while passing in a stream of dry hydrogen chloride. A white solid separated towards the end of the addition of butyl nitrite and HCl was passed for a further 20 minutes. The mixture was left overnight, filtered, and the yellow residue repeatedly washed with water. Recrystallization from alcohol gave 2 g. of crystals, m.p. 106°.

Anal. Calc'd for C_{15}H_{15}NO_{4}: N, 6.28. Found: N, 6.48.
The filtrate and washings were repeatedly extracted with ether. The ether extract was shaken with dilute (2 N) sodium hydroxide in several portions. The alkali extract on cooling and acidification with hydrochloric acid gave a sticky solid, purified by crystallization from dilute alcohol, m.p. 98°; yield, 5.48 g.

Anal. Calc'd for C_{13}H_{13}NO_{4}: N, 6.28. Found: N, 6.52.

These two compounds are evidently stereoisomers and were reduced to the same α-amino-

α-Amino-2,5-dimethoxypropiophenone hydrochloride (11). A solution of 1 g. of either of the forms of α-isonitroso-2,5-dimethoxypropiophenone in 30 ml. of absolute alcohol containing 1 g. of hydrogen chloride was added to a previously reduced suspension of 0.1 g. of Adam's catalyst in 10 ml. of absolute alcohol. During eight hours 203 ml. of hydrogen was absorbed at N.T.P. (2 moles). The alcohol was removed in vacuo and the residue was taken up in absolute alcohol, when an infusible material separated (0.25 g.). The filtrate was evaporated to dryness and the residue recrystallized from absolute alcohol-ether, m.p. 176°; yield, 0.65 g.

Anal. Calc'd for C_{15}H_{15}NO_{4}·HCl: N, 5.70. Found: N, 5.82.
The acetyl derivative was formed by dissolving 0.5 g. of the above hydrochloride in 2 ml. of water and 2 ml. of acetic anhydride and then adding a concentrated sodium hydroxide solution dropwise with good shaking. The precipitated derivative was filtered and recrystallized from dilute alcohol, m.p. 114°.

Anal. Calc'd for C_{13}H_{15}NO_{4}: N, 5.58. Found: N, 5.67.

2,4-Dimethyl-5-(2',5'-dimethoxyphenyl)oxazole. A solution of 1 g. of the acetylamino compound in 10 ml. of toluene was refluxed with 3 ml. of phosphorus oxychloride for 70 minutes. After cooling, the solution was poured into water, the excess oxychloride was decomposed, and the oxazole was removed by extraction with chloroform. After removal of chloroform 0.4 g. of a pale brown oil was obtained. A solution of this oil in alcohol, ether, or

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1 This compound was prepared for comparison with 1,3-dimethyl-5,8-dimethoxyisoquinoline.
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benzene displayed only a feeble fluorescence. A colorless hydrochloride, m.p. 132°, was obtained by passing dry HCl gas through an ethereal solution of the oxazole, but this was too hygroscopic to be analyzed. The picrolonate melted at 162° after recrystallization from alcohol.


1,3-DIMETHYL-5-METHOXYBENZ[g]ISOQUINOLINE

α-2-(1-Methoxynaphthyl)-β-nitropropanol acetate. The pseudonitrosite (7 g.) yielded on treatment with acetic anhydride and sulfuric acid as previously, 7.5 g. of the β-nitropropanol acetate. Recrystallization from methanol gave crystals, m.p. 80°.

Anal. Calc'd for C_16H_18ClNO_2: N, 5.23. Found: N, 4.73.

The picrate melted at 228°.


The amino propanols listed in Table IV were prepared by the procedure described above.
**Acknowledgment.** Our grateful thanks are due to Mr. B. S. Thyagarajan for carrying out the analyses.

**SUMMARY**

1. Eight new 3-methyl substituted isoquinolines have been synthesized by the Bruckner method. Considerable variations in the yields of the pseudonitro-sites occur dependent on the relative positions of other substituents with respect to the propenyl side chain on the aromatic ring.

2. The product of the cyclization of $\alpha$-(2,5-dimethoxyphenyl)-$\beta$-acetylaminopropanol was proved to be 1,3-dimethyl-5,8-dimethoxyisoquinoline by an independent synthesis.

3. $\alpha$-2-(1-methoxynaphthyl)-$\beta$-acetylaminopropanol yielded 1,3-dimethyl-5-methoxybenz[gr]isoquinoline as the only isolable product. The absorption spectrum of this substance shows a striking similarity to that of anthracene, as is to be expected.

4. Eight $\alpha$-aryl-$\beta$-aminopropanols, analogs of Propadrine, have been prepared.

**REFERENCES**


