Synthesis and Analgesic Effect of N-Substituted 5-Arylidene-6-methyl-3-(4H)-pyridazinones

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Two methods of N-substitution were applied to 5-arylidene-6-methyl-3-(4H)-pyridazinones. The resulting derivatives were tested in order to determine the area of pharmacological activity. Most compounds exhibited a dose-dependent analgesic activity. Introduction of a benzyol substituent in the 2-position of the pyridazinone ring 2j induced the most potent activity.

Keywords — aroylidene-pyridazinone; N-alkynalkylpyridazinone; N-alkylpyridazinone; N-arylpyridazinone; analgesic activity; anti-inflammatory activity

Various derivatives containing a 3-(2H)-pyridazinone ring have been described. Recently, it was reported that N-substituted pyridazinones show antiulcer,1) analgesic and anti-inflammatory2,3) activities. In our search for new analgesic and anti-inflammatory agents, we synthetized a number of new pyridazinone derivatives. We found that some of them were active as analgesic compounds.

Results and Discussion

The 5-arylidene-6-methyl-2-substituted-3-(4H)-pyridazinones listed in Table I were prepared according to the following scheme:

\[
\begin{align*}
\text{CH}_2\text{O} & \\
\text{HN} & \\
\text{O} & \\
\end{align*}
\]

5-Arylidene-6-methyl-3-(4H)-pyridazinones (1) were synthesized by a method described in previous papers.4,5) Compound 2a was obtained through a Mannich reaction. Compounds 2b to 2l were prepared by alkylation or acylation procedures. All compounds were evaluated for analgesic activity as described in the experimental section. Physical and pharmacological data are summarized in Table I; spectral data are reported in Table II.

Behavioral effects and oral acute toxicity were first investigated in mice. No significant behavioral effects were observed even at doses up to 800 mg/kg p.o. With such doses, all animals were still alive after an observation period of one week. A number of derivatives showed a good dose-dependent activity in the phenylquinone-induced writhing test in mice.
TABLE I. Physical Constants and Analgesic Activity of 2-Substituted Pyridazinones 2 at 25, 50 and 100 mg/kg

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<th>Yield (%)</th>
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<th>Formula</th>
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TABLE II. Spectral Data for 2-Substituted Pyridazinones 2

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<th>R³</th>
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<td>H</td>
<td>CH₂-CH₂-C₆H₅</td>
<td>1660 1600 2.25 (s, 3H, CH₃), 3.20 (t, 2H, c), 3.85 (s, 2H, a), 4.40 (t, 2H, d), 6.60 (s, 1H, b), 7.35 (m, 5H, Ar), 7.45 (m, 5H, C₆H₅)</td>
<td></td>
</tr>
<tr>
<td>2h</td>
<td>H</td>
<td>H</td>
<td>CH₂-CH₂-CH₂-C₆H₅</td>
<td>1660 1600 2.15 (m, 2H, d), 2.30 (s, 3H, CH₃), 2.80 (t, 2H, e), 3.85 (s, 2H, a), 4.25 (t, 2H, c), 6.55 (s, 1H, b), 7.30 (m, 5H, Ar), 7.40 (m, 5H, C₆H₅)</td>
<td></td>
</tr>
<tr>
<td>2i</td>
<td>H</td>
<td>H</td>
<td>CH=CO-C₆H₅</td>
<td>1695 1660 1.65 (d, 3H, d), 2.15 (s, 3H, CH₃), 3.75 (s, 2H, a), 6.35 (m, 1H, c), 6.55 (s, 1H, b), 7.35 (m, 5H, Ar), 8.00 (m, 5H, C₆H₅)</td>
<td></td>
</tr>
<tr>
<td>2j</td>
<td>H</td>
<td>H</td>
<td>CO-C₆H₅</td>
<td>1740 1670 2.25 (s, 3H, CH₃), 4.00 (s, 2H, a), 6.60 (s, 1H, b), 7.35 (m, 5H, Ar), 7.70 (m, 5H, C₆H₅)</td>
<td></td>
</tr>
<tr>
<td>2k</td>
<td>Cl</td>
<td>Cl</td>
<td>CO-C₆H₅</td>
<td>1730 1670 2.40 (s, 3H, CH₃), 4.15 (s, 2H, a), 6.35 (s, 1H, b), 7.35 (m, 5H, Ar), 7.70 (m, 5H, C₆H₅)</td>
<td></td>
</tr>
<tr>
<td>2l</td>
<td>Cl</td>
<td>Cl</td>
<td>CO-C₆H₅</td>
<td>1725 1660 2.50 (s, 3H, CH₃), 4.15 (s, 2H, a), 6.15 (s, 1H, b), 7.35 (m, 5H, Ar), 7.80 (m, 5H, C₆H₅)</td>
<td></td>
</tr>
</tbody>
</table>

The compounds 2b, g, j, k exhibited remarkable activities as shown in Table I. Considering structure-activity relationship, it is interesting that 2j and 2k showed higher analgesic activities than did 2i containing and additional carbon at the 2-position. Moreover, introduction of a chlorine atom on the phenyl nucleus in the 5-position did not enhance analgesic activity. The active compounds in the above assay were submitted to further pharmacological tests, such as the hot plate test and carrageenin-induced edema test in rats treated orally. However, only a weak anti-inflammatory activity was detected in the pyridazinone 2b.

In conclusion, several compounds were found to possess a significant dose-dependent analgesic activity. The substitution of the pyridazinone ring was therefore advantageous for activity in comparison with unsubstituted pyridazinones 1, which have no analgesic activity.
Experimental

Melting points were determined on a Kofler apparatus and are uncorrected. The infrared (IR) spectra were recorded on a Beckman 4240 spectrophotometer. The proton nuclear magnetic resonance (1H-NMR) spectra were recorded on a Varian EM 360 A spectrometer. Resonance positions are given on the δ scale (parts per million) relative to internal tetramethylsilane. The NMR signals were designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet.

Chemistry—5-Benzylidene-6-methyl-2-morpholinomethyl-(4H)-3-pyridazinone (2a): A solution of 35% aqueous formaldehyde (1.7 ml, 0.02 mol) was added to morpholine (1.74 g, 0.02 mol) with continuous stirring. Then the solution was heated to 60 °C and benzylideneepipyridazinone 1 (4 g, 0.02 mol), acetic acid (1.2 g, 0.02 mol) and ethanol (10 ml) were added. The mixture was refluxed for 6 h and evaporated in vacuo. The residue was neutralized with 20% aqueous sodium hydroxide and extracted with diethyl ether. The combined extracts were dried on sodium sulfate and evaporated in vacuo. The residue was triturated with diisopropyl ether and the solid which was formed, was collected by filtration and dried.

5-Arylidene-6-methyl-2-(β-alkylaminoethyl)-(4H)-3-pyridazinones Hydrochlorides (2b—e): The appropriate pyridazinone 1 (0.02 mol) was added to an ethanolic solution (50 ml) of sodium (0.46 g, 0.02 g atom). On the other hand, a solution of 2-chloroethylamine hydrochloride (0.02 mol) in absolute ethanol (40 ml) was added to an ethanolic solution (50 ml) of sodium (0.46 g, 0.02 g atom). The two solutions were mixed and stirred at room temperature for 1 h. Afterwards, the mixture was heated to 50 °C for 2 h and then refluxed for 8 h. The cooled suspension was filtered and the filtrate was evaporated to dryness in vacuo. The residue was dissolved in absolute ethanol (20 ml) and the solution was saturated with gaseous hydrochloric acid. Compounds 2b—e were precipitated by addition of diethyl ether and recrystallized from ethanol.

5-Benzylidene-6-methyl-2-phenylalkyl-(4H)-3-pyridazinones (2f—i): Potassium hydroxide (1.12 g, 0.02 mol) and N-tetrahydroammonium bromide (0.76 g, 0.002 mol) were added to a solution of benzylidene pyridazinone 1 (4 g, 0.02 mol) and phenylalkyl bromide (0.02 mol) in benzene (100 ml). The mixture was stirred and refluxed for 18 h. After evaporation the residue was triturated with diisopropyl ether. The crude product was chromatographed on silica gel (ethyl acetate) and recrystallized from ethanol.

5-Arylidene-6-methyl-2-benzoyl-(4H)-3-pyridazinones (2j—l): Benzoyl chloride (3.37 g, 0.02 mol) was added dropwise in an ice bath to a solution of an aryldeneepipyridazinone 1 (0.02 mol) in anhydrous pyridine (80 ml). The solution was stirred overnight at room temperature and refluxed for 5 h. After evaporation, the residue was triturated with diisopropyl ether. The crude product was chromatographed on silica gel (ethyl acetate) and recrystallized from ethanol.

Pharmacology—All compounds were administered orally in a 0.5% hydroxypropyl methyl cellulose suspension to Ifaa Credo OF1, male mice (20 g).

Behavioral Effects and Acute Toxicity in Mice: The compounds were administered at various doses. The animals were observed over 24 h and the symptomatology was noted. In addition, they were kept under observation for 8 d to detect any sign of toxicity.

Phenylquinone Withing Test\textsuperscript{1,11}. Groups of five mice were given i.p. a 0.02% solution (ethanol–water, 5:95) of phenylquinone (P.B.Q) 30 min after oral administration of test drugs. The writhing response frequency of each animal was counted between the 5th and the 15th min after the injection of the irritant agent.

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References and Notes