THE SYNTHESIS OF 9H-IMIDAZO[1,2-\(a\)]1,3-DIAZEPINES

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Abstract — Ethyl 7-acetyl-2,3-diphenyl-9H-imidazo[1,2-\(a\)]1,3-diazepine-5-carboxylate (8) and its acetate (7) were synthesized via the ring-expansion reaction of ethyl 5a-acetyl-4a,5a-dihydro-2,3-diphenyl-5H-cyclopropa[4a,5a]imidazo[1,2-\(a\)]pyrimidine-4a-carboxylate (3).

Relatively little work has been carried out on 1,3-diazepines with a benzene ring fused to the diazepine system. A few derivatives of pyrimido[2,1-b][1,3]-diazepine have been prepared. The synthesis of bicyclic guanidines such as 5,6,7,8-tetrahydro- or 2,3,5,6,7,8-hexahydro-1H-imidazo[1,2-\(a\)]1,3-diazepine derivatives, some of which showed the anticonvulsant and hypoglycemic activity, has also been reported. However, to our knowledge, 9H-imidazo[1,2-\(a\)]1,3-diazepines have not hitherto been reported. In this communication, we report the synthesis of the title compounds via the ring-expansion of cyclopropaimidazopyrimidine (2).

Recently, we reported the synthesis and ring transformation reaction of 6H-cyclopropa[5a,6a]pyrazolo[1,5-\(a\)]pyrimidines, which were readily obtained by the reaction of 6-acetyl-7-ethoxycarbonylpyrazolof1,5-\(a\)pyrimidine-3-carbonitrile with diazomethane under ice-cooling. Thus, we selected ethyl 6-acetyl-2,3-diphenylimidazo[1,2-\(a\)]pyrimidine-5-carboxylate (1) as a starting material for the synthesis of the title compounds. The compound 1 was synthesized by condensation of ethyl 3-ethoxymethylene-2,4-dioxovalerate with 2-amino-4,5-diphenylimidazole in refluxing ethanol in 86% yield. Treatment of 1 with a large excess of diazomethane under ice-cooling gave ethyl 5a-acetyl-4a,5a-dihydro-2,3-diphenyl-5H-cyclopropa[4a,5a]imidazo[1,2-\(a\)]pyrimidine-4a-carboxylate (2) [mp 193-195°; \(\nu\) max. (KBr) cm\(^{-1}\): 1750, 1720, 1660; \(\delta\) (DMSO-\(d_6\)) : 0.85 (3H, t, \(J=7\) Hz, CH\(_2\)CH\(_3\)), 1.85 and 2.75 (each 1H, each d, \(J=6\) Hz, CH\(_2\)), 2.39 (3H, s, COCH\(_3\)), 3.20-3.70 (2H, m, CH\(_2\)CH\(_3\)), 7.10-7.60 (10H, m, Ar-H), 8.61 (1H, s, C\(_6\)-H)] in 73% yield.
Next, hydrogenolytic ring-expansion reaction of \( \mathcal{Z} \) was examined. Catalytic hydrogenation of \( \mathcal{Z} \) over PtO\(_2\) under atmospheric pressure in dioxane gave 6,7-dihydro compound (\( \mathcal{Y} \)), mp 247-249° (CH\(_3\)CN). The NMR spectrum (DMSO-d\(_6\)) of \( \mathcal{Y} \) showed the presence of cyclopropane ring protons at \( \delta \) 1.92 and 2.36 (each 1H, each d, \( \mathcal{J}=6 \) Hz). On the other hand, when catalytic hydrogenation of \( \mathcal{Z} \) was carried out over 5% Pd-C under the same condition, ethyl 7-acetyl-5,6-dihydro-2,3-diphenyl-9H-imidazo[1,2-\(a\)]1,3]diazepine-5-carboxylate (\( \mathcal{Y} \)), mp 216-218° (EtOH) (Found: C, 72.08; H, 5.71; N, 10.51. C\(_{23}\)H\(_{23}\)N\(_3\)O\(_3\) requires C, 71.80; H, 5.78; N, 10.47), was interestingly obtained in 66.3% yield. The spectral data \( \nu \) max. (KBr) cm\(^{-1}\) : 3200-2600, 1750, 1610; \( \lambda \) max. (EtOH) nm (log \( \varepsilon \)) : 248 (4.19), 332 (4.26); \( \delta \) (DMSO-d\(_6\)) : 1.13 (3H, t, \( \mathcal{J}=7 \) Hz, CH\(_2\)CH\(_3\)), 1.78 (3H, s, COCH\(_3\)), 2.45 (1H, br d, \( \mathcal{J}=15 \) Hz, C\(_6\)-H), 3.90 (1H, d d, \( \mathcal{J}=15 \), 6 Hz, C\(_6\)-H), 3.90-3.90 (2H, m, CH\(_2\)CH\(_3\)), 4.90 (d d, \( \mathcal{J}=3 \) Hz, C\(_5\)-H), 6.76 (1H, br s, C\(_8\)-H), 7.10-7.50 (10H, m, Ar-H), 12.55 (1H, br s, NH) established its structure. An attempt to direct preparation of ethyl 7-acetyl-2,3-diphenyl-9H-imidazo[1,2-\(a\)]1,3]diazepine-5-carboxylate (\( \mathcal{E} \)) from \( \mathcal{Y} \) with DDQ oxidation was unsuccessful, only a tarry mixture being obtained. Thus, compound \( \mathcal{Y} \) was acetylated with acetic anhydride and pyridine to obtain \( \mathcal{Z} \), mp 158-160°. The fact that an attractive signal was seen in its NMR spectrum at \( \delta \) 8.28\(^7\) as singlet assignable to C\(_5\)-proton shifted downfield by the effect of N-acetyl group would strongly support the structure of \( \mathcal{Y} \). The acetate reacted with 1.2 equivalent moles of NBS in CCl\(_4\) in the presence of benzoyl peroxide to give ethyl 6-bromo-7,9-diacetyl-5,6-dihydro-2,3-diphenyl-9H-imidazo[1,2-\(a\)]1,3]diazepine-5-carboxylate (\( \mathcal{E} \)), mp 150-154° (benzene-ligroin), in a quantitative yield. Since the NMR spectrum of \( \mathcal{E} \) revealed C\(_5\)- and C\(_6\)-protons as two sets of doublets at \( \delta \) 4.97 and 5.81 with a coupling constant of 5 Hz\(^8\)), the configuration of \( \mathcal{E} \) was characterized as trans. Treatment of \( \mathcal{E} \) with triethylamine in refluxing benzene afforded ethyl 7,9-diacetyl-2,3-diphenyl-9H-imidazo[1,2-\(a\)]1,3]diazepine-5-carboxylate (\( \mathcal{Y} \)) as pale yellow crystals, mp 206-208°(EtOH), in 47.3% yield. Dehydrobromination of \( \mathcal{E} \) with DBU\(^9\) to \( \mathcal{Z} \) was achieved more readily. Thus, a mixture of \( \mathcal{E} \) and an equimolar amount of DBU in benzene was stirred at room temperature for 10 min, and \( \mathcal{Z} \) was isolated in 73% yield. Compound \( \mathcal{Z} \), on treatment with basic Al\(_2\)O\(_3\) in refluxing benzene, underwent hydrolysis of N-acetyl group to give \( \mathcal{E} \) as red crystals, mp 303-305° (CH\(_3\)CN) (Found: C, 71.99; H, 5.31; N, 10.54. C\(_{24}\)H\(_{21}\)N\(_3\)O\(_3\) requires C, 72.16; H, 5.30; N, 10.52) in 40% yield. The structure
determination of 7 and 8 were performed on the basis of spectral data as summarized in Table.

Spectral Data of 9H-Imidazo[1,2-a][1,3]diazepines (7 and 8)

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>v max. (KBr) cm⁻¹</th>
<th>λ max. (CH₃CN) (log ε) nm</th>
<th>δ (DMSO-d₆, J=7 Hz)</th>
<th>Mass (m/z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>1720</td>
<td>238 (4.47)</td>
<td>0.96 (3H, t) 2.48</td>
<td>7.10-7.50</td>
</tr>
<tr>
<td></td>
<td>1700</td>
<td>278 (4.27)</td>
<td>3.65 (2H, q) 2.50</td>
<td>8.00</td>
</tr>
<tr>
<td></td>
<td>1680</td>
<td>348 (3.16)</td>
<td></td>
<td>441 (M⁺)</td>
</tr>
<tr>
<td>8</td>
<td>3200-2600</td>
<td>248 (4.26)</td>
<td>0.84 (3H, t) 2.55</td>
<td>7.00-7.60</td>
</tr>
<tr>
<td></td>
<td>1710</td>
<td>292 (4.23)</td>
<td>3.55 (2H, q)</td>
<td>6.92</td>
</tr>
<tr>
<td></td>
<td>1650</td>
<td>427 (2.97)</td>
<td></td>
<td>399 (M⁺)</td>
</tr>
</tbody>
</table>

* Overlapped with benzene ring protons
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References and Notes


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