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Various pyrazolo[1,5-*a*]pyrimidines **1** are prepared by two different ways. Their chemical reduction by sodium borohydride leads generally to 4,5,6,7-tetrahydro compounds **3**, while lithium aluminum hydride yields 4,7-dihydro derivatives **2** at room temperature, and **3** in refluxing tetrahydrofuran. A complex mixture of oxidizable hydrodimers is obtained by electrochemical reduction. An electroreduction at a more negative potential also gives 4,7-dihydro compounds **2**. A new 4,5-dihydropyrazolo[1,5-*a*]pyrimidine has been obtained by condensation of 5-amino-3-methyl-1*H*-pyrazole with acetophenone.

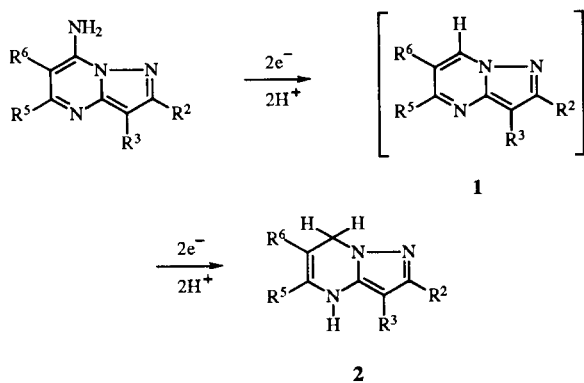
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### Introduction.

We have been interested for some time in the chemical and electrochemical reduction of *N*-heterocyclic compounds.

We have previously described [1] the electrochemical reduction of pyrazolo[1,5-*a*]pyrimidin-7-amines. These fused heterocyclic compounds undergo a deaminative reduction step to give dihydro derivatives **2**, via pyrazolo[1,5-*a*]pyrimidines **1** themselves (Scheme 1). These last products can also be obtained by oxidation with manganese dioxide of dihydropyrazolo[1,5-*a*]pyrimidines **2**.

Scheme 1



Since the publication of our preceding paper, many articles have reported the synthesis and behavior of a great number of functionalized pyrazolo[1,5-*a*]pyrimidines bearing various substituents in different positions, see for example references [2-6]. The most important results regarding pyrazolopyrimidines in general and pyrazolo[1,5-*a*]pyrimidines in particular have been reviewed [7].

The cyclic voltammetry of pyrazolo[1,5-*a*]pyrimidin-7-amines [1] has shown that pyrazolo[1,5-*a*]pyrimidines **1**, which were intermediates in the reduction process, were themselves electroreducible and more than corresponding 7-amines derivatives.

In the present work we investigate the chemical and electrochemical reduction of some pyrazolo[1,5-*a*]pyrimidines, the synthesis of which was described in our preceding paper [1] as well as of several new compounds.

Few papers describe the chemical reduction with sodium borohydride or the catalytic hydrogenation of compounds such as **1** with an ester group in 6-position [8a,b] or 7-position [9] but electrochemical reduction has not yet been reported for these products.

The present work has been divided in two parts. The basic electrochemical investigation has been realized with pyrazolo[1,5-*a*]pyrimidines **1a** to **1d** which had been investigated in our previous work. All of them are substituted in the 6-position by a phenyl group on the pyrimidine ring. Their poor solubility in the usual solvents, particularly for **1a** and **1c**, makes their study difficult. Therefore, we have prepared and investigated a new series of more soluble compounds **1e** to **1i**.

It is well known that the condensation, in acidic medium, of  $\beta$ -diketones with 5-aminopyrazol-3-ones (which exist in the tautomeric form 3-hydroxypyrazoles), easily leads to 5,7-disubstituted-2-hydroxypyrazolo[1,5-*a*]pyrimidines [10-13]. We have transposed this procedure to 5-aminopyrazoles; thus, we have prepared and investigated some 5,7-dimethyl derivatives **1e** to **1g**, 5-methyl-7-phenyl and 5,7-diphenyl compounds **1h** and **1i**. They are easily obtained respectively by condensation of 2,3-butanedione, 1-benzoylacetone or dibenzoylmethane with 5-amino-3-methyl-1*H*-pyrazole (**6a**), 5-amino-3-phenyl-1*H*-pyrazole (**6b**) and 5-amino-4-phenyl-1*H*-pyrazole (**6c**).

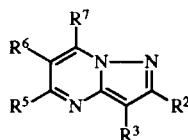
The <sup>1</sup>H nmr spectra of the compounds **1a** to **1i** are reported in Table 1.

### Chemical Reduction.

#### Reduction by Sodium Borohydride.

The reduction of 6-phenylpyrazolo[1,5-*a*]pyrimidines **1a** to **1d** by sodium borohydride in ethanol leads to

Table 1  
<sup>1</sup>H NMR Spectra of Pyrazolo[1,5-a]pyrimidines 1 [a]



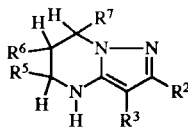
| Compound  | R <sup>2</sup>                | R <sup>3</sup>                | R <sup>5</sup>                | R <sup>6</sup>                | R <sup>7</sup>                | δR <sup>2</sup> | δR <sup>3</sup> | δR <sup>5</sup> | δR <sup>6</sup> | δR <sup>7</sup> |
|-----------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| <b>1a</b> | H                             | C <sub>6</sub> H <sub>5</sub> | H                             | C <sub>6</sub> H <sub>5</sub> | H                             | 8.63<br>s       | 7.3-7.9<br>m    | 9.51            | 7.3-7.9<br>m    | 9.25<br>s       |
| <b>1b</b> | CH <sub>3</sub>               | C <sub>6</sub> H <sub>5</sub> | H                             | C <sub>6</sub> H <sub>5</sub> | H                             | 2.73<br>s       | 7.4-7.8<br>m    | 9.71            | 7.4-7.8<br>m    | 9.25<br>s       |
| <b>1c</b> | CH <sub>3</sub>               | H                             | H                             | C <sub>6</sub> H <sub>5</sub> | H                             | 2.80<br>s       | 7.08<br>s       | 9.77<br>s       | 7.66<br>s       | 9.33<br>s       |
| <b>1d</b> | C <sub>6</sub> H <sub>5</sub> | H                             | H                             | C <sub>6</sub> H <sub>5</sub> | H                             | 7.4-8.1<br>m    | 7.38<br>s       | 9.80<br>s       | 7.4-8.1<br>m    | 9.21<br>s       |
| <b>1e</b> | C <sub>6</sub> H <sub>5</sub> | H                             | CH <sub>3</sub>               | H                             | CH <sub>3</sub>               | 7.3-8.1<br>m    | 6.72            | 2.50            | 6.38            | 2.70            |
| <b>1f</b> | CH <sub>3</sub>               | H                             | CH <sub>3</sub>               | H                             | CH <sub>3</sub>               | 2.44<br>s       | 6.29            | 2.44            | 6.36            | 2.68            |
| <b>1g</b> | H                             | C <sub>6</sub> H <sub>5</sub> | CH <sub>3</sub>               | H                             | CH <sub>3</sub>               | 8.30            | 7.1-8.1<br>m    | 2.60            | 6.50            | 2.72            |
| <b>1h</b> | CH <sub>3</sub>               | H                             | CH <sub>3</sub>               | H                             | C <sub>6</sub> H <sub>5</sub> | 2.43            | 6.38            | 2.50            | 6.61            | 7.3-8.1<br>m    |
| <b>1i</b> | CH <sub>3</sub>               | H                             | C <sub>6</sub> H <sub>5</sub> | H                             | C <sub>6</sub> H <sub>5</sub> | 2.53            | 6.60            | 7.4-8.2<br>m    | 7.24            | 7.4-8.2<br>m    |

[a] Spectra **1a** to **1d**: solvent trifluoroacetic acid; **1e** to **1i**: deuteriochloroform.

4,5,6,7-tetrahydro compounds **3a** to **3d**. Their spectral data (<sup>1</sup>H nmr) are given in Table 2. In contrast, under the same conditions, no reaction is observed with compounds

**1e** to **1g** which have no phenyl substituent on the pyrimidine ring. A less conjugated six membered ring is then non-reducible.

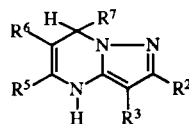
Table 2  
<sup>1</sup>H NMR Spectra of 4,5,6,7-Tetrahydropyrazolo[1,5-a]pyrimidines 3 [a]



|           | R <sup>2</sup>                | R <sup>3</sup>                | R <sup>5</sup>                | R <sup>6</sup>                | R <sup>7</sup>                | δR <sup>2</sup> | δR <sup>3</sup> | δR <sup>5</sup> | δR <sup>6</sup>  | δR <sup>7</sup> | δH <sup>5</sup> | δH <sup>7</sup> |
|-----------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-----------------|-----------------|-----------------|------------------|-----------------|-----------------|-----------------|
| <b>3a</b> | H                             | C <sub>6</sub> H <sub>5</sub> | H                             | C <sub>6</sub> H <sub>5</sub> | H                             | 7.52<br>s       | 6.9-7.4<br>m    | 3.37 m (3H)     | 4.22 m (2H)<br>m |                 | —               | —               |
| <b>3b</b> | CH <sub>3</sub>               | C <sub>6</sub> H <sub>5</sub> | H                             | C <sub>6</sub> H <sub>5</sub> | H                             | 2.15<br>s       | 7.32            | 3.33 m (3H)     | 4.13 m (2H)<br>m |                 | —               | —               |
| <b>3c</b> | CH <sub>3</sub>               | H                             | H                             | C <sub>6</sub> H <sub>5</sub> | H                             | 1.98<br>s       | 5.05<br>s       | 3.29 m (3H)     | 4.05 m (2H)<br>m |                 | —               | —               |
| <b>3d</b> | C <sub>6</sub> H <sub>5</sub> | H                             | H                             | C <sub>6</sub> H <sub>5</sub> | H                             | 7.0-8.4<br>m    | 5.75<br>s       | 3.35 m (3H)     | 4.27 m (2H)<br>m |                 | —               | —               |
| <b>3e</b> | C <sub>6</sub> H <sub>5</sub> | H                             | CH <sub>3</sub>               | H                             | CH <sub>3</sub>               | 7.1-7.8<br>m    | 5.55<br>s       | 1.12<br>d       | 2.02<br>m        | 1.55<br>m       | 3.37<br>m       | 4.15<br>m       |
| <b>3f</b> | CH <sub>3</sub>               | H                             | CH <sub>3</sub>               | H                             | CH <sub>3</sub>               | 1.95<br>s       | 5.02<br>s       | 1.10<br>d       | 1.93<br>m        | 1.51<br>d       | 3.34<br>m       | 4.09<br>m       |
| <b>3g</b> | H                             | C <sub>6</sub> H <sub>5</sub> | CH <sub>3</sub>               | H                             | CH <sub>3</sub>               | 7.47<br>s       | 7.1-7.9<br>m    | 1.15<br>d       | 2.03<br>m        | 1.53<br>d       | 3.41<br>m       | 4.18<br>m       |
| <b>3h</b> | CH <sub>3</sub>               | H                             | CH <sub>3</sub>               | H                             | C <sub>6</sub> H <sub>5</sub> | 2.01<br>s       | 5.05<br>s       | 1.17<br>d       | 2.07<br>m        | 7.1-7.8<br>m    | 3.40<br>m       | 5.38<br>m       |
| <b>3i</b> | CH <sub>3</sub>               | H                             | C <sub>6</sub> H <sub>5</sub> | H                             | C <sub>6</sub> H <sub>5</sub> | 2.06<br>s       | 5.08<br>s       | 7.1-7.9<br>m    | 2.13<br>m        | 7.1-7.8<br>m    | 5.33<br>m       | 5.42<br>m       |

[a] Spectra **3a** to **3d**: solvent dimethyl sulfoxide-d<sub>6</sub>; **3e** to **3i**: deuteriochloroform.

Table 3

<sup>1</sup>H NMR Spectra of 4,7-Dihydropyrazolo[1,5-*a*]pyrimidines **2** [a]

|           | R <sup>2</sup>                | R <sup>3</sup>                | R <sup>5</sup>                | R <sup>6</sup>                | R <sup>7</sup>                | δR <sup>2</sup> | δR <sup>3</sup> | δR <sup>5</sup> | δR <sup>6</sup> | δR <sup>7</sup> | δH <sup>7</sup> |
|-----------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| <b>2a</b> | H                             | C <sub>6</sub> H <sub>5</sub> | H                             | C <sub>6</sub> H <sub>5</sub> | H                             | 7.83            | 7.30-7.70<br>m  | 7.10<br>d       | —               | —               | 5.12            |
| <b>2b</b> | CH <sub>3</sub>               | C <sub>6</sub> H <sub>5</sub> | H                             | C <sub>6</sub> H <sub>5</sub> | H                             | 2.25            | 7.10-7.90<br>m  | 6.91<br>d       | —               | —               | 5.04            |
| <b>2c</b> | CH <sub>3</sub>               | H                             | H                             | C <sub>6</sub> H <sub>5</sub> | H                             | 2.09            | 5.30            | 6.95<br>d       | —               | —               | 4.84            |
| <b>2d</b> | H                             | H                             | H                             | C <sub>6</sub> H <sub>5</sub> | H                             | 7.10-7.90<br>m  | 5.98            | 7.05<br>d       | —               | —               | 5.03            |
| <b>2e</b> | C <sub>6</sub> H <sub>5</sub> | H                             | CH <sub>3</sub>               | H                             | CH <sub>3</sub>               | 7.10-7.80<br>m  | 5.54            | 2.21            | 6.41            | 1.46<br>d       | 4.32<br>q       |
| <b>2f</b> | CH <sub>3</sub>               | H                             | CH <sub>3</sub>               | H                             | CH <sub>3</sub>               | 2.04            | 5.10            | 2.19            | 6.37            | 1.44<br>d       | 4.28<br>q       |
| <b>2g</b> | H                             | C <sub>6</sub> H <sub>5</sub> | CH <sub>3</sub>               | H                             | CH <sub>3</sub>               | 7.76            | 7.0-8.0<br>m    | 2.24            | 6.43            | 1.48<br>d       | 4.30<br>q       |
| <b>2h</b> | CH <sub>3</sub>               | H                             | CH <sub>3</sub>               | H                             | C <sub>6</sub> H <sub>5</sub> | 2.12            | 5.32            | 2.25            | 6.50            | 7.15-7.90<br>m  | 5.35            |
| <b>2i</b> | CH <sub>3</sub>               | H                             | C <sub>6</sub> H <sub>5</sub> | H                             | C <sub>6</sub> H <sub>5</sub> | 2.15            | 5.36            | 7.10-7.80<br>m  | 6.59            | 7.10-7.80<br>m  | 5.41            |

[a] Spectra **2a** to **2d**: solvent dimethyl sulfoxide-*d*<sub>6</sub>; **2e** to **2i**: deuteriochloroform.

### Reduction by Lithium Aluminum Hydride.

Reaction with lithium aluminum hydride in tetrahydrofuran at room temperature of compounds **1a** to **1d** gives 4,7-dihydro derivatives **2a** to **2d**. The <sup>1</sup>H nmr spectra of these products are reported in Table 3.

In the case of 5,7-dimethyl, 5-methyl-7-phenyl and 5,7-diphenyl compounds **1e** to **1i**, the same reaction performed in the refluxing solvent during the same time periods, yields 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidines **3e** to **3i** (Table 2). Thus, for compounds **1a** to **1d**, at the same temperature, the action of sodium borohydride leads to products, the reduction degree of which is higher than for compounds obtained from lithium aluminum hydride reduction, although this latter reducing reagent is generally considered as more powerful. Other analogous examples are described in the literature, particularly with 2-substituted isoquinolinium salts [14].

Furthermore, we have verified that the reaction of sodium borohydride in ethanol at room temperature with 4,7-dihydropyrazolo[1,5-*a*]pyrimidines **2** effectively yields 4,5,6,7-tetrahydro derivatives **3**.

It should be noted that dihydro compounds **2a** to **2d** obtained by the above method, are identical to those obtained from preparative electrochemical reduction of pyrazolo[1,5-*a*]pyrimidin-7-amines in our preceding paper [1]. Thus, compounds also called **2a** to **2d** in this

last publication, have been described mistakenly as 4,5-dihydro derivatives; they are in fact 4,7-dihydro compounds (while **2e** in [1] is really a 4,5-dihydro derivative). Their very poor solubility in the usual solvents only permitted, at the time, to obtain their <sup>1</sup>H nmr spectra in trifluoroacetic acid. More recently, nmr spectra were recorded with a 200 MHz apparatus in dimethyl sulfoxide-*d*<sub>6</sub>, and **2a** to **2d** all exhibit, towards 7 ppm, very close to the aromatic protons, a doublet assigned to the ethylenic proton H<sup>5</sup>. By addition of deuterium oxide, this signal turns into a singlet after disappearance of the H<sup>4</sup>-N proton signal, which often appears as a broad doublet. All these facts could not be observed in trifluoroacetic acid and are in agreement with a 4,7-dihydro structure.

With regard to the 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidines unsubstituted in the 3-position, addition of deuterium oxide induces the immediate disappearance of <sup>4</sup>H-N signal, but also those, more slowly (in few hours), of H<sup>3</sup> (R<sup>2</sup> = CH<sub>3</sub>, C<sub>6</sub>H<sub>5</sub>). This H-D exchange could be explained by an imine-enamine equilibrium, the first form being present in very small proportion, and not detectable by nmr.

We have also verified that this phenomenon was observed with the corresponding 4,7-dihydro derivatives **2**. Such an exchange has already been observed in the case of β-enaminoesters without substituent in the β-position of the nitrogen atom [15]; it is complete in a few minutes.

### Catalytic Hydrogenation.

The catalytic hydrogenation of pyrazolo[1,5-*a*]pyrimidines **1** over 10% Pd-C in methanol at atmospheric pressure, leads exclusively to the 4,7-dihydrogenated compounds **2**.

### Electrochemical Reduction.

#### Polarographic Behavior.

The polarographic behavior of pyrazolo[1,5-*a*]pyrimidines **1** in hydroorganic medium (acetonitrile 50% v/v;  $c = 5 \cdot 10^{-4} M$ ) are different according to the nature and the location of the substituents on the pyrimidine ring, which is solely affected by the reduction.

The polarograms were investigated between pH 0 and pH 7; beyond, the height of the waves rapidly decreases then disappears or they are strongly affected by absorption phenomena. For 5,7-dimethyl compounds **1e** to **1g**, a single one-electron cathodic wave is observed, very near to the background discharge. The half wave potentials are linearly dependent upon the pH (Table 4). For 5-methyl-7-phenyl **1h** and 5,7-diphenyl compound **1i**, the first cathodic wave is followed by a second pH-dependent one-electron wave. The presence of a phenyl substituent on the pyrimidine ring makes the latter more easily reducible and the second wave then appears very near to the background discharge.

Table 4  
 $E_{1/2} = f(\text{pH})$  Plot for Pyrazolo[1,5-*a*]pyrimidines **1**  
in Hydroorganic Medium

| Compound  | First Wave   | Second Wave    |
|-----------|--|----------------|
| <b>1b</b> | -0.66-0.12 pH (pH <2.7)<br>-0.82-0.06 pH (pH >2.7) | -0.98-0.06 pH  |
| <b>1c</b> | -0.60-0.13 pH (pH <2.5)<br>-0.79-0.06 pH (pH >2.5) | -1.02-0.06 pH  |
| <b>1e</b> | -0.81-0.077 pH                                     | ---            |
| <b>1f</b> | -0.82-0.085 pH                                     | ---            |
| <b>1g</b> | -0.85-0.076 pH                                     | ---            |
| <b>1h</b> | -0.60-0.080 pH                                     | -0.90-0.078 pH |
| <b>1i</b> | -0.43-0.075 pH                                     | -0.74-0.070 pH |

For compounds previously prepared [1] with a phenyl group in the 6-position, two one-electron cathodic waves are also observed. The variation of half wave potential *versus* pH is not linear for the first wave. A change of the slope is observed about pH = 2.5-2.7 indicating that a protonated species is involved in the reduction process in strong acidic medium.

Similar behavior has been reported for quinazolines and 4-substituted quinazolines [16].

Equations of  $E_{1/2} = f(\text{pH})$  plot are reported for some products in Table 4.

### Preparative Electrolysis.

The basic investigation has been carried out on

6-phenylpyrazolo[1,5-*a*]pyrimidines **1a** to **1d**. We have verified that all others compounds show the same behavior.

Preparative electrolysis was performed in acidic or neutral medium at the level of the second plateau. For example an electrolysis of **1a**: pH = 1.4;  $c = 5 \cdot 10^{-3} M$ ; acetonitrile 50%;  $E = -1.15 V$ , leads to the corresponding 4,7-dihydro derivative **2a**, after consumption of about 2 Faraday per mole. In the same way, reduction of **1b**, **1c** and **1d** under very similar conditions yields **2b**, **2c** and **2d**.

Controlled potential preparative electrolysis performed at the level of the first plateau consumes about one Faraday per mole and give a complex mixture, the nmr analysis of which is difficult.

Electrolysis in dilute solution have been carried out in order to elucidate the reduction process. For example, electrolysis of **1c** in sulfuric acid, pH = 1.35;  $c = 5 \cdot 10^{-4} M$ ; acetonitrile 50%;  $E = -0.8 V$  under nitrogen, consumes about 1 F per mole, the height of the wave decreases during the electrolysis and completely disappears at the completion of the electrolysis. If the solution is then reoxygenated, the wave attributed to **1c** progressively reappears and its height increases up to its initial value. This allows us to conclude that the reduction of **1c**, at the level of the first plateau, leads to one (or several) hydrodimer(s) easily oxidizable(s) and entirely giving back, by oxidation, the initial pyrazolo[1,5-*a*]pyrimidine **1**.

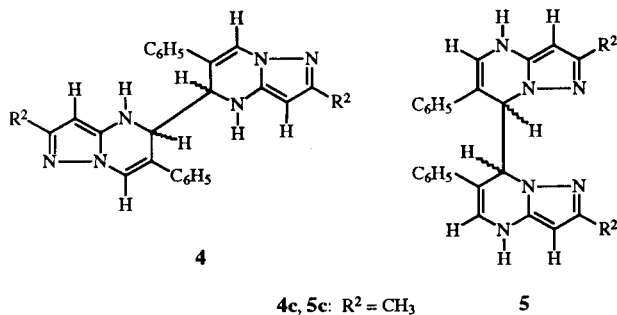
On the  $^1H$  nmr spectrum of the reduction mixture of **1c**, a small quantity (<20%) of the initial product issued from the oxidation of dimer(s) during work-up (evaporation of the solvent, filtration, washing...) is always observed. Its signals are easily identified.

In the case of **1c**, in addition to the 2-CH<sub>3</sub> signal at 2.50 ppm for the initial product (obtained from the oxidation), five distinct signals are observed between 1.90 and 2.15 ppm, for the methyl groups of the reduction product(s) indicating the presence of several oxidizable dimers. Furthermore, we observed the presence of a large broad signal beyond 3.80 ppm, exchangeable with deuterium oxide ( $^4H-N$ ) the integration of which is near of these of signal group between 4.3 and 5.4 ppm assigned to the junction protons. That permits us to propose, as the most probable structures, compounds **4c** or **5c** obtained from a -5,5' or -7,7' coupling (Scheme 2:  $R^2 = CH_3$ ). The absence of a signal which can be assigned to the 5-CH<sub>2</sub> and the presence of exchangeable protons rule out a coupling by the nitrogen atom of the -4,4' type.

After few hours, the nmr solution in dimethyl sulfoxide-*d*<sub>6</sub>, does not present anymore the signals assigned to dimers but exclusively those of **1c**.

In the same way, several *N*-heterocyclic compounds lead, after a  $1e^-$ ,  $1H^+$  reduction, to hydrodimers more or less stable under an oxygen atmosphere. A coupling by a carbon in the  $\alpha$ -position to nitrogen atom is generally observed. Thus, benzopyranno[4,3-*d*]pyrimidines we had previously

Scheme 2



described [17] furnished a single oxidizable dimer with a 4,4'-coupling. For pyrimidines themselves [18] or phthalazines [19] a single type of junction is also reported but, in this last case, a mixture of *meso* and *d,l* compounds is mentioned. It should be also the case for our compounds, in view of the complexity of the <sup>1</sup>H nmr spectra.

All others pyrazolo[1,5-*a*]pyrimidines exhibit a behavior similar to that of 1c. However, it is not possible, in view of the complexity of the nmr spectra and the oxidizability of these hydrodimers to be precise, whether in each case, both types of -5,5' and -7,7' junction are observed or whether only one is present.

The literature records only few examples of reduced pyrazolo[1,5-*a*]pyrimidines derivatives. Auzzi and Cecchi [8a,b] have reduced such fused heterocycles with a carboethoxy group in the 6-position by sodium borohydride in methanol. Some 4,7-dihydro compounds are then obtained, but if the same substituent is in the 5-position, only transesterification by the solvent is observed. Others 4,7-dihydro derivatives, carboethoxylated in the 7-position, are prepared by catalytic hydrogenation over 5% Pd/C in methanol [9].

Furthermore, a single example of a partially reduced pyrazole ring is mentioned for these compounds [20]. However the 3*H*-pyrazolo[1,5-*a*]pyrimidine structure reported is then obtained by condensation of an acyclic nitrile and an azine compound, and not by reduction of the corresponding fused heterocyclic system.

We have thought of a direct and simple route to dihydropyrazolo[1,5-*a*]pyrimidines from 5-aminopyrazoles, which are versatile intermediates both in the synthesis of pyrazolo[1,5-*a*]pyrimidines 1 and their 7-amino derivatives [1,2,7,21].

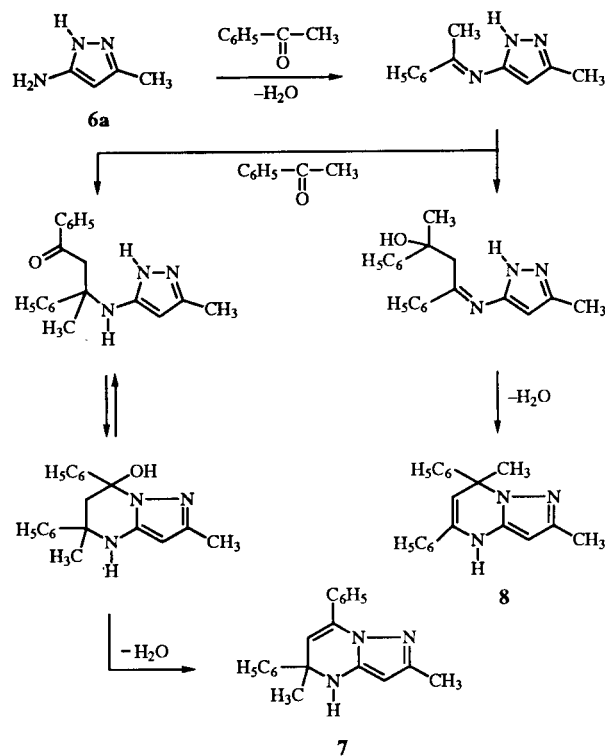
By condensation of 5-amino-1*H*-1,2,4-triazole with acetophenone in the presence of zinc chloride at high temperature, Wermann and Hartmann have recently obtained a mixture of 4,5-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine and 4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine [22].

We have transposed this reaction to substituted 5-aminopyrazoles, in order to obtain one or several dihydro derivatives of pyrazolo[1,5-*a*]pyrimidines. We could success-

fully condense 5-amino-3-methyl-1*H*-pyrazole (6a) with acetophenone in the presence of zinc chloride during 6 hours at 180° to obtain two dihydropyrazolo[1,5-*a*]pyrimidines: a 4,5-dihydro compound 7 and a 4,7-dihydro compound 8.

Two different pathways could be proposed in Scheme 3 to explain the formation of 7 or 8.

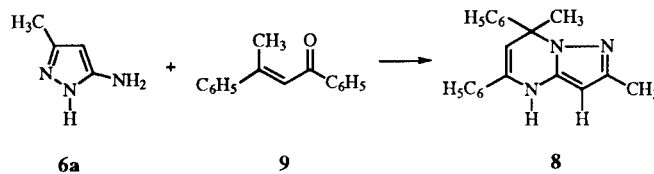
Scheme 3



In fact, only one product is really obtained as shown by <sup>1</sup>H and <sup>13</sup>C nmr spectra. But the choice between the two possible regioisomers 7 or 8 is rather difficult. In order to establish unambiguously the structure of this dihydro compound, we have condensed the 5-amino-3-methyl-1*H*-pyrazole (6a) with the 1,3-diphenyl-but-2-ene-4-one (dypnone) (9) with the same experimental procedure. The condensation only furnishes, in an univocal manner, the 4,7-dihydro derivative 8 (Scheme 4).

The <sup>1</sup>H and <sup>13</sup>C nmr spectra of 8 compared to that of the condensation product of 6a with acetophenone in the presence of zinc chloride are different. It is thus possible

Scheme 4



to conclude that the condensation leads only to a 4,5-dihydro derivate **7**, the 2,5-dimethyl-5,7-diphenyl-4*H*-pyrazolo[1,5-*a*]pyrimidine.

The availability of starting materials, the simplicity of the operation and the good yields which are obtained indicate that this method may provide an interesting and useful route to various 4,5-dihydropyrazolo[1,5-*a*]pyrimidines, while the electrochemical reduction generally leads to 4,7-dihydro derivatives as previously described.

It is also the first time that pyrazolo[1,5-*a*]pyrimidines tetrahydrogenated on the six membered ring are obtained. Up to now, only dihydro products have been prepared by chemical reduction with sodium borohydride. It points to the importance of the nature and position of substituents on the pyrimidine ring for the degree of reduction of the products obtained.

## EXPERIMENTAL

The apparatus and techniques used for polarography and electrolysis have been described previously [23]. The reference electrode was a saturated calomel electrode (sce). The *pH* values were measured with a Radiometer model 4 *pH*-meter equipped with a combined glass-calomel electrode GK 2302 B standardized in aqueous buffer. Melting points are uncorrected. The <sup>1</sup>H and <sup>13</sup>C nmr spectra were recorded on a Bruker WH 80 and a Bruker 200 MHz spectrometer, using tetramethylsilane (TMS) as the internal standard. The microanalyses were performed by Service de Microanalyse, Université Pierre et Marie Curie. All compounds described gave correct elemental analysis; the following abbreviations are used in reporting nmr results: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet.

### Preparation of Compounds **1a** to **1d**.

The pyrazolo[1,5-*a*]pyrimidines **1a** to **1d** were prepared by rearomatization with manganese dioxide of 4,7-dihydropyrazolopyrimidines obtained by preparative electrolysis of corresponding pyrazolo[1,5-*a*]pyrimidin-7-amines as described in [1].

### Preparation of 5,7-Dimethyl-2-phenylpyrazolo[1,5-*a*]pyrimidine (**1e**).

A mixture of 2,3-butanedione, 1.34 g, ( $1.33 \cdot 10^{-2}$  mole) and 5-amino-3-phenyl-1*H*-pyrazole (**6b**), 2.12 g ( $1.33 \cdot 10^{-2}$  mole) was refluxed in 20 ml of concentrated hydrochloric acid for 1.5 hours. The solid residue (hydrochloride of **1e**) was dissolved in 50 ml of water and the solution neutralized with sodium hydroxide. The precipitate was filtered, washed with water and dried to give 2.25 g (76%) of **1e**, mp 168-169° (lit 170°) [24]; <sup>1</sup>H nmr see Table 1.

### Preparation of 2,5,7-Trimethylpyrazolo[1,5-*a*]pyrimidine (**1f**).

2,3-Butanedione, 2 g ( $2 \cdot 10^{-2}$  mole) in 10 ml of concentrated hydrochloric acid was refluxed for 3 hours with 5-amino-3-methyl-1*H*-pyrazole (**6a**), 2 g ( $2.06 \cdot 10^{-2}$  mole). The mixture was cooled, neutralized with a concentrated solution of sodium hydroxide and the solution was extracted twice with 50 ml of chloroform, dried over magnesium sulfate and evaporated to give 2.9 g (90%) of **1f**, mp 78°.

*Anal.* Calcd. for C<sub>9</sub>H<sub>11</sub>N<sub>3</sub>: C, 67.05; H, 6.88; N, 26.07. Found: C, 66.92; H, 6.97; N, 26.13.

### Preparation of 5,7-Dimethyl-3-phenylpyrazolo[1,5-*a*]pyrimidine (**1g**).

With the same procedure as for **1f**, 1.59 g of 5-amino-4-phenyl-1*H*-pyrazole (**6c**) ( $10^{-2}$  mole) and 1 g of 2,3-butanedione in 10 ml of hydrochloric acid were refluxed for 10 hours to give 1.86 g of **1g** (85%) which was recrystallized in a mixture ethanol:hexane 80:20 v/v, mp 92°.

*Anal.* Calcd. for C<sub>14</sub>H<sub>13</sub>N<sub>3</sub>: C, 75.31; H, 5.87; N, 18.82. Found: C, 75.60; H, 5.82; N, 18.76.

### Preparation of 2,5-Dimethyl-7-phenylpyrazolo[1,5-*a*]pyrimidine (**1h**).

With the same work-up as for **1e**, 1.94 g of 5-amino-3-methyl-1*H*-pyrazole (**6a**) ( $2 \cdot 10^{-2}$  mole) and 3.34 g of 1-benzoylacetone ( $2 \cdot 10^{-2}$  mole) in 10 ml of hydrochloric acid refluxed for 10 hours gave, after recrystallization from petroleum ether, 3.38 g of **1h** (87%), mp 87°.

*Anal.* Calcd. for C<sub>14</sub>H<sub>13</sub>N<sub>3</sub>: C, 75.31; H, 5.87; N, 18.82. Found: C, 75.68; H, 5.67; N, 18.97.

### Preparation of 2-Methyl-5,7-diphenylpyrazolo[1,5-*a*]pyrimidine (**1i**).

With the same procedure as for **1e**, 4.10 g of 3-methyl-5-amino-1*H*-pyrazole (**6a**) and 9.46 g of dibenzoylmethane ( $4.2 \cdot 10^{-2}$  mole) in 25 ml of hydrochloric acid, refluxed for 5 hours, gave after recrystallization in a mixture ethanol:hexane 85:15 v/v, 10.94 g of **1i** (91%) mp 115°.

*Anal.* Calcd. for C<sub>19</sub>H<sub>15</sub>N<sub>3</sub>: C, 79.97; H, 5.30; N, 14.73. Found: C, 80.07; H, 5.22; N, 14.59.

## Chemical Reductions of Pyrazolo[1,5-*a*]pyrimidines.

### Reduction by Sodium Borohydride of **1**. Preparation of **3**.

#### 4,5,6,7-Tetrahydro-3,6-diphenylpyrazolo[1,5-*a*]pyrimidine (**3a**).

Sodium borohydride (180 mg) was added to a solution of 130 mg of **1a** in ethanol (20 ml). After 7 hours at room temperature the mixture was poured in 400 ml of water. After a few hours the precipitate which was formed was filtered, washed with water and dried to give 127 mg of **3a** (95%) mp 177°; <sup>1</sup>H nmr see Table 2.

*Anal.* Calcd. for C<sub>18</sub>H<sub>17</sub>N<sub>3</sub>: C, 78.51; H, 6.22; N, 15.26. Found: C, 78.45; H, 6.16; N, 15.38.

#### 4,5,6,7-Tetrahydro-2-methyl-3,6-diphenylpyrazolo[1,5-*a*]pyrimidine (**3b**).

A mixture of 315 mg of **1b** and 350 mg of sodium borohydride in 25 ml of ethanol was stirred 17 hours at room temperature. The same work-up as above gave 271 mg of **3b** (85%), mp 160°.

*Anal.* Calcd. for C<sub>19</sub>H<sub>19</sub>N<sub>3</sub>: C, 78.86; H, 6.62; N, 14.52. Found: C, 79.02; H, 6.54; N, 14.71.

#### 4,5,6,7-Tetrahydro-2-methyl-6-phenylpyrazolo[1,5-*a*]pyrimidine (**3c**).

A mixture of 213 mg of **1c** and 230 mg of sodium borohydride in 10 ml of ethanol was stirred 5 hours at 50°. The solution was poured in 350 ml of water, then extracted four times with 15 ml of chloroform. The organic layers were dried over sodium sulfate and chloroform was evaporated to give 180 mg of **3c** (83%), mp 216°.

*Anal.* Calcd. for C<sub>13</sub>H<sub>15</sub>N<sub>3</sub>: C, 73.21; H, 7.09; N, 19.70. Found: C, 72.98; H, 7.16; N, 19.60.

4,5,6,7-Tetrahydro-2,6-diphenylpyrazolo[1,5-*a*]pyrimidine (**3d**).

With the same procedure as for **3a** and **3b**, 230 mg of **1d** and 300 mg of sodium borohydride in 30 ml of ethanol gave 182 mg of **3d** (78%) mp 151°.

*Anal.* Calcd. for C<sub>18</sub>H<sub>17</sub>N<sub>3</sub>: C, 78.51; H, 6.22; N, 15.26. Found: C, 78.55; H, 6.30; N, 15.12.

Reduction by Sodium Borohydride of **1h** and **1i**. Preparation of **3h** and **3i**.

4,5,6,7-Tetrahydro-2,5-dimethyl-7-phenylpyrazolo[1,5-*a*]pyrimidine (**3h**).

With the same procedure as above, **3h** is obtained (72%) mp 95-97°.

*Anal.* Calcd. for C<sub>13</sub>H<sub>15</sub>N<sub>3</sub>: C, 73.21; H, 7.09; N, 19.70. Found: C, 73.03; H, 7.19; N, 19.88.

4,5,6,7-Tetrahydro-2-methyl-5,7-diphenylpyrazolo[1,5-*a*]pyrimidine (**3i**).

With the same work-up, **3i** is obtained (83%) mp 107-108° dec.

*Anal.* Calcd. for C<sub>19</sub>H<sub>19</sub>N<sub>3</sub>: C, 78.86; H, 6.62; N, 14.52. Found: C, 79.01; H, 6.58; N, 14.37.

Reduction by Lithium Aluminum Hydride of Compounds **1a** to **1d**. General Procedure.

Pyrazolo[1,5-*a*]pyrimidine **1** (1 mmole) was dissolved in 40 ml of freshly distilled tetrahydrofuran. After 24 hours of stirring at room temperature, the mixture was quenched with 10 ml of water and filtered. The solution was extracted three times with 25 ml of chloroform. The organic layer was dried on sodium sulfate, then evaporated to give corresponding 4,7-dihydropyrazolo[1,5-*a*]pyrimidine **2**. For melting points, see [1] (compounds called **2a** to **2d**); <sup>1</sup>H nmr were reported in Table 3.

General Procedure for Compounds **1e** to **1i**.

Compound **1e** to **1i** (1 mmole) and 200 mg of lithium aluminum hydride are stirred at room temperature for 48 hours in 30 ml of tetrahydrofuran. After treatment as above, the 4,7-dihydro derivative was isolated; for <sup>1</sup>H nmr see Table 3.

4,7-Dihydro-5,7-dimethyl-2-phenylpyrazolo[1,5-*a*]pyrimidine (**2e**).

With the same procedure, compound **2e** precipitates. A white solid is obtained (76%) mp 140-141°.

*Anal.* Calcd. for C<sub>14</sub>H<sub>15</sub>N<sub>3</sub>: C, 74.64; H, 6.71; N, 18.65. Found: C, 74.39; H, 6.75; N, 18.81.

4,7-Dihydro-2,5,7-trimethylpyrazolo[1,5-*a*]pyrimidine (**2f**).

With the same work-up as above, a white precipitate is isolated (66%) mp 92-94° dec.

*Anal.* Calcd. for C<sub>9</sub>H<sub>13</sub>N<sub>3</sub>: C, 66.22; H, 8.03; N, 25.75. Found: C, 66.34; H, 7.98; N, 25.59.

4,7-Dihydro-5,7-dimethyl-3-phenylpyrazolo[1,5-*a*]pyrimidine (**2g**).

With the same procedure, a white solid is obtained (62%) mp 98-99° dec.

*Anal.* Calcd. for C<sub>14</sub>H<sub>15</sub>N<sub>3</sub>: C, 74.64; H, 6.71; N, 18.65. Found: C, 74.81; H, 6.83; N, 18.78.

4,7-Dihydro-2-methyl-7-phenylpyrazolo[1,5-*a*]pyrimidine (**2h**).

Compound **2h** precipitates as a white solid (71%) mp 114-115° dec.

*Anal.* Calcd. for C<sub>14</sub>H<sub>15</sub>N<sub>3</sub>: C, 74.64; H, 6.71; N, 18.65. Found: C, 74.48; H, 6.62; N, 18.47.

4,7-Dihydro-2-methyl-5,7-diphenylpyrazolo[1,5-*a*]pyrimidine (**2i**).

With the same work-up as above a white solid **2i** is isolated (80%) mp 120-122°.

*Anal.* Calcd. for C<sub>19</sub>H<sub>17</sub>N<sub>3</sub>: C, 79.41; H, 5.96; N, 14.62. Found: C, 79.32; H, 6.06; N, 14.79.

Reaction of Lithium Aluminum Hydride with **1e** to **1i** in Refluxing Tetrahydrofuran.

Preparation of **3e** to **3i**. General Procedure.

A mixture of 1 mmole of pyrazolo[1,5-*a*]pyrimidine **1** and 200 mg of lithium aluminum hydride was refluxed in 35 ml of freshly distilled tetrahydrofuran for 48 hours. After cooling, the treatment is similar to the reaction effected at room temperature. **3h** (84%); **3i** (78%); <sup>1</sup>H nmr see Table 2.

4,5,6,7-Tetrahydro-5,7-dimethyl-2-phenylpyrazolo[1,5-*a*]pyrimidine (**3e**).

With the same procedure, a white solid **3e** is obtained (71%) mp 154-156° dec.

*Anal.* Calcd. for C<sub>14</sub>H<sub>17</sub>N<sub>3</sub>: C, 73.97; H, 7.54; N, 18.49. Found: C, 74.10; H, 7.66; N, 18.37.

4,5,6,7-Tetrahydro-2,5,7-trimethylpyrazolo[1,5-*a*]pyrimidine (**3f**).

With the same work-up as above, a white precipitate **3f** is isolated (68%) mp 85°.

*Anal.* Calcd. for C<sub>9</sub>H<sub>15</sub>N<sub>3</sub>: C, 65.42; H, 9.15; N, 25.43. Found: C, 65.39; H, 9.23; N, 25.60.

4,5,6,7-Tetrahydro-5,7-dimethyl-3-phenylpyrazolo[1,5-*a*]pyrimidine (**3g**).

Compound **3g** precipitates and a white solid is obtained (79%) mp 126°.

*Anal.* Calcd. for C<sub>14</sub>H<sub>17</sub>N<sub>3</sub>: C, 73.97; H, 7.54; N, 18.49. Found: C, 73.81; H, 7.49; N, 18.58.

Electrochemical Reduction of Pyrazolo[1,5-*a*]pyrimidines. Preparative Electrolysis.

Electrolysis at the Level of the Second Plateau. Preparation of 4,7-Dihydropyrazolo[1,5-*a*]pyrimidines. General Procedure.

An example of electrolysis is given for **1a**. An electrolysis was carried out at pH 1.25 and E = -1.15 V. The cathodic compartment contained 190 mg of **1a** (0.55 mmole) in 200 ml of solution (acetonitrile 50%, sulfuric acid 0.1 M 50%). At the end of the electrolysis (2.1 F per mole) the solvent was evaporated. The solid precipitated was filtered, washed with water and dried to give 162 mg of **2a** (86%) mp 234° [1]. For some products, when acetonitrile was evaporated, the solution was extracted twice with chloroform, organic layers were dried over sodium sulfate, solvent removed and **2** was then obtained.

Electrolysis at the Level of the First Plateau. Preparation of Hydromers. General Procedure.

An example of electrolysis is given for **1c**. Electrolysis was carried out at pH 1.15 and E = -0.80 V; The cathodic compartment contained 210 mg (10<sup>-3</sup> mole) of **1c** in 200 ml of solution

(acetonitrile 50%; sulfuric acid 0.25 M 50%). At the end of the electrolysis ( $i = 1$  mA), 1.1 F per mole, acetonitrile was evaporated under reduced pressure at room temperature, then sodium hydrogen carbonate was added until pH 7-8. The solid which precipitated was filtered under argon, washed with deoxygenated water and dried over phosphorus pentoxide to give 200 mg of a white solid. The  $^1\text{H}$  nmr shows that it is a mixture of several hydrodimers and 18% of **1c**, obtained from the reoxidation of dimers during work-up.

In the case of **1a**, the electrolysis was carried out with 150 mg of product. At the end of electrolysis the precipitate in the cell was filtered under argon, washed with deoxygenated water and dried over phosphorus pentoxide to give 128 mg of a solid. The  $^1\text{H}$  nmr shows that it is a mixture of hydrodimers and 15% of **1a** obtained from the reoxidation of dimers during work-up.

Preparation of 2,5-Dimethyl-5,7-diphenyl-4H-pyrazolo[1,5-a]-pyrimidine (**7**).

A mixture of acetophenone (18 g), 5-amino-3-methyl-1H-pyrazole (**6a**) (9.2 g) and anhydrous zinc chloride (1.35 g) was stirred at 170-190° for 6 hours. The water formed during the reaction was removed. After cooling to room temperature, methanol (100 ml) was added and the mixture was allowed to stand in a refrigerator overnight. The crude product was filtered, washed with water and dried. A recrystallization of the crude product in ethyl acetate:petroleum ether 30:70 v/v, gave 33.8 g of **7** (78%) mp 137-139° dec;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  1.80 (s, 3H, 5-CH<sub>3</sub>), 1.85 (s, 3H, 2-CH<sub>3</sub>), 5.50 (s, 1H, 3-H), 5.78 (s, 1H, 6-H), 6.62 (br s, 1H, 4-H), 7.1-7.7 (m, 10H, 5- and 7-C<sub>6</sub>H<sub>5</sub>);  $^{13}\text{C}$  nmr (deuteriochloroform):  $\delta$  11.8, 31.8, 60.0, 102.5, 122.9, 125.4, 126.3, 127.2, 128.3, 128.4, 128.7, 128.9, 132.1, 137.2, 137.4, 147.6, 155.4.

Reaction of Dypnone (**9**) with 5-Amino-3-methyl-1H-pyrazole (**6a**). Preparation of 2,7-Dimethyl-5,7-diphenyl-4H-pyrazolo[1,5-a]pyrimidine (**8**).

A mixture of 1,3-diphenylbut-2-ene-4-one (dypnone) (**9**) (7 g, 0.03 mole), 5-amino-3-methyl-1H-pyrazole (**6a**) (3 g, 0.03 mole) and 0.9 g of anhydrous zinc chloride was stirred at 170-180° for 5 hours. The water formed was removed. After cooling, the crude material was chromatographed on silica with a mixture of ethyl acetate:petroleum ether 20:80 v/v. Pure compound **8** (6.36 g, 71%) was obtained, mp 145-147° dec;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  1.88 (s, 3H, 2-CH<sub>3</sub>), 2.13 (s, 3H, 7-CH<sub>3</sub>), 5.31 (s, 1H, 6-H), 5.45 (s, 1H, 3-H), 7.0-7.9 (m, 10H, 5 and 7-C<sub>6</sub>H<sub>5</sub>), 9.10 (br s, 1H, 4-H).

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