Research in 7-aminoindazole series: Synthesis of new halo-7H-4-methylpyrazolo[1,5,4-ef][1,5]benzodiazepin-6-ones and 5H-9-halo-6-methylpyrazolo[1,5,4-ef][1,5]benzodiazepin-4-ones

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A new class of 7-aminohaloindazoles has been synthesized. Reactivity of the amino groups of these bicyclic systems has been investigated. The halogenated pyrazolo-1,5-benzodiazepinones have been synthesized by the condensation of 7-aminoindazoles with ethyl acetooacetate

Our laboratories have investigated the synthesis and reactivities of 7-aminoindazoles. Our objective was centered around the preparation of halo-7-aminoindazoles 1-4 and their condensation with ethyl acetooacetate to generate new halopyrazolo-1,5-benzodiazepine derivatives 14-19. These new compounds facilitated us to obtain the N-alkyl derivatives 20-25.

The new halodiazepines 14-25 possess the same framework as the well known tranquillizers Chlordiazepoxide I, Diazepam II and Clobazam III. Compounds 14-25 were prepared in order to test their tranquillizing properties.

Compounds 1-4 were prepared by reducing their corresponding halo-7-nitroindazoles 6, 7, 10 and 13 in the presence of palladium catalyst under hydrogen atmosphere. 7-Nitroindazoles 5, 10 and 13 were synthesized by reacting sodium nitrite with 2-methyl-6-nitroanilines 11, 9 and 12 in the presence of acetic acid.

Three different halogenation sites were studied:
(i) Halogenation of 7-nitroindazole 5 by the Von Auwers and Denmuth method.
(ii) Nitration at position-6 of 3-chloro-2-methyl aniline 8 as described by Morgan and Glover.
(iii) Halogenation at position-4 of 2-methyl-6-nitroaniline 11.

Results and Discussion
Compounds 3 and 4 were prepared according to the first method mentioned above: halogenation of 7-nitroindazoles, followed by catalytic reduction (Scheme I). The halogenation takes place at the posi-
tion 3 to give the 3-halo-7-nitroindazoles 6a and 6b. If the reaction was run for a long period, dihalogenated products 7a and 7b were obtained. Compounds 6a, 6b and 7b were also prepared according to a method used to synthesize nitroindazoles and published earlier by our group11.

7-Amino-4-chloroindazole 1 was obtained according to the second method, nitration9 followed by cyclization using sodium nitrite in the presence of acetic acid10 and catalytic reduction (Scheme II).

The third method was utilized to prepare the 7-amino-5-haloidazoles 2. Nitroanilines 12 were obtained by direct halogenation of 2-methyl-6-nitroaniline 11 with N-halosuccinimide in good yields. This method has been previously described with X = Cl (ref. 10). Reaction of sodium nitrite in the presence of acetic acid with these compounds followed by catalytic reduction afforded 7-amino-5-haloidazoles 2 only (Scheme III).

Table I summarizes some analytical and spectral data of compounds 1-4 and their intermediates.

The reactivities of these indazoles 1-4 were thereafter studied. This study had two purposes:

(a) Synthesis of new halogenated pyrazolo-1,5-benzodiazepinones derivatives with the objective to halogenate the same position as in the tranquillizers 1-III.

(b) to study the effect of the halogen group during the cyclization of aminoidazoles.

We have shown that the reaction of a 7-aminoidazole with ethyl acetooacetate afforded only pyrazolo-[1,5]-benzodiazepine derivatives7. It is worth mentioning the importance of the condensation of ethyl acetooacetate with 7-aminoidazoles 3 and 4, which provided pyrazolo-[1,5]-benzodiazepin-6-ones 14, 15 derivatives. This cyclization reaction took place in refluxing xylene for five hours (Scheme IV).

The 1H NMR spectra of 14 and 15 showed a signal at 5.10-5.40 ppm due to the vinylic proton. On the other hand, the condensation of ethyl acetooacetate with 7-aminohaloidazoles 1 and 2 under the same conditions as before, gives a mixture of two isomers 16, 18 and 17, 19 in 1:1 ratio. These products resulted from two different modes of attack on 7-aminohaloidazole (Scheme V).
### Table I—Characteristic data of the intermediates and of the 7-aminohaloindazoles 1-4.

| Product | Yield (%) | mp (°C) | \(^1\text{H} \text{NMR, } \delta \text{ (ppm)} | \#
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<tr>
<td>1</td>
<td>92</td>
<td>157</td>
<td>8.04 (s, 1H, H-3), 7.12 (d, J = 7 Hz, 1H, H-Ar, whether H-5 or H-6), 6.84 (d, J = 7 Hz, 1H, H-Ar, whether H-5 or H-6), 5.35 (s, 2H, NH3).</td>
</tr>
<tr>
<td>2a</td>
<td>91</td>
<td>165</td>
<td>8.24 (s, 1H, H-3), 7.82 (d, J = 2.1 Hz, 1H, H-Ar, whether H-4 or H-6), 7.05 (d, J = 2.1 Hz, 1H, H-Ar, whether H-5 or H-6), 5.24 (s, 2H, NH3).</td>
</tr>
<tr>
<td>2b</td>
<td>85</td>
<td>149</td>
<td>8.03 (s, 1H, H-3), 7.54 (d, J = 1.8 Hz, 1H, H-Ar, whether H-5 or H-6), 6.81 (d, J = 1.8 Hz, 1H, H-Ar, whether H-4 or H-6), 4.94 (s, 2H, NH3).</td>
</tr>
<tr>
<td>3a</td>
<td>91</td>
<td>147</td>
<td>7.65-6.05 (m, 3H, H-Ar), 5.24 (s, 2H, NH3).</td>
</tr>
<tr>
<td>3b</td>
<td>93</td>
<td>135</td>
<td>7.34-6.78 (m, 3H, H-Ar), 4.85 (s, 2H, NH3).</td>
</tr>
<tr>
<td>4a</td>
<td>95</td>
<td>153</td>
<td>7.08 (d, J = 1.8 Hz, 1H, H-Ar, whether H-4 or H-6), 6.52 (d, J = 1.8 Hz, 1H, H-Ar, whether H-4 or H-6), 5.10 (s, 2H, NH3).</td>
</tr>
<tr>
<td>4b</td>
<td>92</td>
<td>137</td>
<td>7.28 (d, J = 1.2 Hz, 1H, H-Ar, whether H-4 or H-6), 6.64 (d, J = 1.2 Hz, 1H, H-Ar, whether H-4 or H-6), 4.90 (s, 2H, NH3).</td>
</tr>
<tr>
<td>5</td>
<td>80</td>
<td>185</td>
<td>[11]</td>
</tr>
</tbody>
</table>

Recrystallizing solvents: 1-4 (xylene); 6, 7, 10, 13 (EtOH); 9, 12 (H2O) NMR solvents: 1-4, 6, 7, 10, 13 (DMSO-d6), 9, 12 (CDCl3).

The \(^1\text{H} \text{NMR spectra of compounds 17 and 19} showed a signal at 3.90-4.10 ppm due to the methylene protons in position-5 of the tricyclic system and a clear deshielding of the pyrazolic proton probably due to the effect of the carbonyl group bonded to the nitrogen atom. The identification of compounds 16-19 was done by NMR, MS and IR data and from elemental analyses.

Thus, the presence of a halogen atom in position 3 only, or in positions 3 and 5 does not affect the reactivity of 7-aminoundazole towards ethyl acetoacetate, only the diazepin-6-ones 14 and 15 are obtained. The presence of a halogen atom in position 4 or 5 of the indazolic system modifies this reaction and gives a mixture of two isomers: the diazepin-6-ones and diazepin-4-ones.

In order to increase the activity spectrum of the compounds 14-16 and to study the reactivity of the lactam function, we have alkylated some pyrazolo[1,5-b]benzodiazepino-nes with ethyl iodide or allyl bromide under phase transfer conditions. Thus, the action of ethyl iodide or allyl bromide in methylene chloride as solvent, in the presence of a NaOH solution (30%) and tetra-n-butylammonium bromide as
It is worth noting that the infra-red spectra of the alkyl compounds in KBr, show one C=O band around 1660-1665 cm⁻¹, which means that the alkylation of oxygen atom at position-6 of the pyrazolo[1,5]benzodiazepinones does not take place. Besides the signals due to the pyrazolo[1,5]benzodiazepinone skeleton, the ¹H NMR spectra show signals corresponding to the ethyl and allyl protons (Table II).

In conclusion, it has been possible for us to prepare new halo-7H-4-methylpyrazolo[1,5,4-cf][1,5]benzodiazepin-6-ones 14-16, 18 as well as their N-alkylated derivatives 20-25. The presence of a halogen atom in position-4 or -5 alters the reactivity of 7-aminoindazoles towards ethyl acetate and allowed us to obtain the 5H-9-halo-6-methylpyrazolo [1,5,4-cf] [1,5]benzodia-zepin-4-ones 17 and 19.

Experimental section

General. Melting points were determined on a Büchi-Tottoli apparatus and are uncorrected. Spectra were recorded using the following instruments—IR: Perkin-Elmer 577 spectrometer (KBr disks); ¹H NMR: Bruker AC-250 (250 MHz) spectrometer, chemical shifts are given in δ ppm downfield from TMS internal standard; MS (El) Nermag R10-10C spectrophotometer

Commercial chemicals: 3-chloro-2-methyl-aniline and 2-methyl-6-nitroaniline were used without purification. The following compounds were prepared according to methods described in the literature: 4-
chloro-2-methylnitroaniline \(^9\); 7-nitroindazoles \(^5,10,13\) starting from the corresponding 2-methyl halo-6-nitroanilines\(^7\); 3-halo-7-nitroindazole \(^6\) and 3,5-dihalo-7-nitroindazoles \(^7,11\).

**Synthesis of 4-halo-2-methyl-6-nitroaniline-12.** For compounds 12 we used different experimental conditions than those described in the literature\(^10\). To a solution of 2-methyl-6-nitroaniline \(^11\) (40 mmoles) in 100 mL of carbon tetrachloride was added the N-halosuccinimide (50 mmoles). The reaction mixture was refluxed for 12 hr and the precipitate formed after cooling was filtered and washed with water to remove the N-succinimide. The products obtained were purified by recrystallization from water. \(^12a\): 65% yield, mp 120°C; \(^12b\): 60% yield, mp 155°C.

**Synthesis of 7-aminooindazoles 1-4: General experimental procedure.** Into an hydrogenation reactor, were introduced the derivative of 7-nitroindazole (25 mmoles), 0.5 g of palladium on carbon (10%) and 150 mL of ethanol. Air was removed under hydrogen over (1 atm). When the reaction was completed (no longer consumption of hydrogen), the solution was quickly filtered under vacuum and concentrated under reduced pressure.

**7-Amino-5-chloroindazole 2a.** Anal. Calcd for C\(_7\)H\(_6\)ClN\(_5\): C, 50.29; H, 3.59; N, 25.14%. Found: C, 50.23; H, 3.61; N, 25.10%.

**7-Amino-5-bromoindazole 2b.** Anal. Calcd for C\(_7\)H\(_6\)BrN\(_5\): C, 39.80; H, 2.84; N, 19.90%. Found: C, 39.75; H, 2.82; N, 19.86%.

**7-Amino-3-chloroindazole 3a.** Anal. Calcd for C\(_7\)H\(_6\)ClN\(_5\): C, 50.29; H, 3.59; N, 25.14%. Found: C, 50.33; H, 3.58; N, 25.17%.

**7-Amino-3-bromoindazole 3b.** Anal. Calcd for C\(_7\)H\(_6\)BrN\(_5\): C, 39.80; H, 2.84; N, 19.90%. Found: C, 39.76; H, 2.80; N, 19.86%.

**7-Amino-3,5-dichloroindazole 4a.** Anal. Calcd for C\(_7\)H\(_6\)Cl\(_2\)N\(_5\): C, 41.79; H, 2.49; N, 20.89%. Found: C, 41.73; H, 2.43; N, 20.82%.

**7-Amino-3,5-dibromoindazole 4b.** Anal. Calcd for C\(_7\)H\(_6\)Br\(_2\)N\(_5\): C, 29.06; H, 1.73; N, 14.53%. Found: C, 29.10; H, 1.71; N, 14.55%.

Condensation of ethyl acetoacetate with 7-aminohalooindazoles 1-4: synthesis of compounds 14-19: General experimental procedure. To a solution of 7-aminooindazole (20 mmoles) in 150 mL of xylene, ethyl acetoacetate (25 mmoles) in 20 mL of xylene was added. The reaction mixture was refluxed for 5 hr using an azotropic separator. At the end of the reaction 0.5 g of active carbon was added to the mixture and heating was continued for 5 min. The warm mixture is filtered under vacuum. The resulting yellow precipitate was collected and dried. In case of compounds 16-19, obtained from the 7-aminohaloindazole 1,2, the mixture of two isomers was chromatographed over silica gel column using a 90:10 mixture of chloroform and ethyl acetate as eluant.

**7H-1-Chloro-4-methylpyrazolo[1,5,4-cf][1,5] benzodiazepin-6-one 14a.** This compound was obtained from 7-amino-3-chloroindazole 3a. Yield 40%, mp 300-302°C (xylene); IR (KBr): 1650 (C=O), 3400 cm\(^{-1}\) (NH); \(^1\)H NMR (TFA): \(\delta\) 2.52 (s, 3H, CH\(_3\)), 5.40 (s, 1H, H-5), 6.85-7.45 (m, 3H, H-Ar), MS (EI): m/z = 233, 235 (M\(^+\), Cl). Anal. Calcd for C\(_9\)H\(_8\)CIN\(_3\)O: C, 56.65; H, 3.43; N, 18.02%. Found: C, 56.52; H, 3.42; N, 17.98%.

**7H-1-Bromo-4-methylpyrazolo[1,5,4-cf][1,5] benzodiazepin-6-one 14b.** This compound is obtained from 7-amino-3-bromoindazole 3b. Yield 36%, mp 283-285°C (xylene); IR (KBr): 1645 (C=O), 3370 cm\(^{-1}\) (NH); \(^1\)H NMR (TFA): \(\delta\) 2.42 (s, 3H, CH\(_3\)), 5.35 (s, 1H, H-5), 6.84-7.40 (m, 3H, H-Ar), MS (EI): m/z = 277, 279 (M\(^+\), Br). Anal. Calcd for C\(_9\)H\(_8\)BrN\(_3\)O: C,
5-chloroindazole 2a.
methylpyrazolo[1,5,4-ej][1,5]benzodiazepin-6-one 19a. These compounds were obtained from 7-amino-3,5-dichloroindazole 4a. Yield 34%, mp 279-290°C (xylene); IR (KBr): 1660 cm⁻¹ (C=O); 1H NMR (TFA): 2.36 (s, 3H, CH₃), 5.15 (s, 1H, H-5), 6.74 (d, J = 2 Hz, 1H, H-Ar), 6.95 (d, J = 2 Hz, 1H, H-Ar); MS (EI): m/z 267, 269 (M⁺, 2CI). Anal. Calcld for C₁₁H₁₇BrN₃O: C, 35.40; H, 3.77; N, 15.77%. Found: C, 35.40; H, 3.79; N, 15.80%

7H-1,9-Dibromo-4-methylpyrazolo[1,5,4-ej][1,5]benzodiazepin-6-one 18b and 7H-9-chloro-6-chloro-4-methylpyrazolo[1,5,4-ej][1,5]benzodiazepin-4-one 19b. These compounds were obtained from 7-amino-3,5-dichloroindazole 4b. Yield 36%, mp 274-276°C (EtOH); IR (KBr): 3360 cm⁻¹ (C=O); 1H NMR (TFA): 2.30 (s, 3H, CH₃), 3.90 (s, 2H, CH₂-5), 5.10 (s, 1H, H-5), 6.91 (d, J = 1.2 Hz, 1H, H-Ar), 7.15 (d, J = 1.2 Hz, 1H, H-Ar); MS (EI): m/z = 355, 359, 377 (M⁺, 2Br). Anal. Calcld for C₁₁H₁₇BrN₃O: C, 37.18; H, 1.97; N, 11.83%. Found: C, 36.97; H, 1.96; N, 11.76%

7H-1,9-Dibromo-4-methylpyrazolo[1,5,4-ej][1,5]benzodiazepin-6-one 16 and 7H-1,2,3,5,4-ej-6-chloro-4-methylpyrazolo[1,5,4-ej][1,5,4-ej][1,5]benzodiazepin-4-one 17. These compounds are obtained from 7-amino-3,5-dichloroindazole 1.

Compound 16: It was obtained in 28% yield, mp 309-310°C (xylene); IR (KBr): 1665 cm⁻¹ (C=O), 3360 cm⁻¹ (NH); 1H NMR (TFA): 2.40 (s, 3H, CH₃), 5.12 (s, 1H, H-5), 6.65 (d, J = 8.1 Hz, 1H, H-Ar), 7.15 (d, J = 8.1 Hz, 1H, H-Ar), 8.10 (d, 1H, H-1); MS (EI): m/z 233, 235 (M⁺, 2Br). Anal. Calcld for C₁₁H₁₇N₃O: C, 56.65; H, 3.43; N, 18.02%. Found: C, 56.60; H, 3.47; N, 18%.

Compound 17: It was obtained in 35% yield, mp 291-293°C (xylene); IR (KBr): 1690 cm⁻¹ (C=O); 1H NMR (TFA): 2.50 (s, 3H, CH₃), 4.15 (s, 2H, CH₂-5), 6.30 (d, J = 7.8 Hz, 1H, H-Ar), 7.65 (d, J = 7.8 Hz, 1H, H-Ar), 8.74 (s, 1H, H-1); MS (EI): m/z 233, 235 (M⁺, 2Br). Anal. Calcld for C₁₁H₁₇N₃O: C, 56.65; H, 3.43; N, 18.02%. Found: C, 56.50; H, 3.40; N, 17.95%.

7H-9-chloro-4-methylpyrazolo[1,5,4-ej][1,5]benzodiazepin-6-one 18a and 7H-9-chloro-6-chloro-4-methylpyrazolo[1,5,4-ej][1,5]benzodiazepin-4-one 19a. These compounds were obtained from 7-amino-3,5-dichloroindazole 2a.

Compound 18a: It was obtained in 29% yield,
chromatographed on a silica gel column using ether as eluant.

The physicochemical characteristics of the isolated products are given in the Table III.

Acknowledgement

Research done with a grant of PARS (Programme d’Appui à la Recherche Scientifique).

Table III—Physical and chemical data of the products 20-25

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<th>Yield %</th>
<th>mp °C (E.A.)</th>
<th>Mol. formula</th>
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<tr>
<td>20</td>
<td>58</td>
<td>124-126</td>
<td>C_{13}H_{12}BrN_{3}O</td>
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<tr>
<td>21</td>
<td>63</td>
<td>186-188</td>
<td>C_{15}H_{14}ClN_{3}O</td>
</tr>
<tr>
<td>22</td>
<td>65</td>
<td>138-140</td>
<td>C_{13}H_{12}ClN_{3}O</td>
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<td>156-158</td>
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<td>24</td>
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<td>136-138</td>
<td>C_{14}H_{12}BrN_{3}O</td>
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<tr>
<td>25</td>
<td>76</td>
<td>114-116</td>
<td>C_{14}H_{12}ClN_{3}O</td>
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References
7. Noeling E, Ber, 37, 1904, 2556.