SATURATED HETEROCYCLES, 47.1 SYNTHESIS OF SOME TETRAHYDROISOQUINOLINE CONDENSED 1,3-HETEROCYCLES

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Abstract - Calycotomine (2) and homocalycotomine (3) reacted with isothiocyanates to give the corresponding thiocarbamides (4, 5). The latter were treated with methyl iodide, and subsequent elimination of methyl mercaptan on treatment with alkali afforded 1,3-oxazolo[4,3-α]-isoquinolines (6) and 1,3-oxazino[4,3-α]isoquinolines (7). 1,3-Thiazolo[4,3-α]-isoquinolines (8) and 1,3-thiazino[4,3-α]isoquinolines (9) were prepared from 4 and 5 with hydrogen chloride. Compound Z8 was also synthesized by the reaction of 3 with phenyl isocyanate, followed by the elimination of water; Z8 was obtainable from Z8 by treatment with P4S10. The structures of compounds 6-9 were confirmed by 1H NMR.

In recent decades several guanidine derivatives have found medical use (e.g. Debrisoquine, Guanethidine, Clonidine).2 Substitution of one of the guanidine nitrogens by a bioisosteric atom (O, S) gives compounds of high and varied pharmacological activities. Of the heterocyclic derivatives in this group, the main objects of research were the 2-imino-substituted 1,3-thiazoles, 1,3-thiazines, 1,3-oxazoles and 1,3-oxazines.3-7
Detailed studies have been carried out in this laboratory concerning the ring-closure reactions of alicyclic 1,3-aminocycloalkanol and 2-(hydroxymethyl)-1-cycloalkylamine (see e.g. ref. 8-10). The present report is concerned with the synthesis of 1,3-thiazolidine, 1,3-oxazolidine, 1,3-thiazine and 1,3-oxazine derivatives fused with the tetrahydroisoquinoline skeleton (6-9); these compounds are obtainable by the cyclization of aminocycloalcohols of the isoquinoline series, such as 1-(α-hydroxymethyl)- (2) and 1-(β-hydroxyethyl)-tetrahydroisoquinolines (5). Though these products are closely related cyclic analogues of Debrisoquine (1), their syntheses have not been reported.

The synthetic pathway is shown in Scheme. The general procedure is a modification of the method developed earlier 3 for the preparation of 1,3-oxazines and 1,3-thiazines. Calycotamine (2) or homocalycotamine (3) (prepared by described methods 11,12) was refluxed in benzene for 1 h with an equivalent amount of isothiocyanate to obtain the corresponding thiocarbamides (4, 5) in nearly quantitative yield. Mps 4a: 171-172°C; 4b: 105-107°C; 5a: 185-188°C; 5b: 186-188°C (All compounds were recrystallized from EtOH 13).
Compounds 4 and 5 were allowed to stand for 1 h at room temperature with excess methyl iodide to give the thiuronium salts. In one case, when starting from 5, the thiuronium salt was isolated (mp 154-156°C, from EtOH[13]). The residue obtained on evaporation of the methyl iodide-containing reaction mixture was stirred at room temperature in methanol containing 3 N potassium hydroxide. After methyl mercaptan had been completely expelled (2-4 h), the reaction mixture was evaporated. When R = C6H5, the residue was mixed with water and the crystalline product was filtered off; in the case of R = C6H11, the product was isolated by extraction of the evaporation residue with hot benzene. Both methods of work-up gave the 1,3-oxazolo[4,3-α]isoquinolines (6) and 1,3-oxazino[4,3-α]isoquinolines (7), respectively, in good yields.

Refluxing of 4 and 5 for 15 min in ethanol containing 20% dry hydrogen chloride gave, after evaporation and neutralization, 1,3-thiazolo[4,3-α]isoquinolines (8) and 1,3-thiazino[4,3-α]isoquinolines (9), respectively.

The mp, IR and 1H NMR data on the synthesized compounds are shown in the Table. The 1,3-oxazine 7 was also prepared from homocalycotamine (3) and phenyl isocyanate via the urea derivative 1 (mp 167-169°C, from EtOH[12]), by treatment with thionyl chloride; however, the yield was only 17%.

The 1,3-thiazine (9) was synthesized in an alternative route[14] by heating 7 with phosphorus pentasulphide for 2 h at 150°C; the product (9) was obtained in 31% yield.

Crabb and Mitchell[15] synthesized and made a detailed 1H NMR study of the closely analogous compounds, cis-4-(p-nitrophenyl)-1,6,7,11b-tetrahydro-2H,4H-1,3-oxazino[4,3-α]isoquinoline (11) and cis-4-(p-nitrophenyl)-1,6,7,11b-tetrahydro-2H,4H-1,3-thiazino[4,3-α]isoquinoline (12). In the oxazino 11 and in the related thiazino derivative 12 Bohlmann bands were absent and the NMR spectrum indicated predominance of the S (or Z) inside form as concerns the two possible B/C cis conformers.

The 1H NMR spectra of the compounds 6-9 synthesized in the present work are in good agreement with the data measured by Crabb (cf. Table). As the lone electron pair of 5-N is considerably conjugated with the near-by hetero atoms, the appearance of Bohlmann bands cannot be expected. The presence of N=C=O or N=C=S groups makes the conformation of the hetero ring near-planar. This is
<table>
<thead>
<tr>
<th>No</th>
<th>Mp (°C)</th>
<th>IR (cm⁻¹)</th>
<th>( \nu_{\text{max}} )</th>
<th>( {^1}\text{H} \text{ NMR} ) data</th>
<th>Coupling constants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chemical shifts (ppm)</td>
<td>( J_{11b, 1\alpha} )</td>
<td>( J_{11b, 1\beta} )</td>
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<tr>
<td>6a</td>
<td>129-130</td>
<td>1680</td>
<td>3.82</td>
<td>4.6</td>
<td>4.15</td>
</tr>
<tr>
<td>6b</td>
<td>104-105</td>
<td>2910, 1675</td>
<td>3.83</td>
<td>4.7</td>
<td>4.15</td>
</tr>
<tr>
<td>7a</td>
<td>115-118</td>
<td>1585, 1550</td>
<td>3.82</td>
<td>4.6</td>
<td>4.15</td>
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<tr>
<td>7b</td>
<td>128-129</td>
<td>2910, 1620</td>
<td>3.84</td>
<td>4.5</td>
<td>4.15</td>
</tr>
<tr>
<td>11c</td>
<td>145-147</td>
<td></td>
<td>4.03</td>
<td>4.17</td>
<td></td>
</tr>
<tr>
<td>8a</td>
<td>147-148</td>
<td>1625</td>
<td>3.83</td>
<td>4.7</td>
<td>3.5</td>
</tr>
<tr>
<td>8b</td>
<td>134-135</td>
<td>2905, 1605</td>
<td>3.82</td>
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<td>3.55</td>
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<td>9a</td>
<td>158-160</td>
<td>1575</td>
<td>3.84</td>
<td>4.7</td>
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<td>9b</td>
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<td>2915, 1575</td>
<td>3.84</td>
<td>4.6</td>
<td>4.35</td>
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<td>12c</td>
<td>114-116</td>
<td></td>
<td>4.15</td>
<td>4.24</td>
<td></td>
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</tbody>
</table>

In order to facilitate comparison, the numbering of compounds 6a-12c in the Table is as follows:

\[ \begin{align*}
6 & \quad 8a, 7a, 11c, 8b, 7b, 9a, 9b, 12c \\
6a & \quad 11b, 3, 2, 1, 11a, 30(S) \\
6b & \quad 11b, 11a, 30(S) \\
9a & \quad 11b, 3, 2, 1, 11a, 30(S) \\
9b & \quad 11b, 11a, 30(S) \\
12c & \quad 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, 11a, 30(S) \\
\end{align*} \]

\[ \begin{align*}
J_{11b, 1\alpha} & = 6.47, J_{11b, 1\beta} = 6.65 \\
& \text{All compounds were recrystallized from ethanol.} \\
& \text{Compounds synthesized and studied by Crabb and Mitchell.}^{15}
\]

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supported by the higher chemical shifts of the CH$_2$-O(S) protons as compared with the corresponding proton in compounds $\text{II}_1$ or $\text{II}_2$, and also by the $J_{11b,1ex}$ values, which are significantly smaller than in usual diaxial couplings.

Results of the current investigation of some reactions of $\text{II}_2$ and a high-resolution NMR study of these compounds will be described in a forthcoming publication.

REFERENCES AND NOTES

13. All prepared compounds gave satisfactory elemental (C, H, N, S) analyses.
16. IR spectra were recorded with a SPECORD 75 IR instrument in KBr pills.
17. $^1$H NMR spectra were recorded at 60 MHz with a JEOL C60 spectrometer at room temperature in CDCl$_3$ solution with TMS as internal standard.

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