phosphate in dimethylformamide followed by removal of the protecting group. Similarly, from isopropylidene-adenosine, -guanosine, -cytidine and -uridine, the corresponding 5'-nucleotides were obtained and from thymidine, its mono- and di-phosphate. Furthermore, inosine 5'-phosphate and 5'-diphosphate were prepared by heating isopropylidene inosine with tri- 

butylammonium-pyrophosphate or -polyphosphate.

(Received January 7, 1966)

UDC 547.852.2.07

146. Takenari Nakagome, Akira Kobayashi, Atsuko Misaki, Toshiaki Komatsu*1, Toru Mori, and Seiichi Nakanishi*2: Synthesis of Pyridazine Derivatives. II.*3 Synthesis of N1-4-Pyridazinylsulfanilamide Derivatives.*4

(Research Department, Pharmaceutical Division, Sumitomo Chemical Co., Ltd.*1 and Development Department, Yodogawa Pharmaceutical Co.*2)

In an earlier paper*1 of this series, the synthesis of a series of N1-4-pyridazinylsulfanilamides including N1-(3,6-dimethoxy-4-pyridazinyl)sulfanilamide*2,3 (II) was reported. A superior chemotherapeutic activity*3 of II prompted further study on the synthetic procedure*1 of II. The present paper describes the new finding which have been revealed in the course of the study.

It has already been reported*1 that 4-amino-3,6-dichloropyridazine (I), on treatment with one molecular proportion of sodium methoxide or caustic alkali in methanol, yielded 3-methoxy compound (II) in good yield, and with an excess of the reagent at an elevated temperature it gave two products, i.e., 4-amino-3,6-dimethoxypyridazidine (III) and an alkali-soluble by-product which afforded 4-amino-6-chloro-3(2H)pyridazinone (IV) after recrystallization from water.

Thin-layer chromatographic study of the crude alkali-soluble product showed an additional spot besides (IV). It was found possible to separate the crude mixture, by fractional acidification of the alkaline solution of the mixture, with the result that less acidic 4-amino-6-methoxy-3(2H)pyridazinone (V), m.p. 276~277° was obtained in addition to the known 4-amino-6-chloro-3(2H)pyridazinone (IV), m.p. 300~301°, in a ratio of 1:9. Structural elucidation of V is dealt with later. By heating with methyl alcoholic sodium methoxide or caustic alkali, V was obtained from III, but not from IV. These experiments indicate that mechanism of the reaction is such that II is first formed from I, and then the replacement of chlorine atom and the demethylation in II take place side by side to yield III and IV respectively, and subsequently part of II suffers cleavage of methoxy group at 3 position to give V.

*1 Kasugade-cho, Konohana-ku, Osaka (中込孟也，小林 是，三崎敬子，小松敏昭).

*2 Nozato-higashi, Nishiyodogawa-ku, Osaka (後林 進，中西清一).


Chart 1.

\[
\begin{align*}
\text{ASC} &= \text{acetylthiophanyl chloride} \\
\text{As} &= \text{SO}_3^- \text{NHCOC}_3 \\
\text{S} &= \text{SO}_3^- \text{NH}_2
\end{align*}
\]

Chart 2.

\[
\begin{align*}
\text{VII} : & \quad R = \text{COCH}_3 \\
\text{XI} : & \quad R = \text{H}
\end{align*}
\]

\[
\begin{align*}
\text{K} : & \quad R = \text{COCH}_3, \quad \text{Yield } 2.0\% \text{ (as (XII))} \\
\text{XII} : & \quad R = \text{H}, \quad \text{Yield } 1.5\% \\
\text{XIII} : & \quad R = \text{H}, \quad \text{Yield } 1.5\% \\
\text{XIV} : & \quad R = \text{H}
\end{align*}
\]
In Part VI, a new substance, N\(^1\)-(3,6-dimethoxy-4-pyridazinyl)-N\(^4\)-acetyl sulfanilamide (X) and an alkaline-insoluble substance (XI) have been obtained by the reaction of III with acetyl sulfanilamyl chloride (ASC) in pyridine solution. The subsequent study revealed the formation of additional by-products and elucidated the constitution of the neutral substance (XI).

The condensation was carried out at 0～5° overnight using 0.5 mole of ASC and the product was divided into three fractions; first, the non-acidic and acidic crystalline solids were separated successively by filtration, then aqueous filtrate being left. Thin-layer chromatographic study indicated the presence of VII, X, XI, and starting material (III) in the aqueous filtrate, as illustrated in Fig. 1. When the acidic fraction (crude VII) was subjected to hydrolysis with dilute aqueous sodium hydroxide solution, it gave a product which was found to be a mixture of three sulfonamides by thin-layer chromatographic examination (Fig. 2). Attempt was made to separate these products by taking advantage of difference of their isoelectric points and, XI and XII were isolated. The results of the reaction between III and acetyl sulfanilamyl chloride followed by hydrolysis of the acidic product with dilute sodium hydroxide is shown in Table II, from which it is seen that when the condensation reaction was carried out at 0～5°, a yield of XIII was only 1%, and it increased at higher temperature. The similar demethylation reaction has been reported by Klötzer and Schantl\(^{4}\) who described that N\(^1\)-(2-hydroxy-4-pyrimidinyl)sulfanilamide was obtained by reaction of 2-methoxy-4-aminopyrimidine (XXI) with acetyl sulfanilamide chloride in pyridine and by treatment of N\(^1\)-(2-methoxy-4-pyrimidinyl)sulfanilamide, prepared by an alternative method, with pyridine containing

Fig. 1. Thin-layer Chromatogram of a Product from the Reaction of III and ASC in Pyridine

Layer: Silica Gel G, activated at 105° for 30 min.
Detection: I\(_2\) vapor
Samples: 1. An acidic fraction (crude VII) 2. A non-acidic fraction (X)
Solvent: (a) CHCl\(_3\)-acetone-AcOH (7:3:0.05), 10 cm., twice developed with the same solvent system
(b) CHCl\(_3\)-MeOH (8:2), 10 cm.

Fig. 2. Thin-layer Chromatogram of a Product from the Alkali Hydrolysis of an Acidic Fraction (crude VII)

Layer: Silica Gel G, activated at 105° for 30 min.
Detection: Diazonium Reagent
Solvent: CHCl\(_3\)-acetone-AcOH (7:3:0.05), 10 cm.
Sample: 1. An acidic fraction
2. A filtrate
3. XI
4. X\(_{III}\)
5. X\(_{V}\)

20% ether-hydrochloric acid on a steam bath. Nitta, et al.5) have also reported similar
observation in the reaction of XXI with p-nitrobenzenesulfonyl chloride.

Many reports have been available concerning the cleavage of ether linkage of
phenolethers using pyridine hydrochloride as a reagent, since a series of studies by
Prey.6) Treatment of VIII and XII with pyridine hydrochloride led to the cleavage of
methoxy group as expected (Chart 2). The formation of X and XII from VII was detected
by thin-layer chromatography, and after hydrolysis XIII was separated in addition to
XII. The yield of the demethylated product (XIII), however, was lower comparing with
that of the reaction of XII with acetylsulfanilamyl chloride under the same reaction
conditions. The formation of demethylated products (X), (X) and (VI) in the reaction mentioned
above, therefore, might be caused by the action of pyridine hydrochloride upon VII or
XII, although it is not attributable only to pyridine hydrochloride. The formation of
XIV was proved by thin-layer chromatography but this failed to be isolated. Treatment
of XII with pyridine at 100° resulted in the recovery of the unchanged starting material.
Compound (X) was failed to be obtained by the reaction of VII and acetylsulfanilamyl
chloride in pyridine.85 Thus, both conceivable reaction sequences (XIII)→(VI)→(X)
and (XII)→(XI) were excluded. Thin-layer chromatographic examination showed no formation
of XIII or XIV when VII was refluxed with dilute sodium hydroxide solution.

The sulfonamide (XIII), readily obtained from XII as mentioned above, gave a positive
diazo reaction and was soluble in dilute bicarbonate solution, a behavior which is
characteristic of N1-heterocyclic sulfonamides. The assignment of the structure (XIII)
to the compound was substantiated by the fact that it was not identical with N1-(3-oxo-
6-methoxy-2,3-dihydro-4-pyridazinyl)sulfanilamide (XIV) prepared from 4-amino-6-
methoxy-3(2H)pyridazinone (V).

A non-acidic substance (XI) remained unchanged when boiled in water. However,
by heating with dilute sodium hydroxide solution it afforded sulfanilic acid (VII) and
3-methoxy-4-amino-6(1H)pyridazinone (VI). The constitution of VI was proved by its
synthesis through a sequence of reactions starting from known 3-methoxy-4-methyl-6(1H)-
pyridazinone (XII)7) as shown in Chart 4. Dichromate-sulfuric acid oxidation of XVII
gave the carboxylic acid (XVIII) which by the action of methanolic hydrogen chloride was
readily transformed into the methyl ester (XIX) and then into the carbamyl derivative
(XX) on treatment with methanolic ammonia. The Hoffmann degradation product of XX
must be 3-methoxy-4-amino-6(1H)pyridazinone (VI) from the method of preparation. The
same compound (VI) was also obtained by refluxing 4-amino-3,6-dimethoxy pyridazine (III)
with dilute hydrochloric acid or with pyridine hydrochloride. In the latter reaction
with the pyridine hydrochloride, however, VI was accompanied by small amount of V.
The constitution of the isomeric (V) was, therefore, 4-amino-6-methoxy-3(2H)pyridazi-
none as represented in Chart 1.

The non-acidic product from the condensation between III and acetylsulfanilamyl
chloride in pyridine may have either of the structures (X) or (XV). It has been shown
by the present authors that 3-methoxy-6-pyridazinol p-toluensulfonate is less resistant
to hydrolysis than 2-p-toluensulfonfyl-6-methoxy-3(2H)pyridazinone, and the former
undergoes hydrolysis by boiling with water whereas the latter does not. This

5) The reaction gave a product which was presumed to be a mixture of the O-sulfonate and the N1-sulfonoyl compound (unpublished work).
observation will be described more fully in a subsequent paper.\(^8\) Considering the stability of the product in question in boiling water, it seems reasonable to allocate the structure (X) to it.

\[
\begin{align*}
\text{CH}_3\text{O}-\text{N}^\equiv\text{N}^\equiv\text{O} & \rightarrow \text{CH}_3\text{O}-\text{N}^\equiv\text{N}^\equiv\text{O} \quad \text{X} \quad 33\% \\
\text{CH}_3\text{O}-\text{N}^\equiv\text{N}^\equiv\text{O} & \rightarrow \text{CH}_3\text{O}-\text{N}^\equiv\text{N}^\equiv\text{O} \quad \text{XII} \quad 43\%
\end{align*}
\]

\[
\text{NH}_2 \quad \text{N}^\equiv\text{N}^\equiv\text{O} \quad \text{V} \quad \text{NH}_2 \quad \text{N}^\equiv\text{N}^\equiv\text{O} \quad \text{VI} \\
\]

Chart 3.

\[
\begin{align*}
\text{O} & \text{N}^\equiv\text{N}^\equiv\text{O} \quad \text{CH}_3 \quad \text{K}_{2}\text{Cr}_2\text{O}_7 \quad \text{conc. H}_2\text{SO}_4 \quad \text{COOH} \\
\text{O} & \text{N}^\equiv\text{N}^\equiv\text{O} \quad \text{CH}_3\text{O} \quad \text{CH}_3\text{OH} \quad \text{HCl} \quad \text{COOCH}_3 \\
\text{NH}_2 \quad \text{CH}_3\text{OH} \quad \text{CONH}_2 \quad \text{Br}_2 \quad \text{NaOH} \quad \text{O} \quad \text{N}^\equiv\text{N}^\equiv\text{O} \quad \text{XX} \quad \text{XIX} \\
\end{align*}
\]

Chart 4.

In view of a marked antimicrobial activity \textit{in vitro} of several \(N^1\)-(3-oxo-2,3-dihydro-4-pyridazinyl)sulfanilamides with or without substituents at 6-position of the pyridazine nucleus which were prepared in the previous work,\(^9\) it was of interest to synthesize a sulfonamide of this series, \(N^1\)-(3-oxo-6-methoxy-2,3-dihydro-4-pyridazinyl)sulfanilamide (XIV).

When \(V\) was allowed to react with acetylsulfanilyl chloride in pyridine according to the usual procedure, it yielded two products, as shown in Chart 3. The desired sulfonamide (XIV) was obtained from the acidic product (X) by hydrolysis with dilute sodium hydroxide solution. The sulfonamide (X) and (XIV) must be \(N^1\)-(3-oxo-6-methoxy-2,3-dihydro-4-pyridazinyl)-\(N^4\)-acetylsulfanilamide and \(N^1\)-(3-oxo-6-methoxy-2,3-dihydro-4-pyridazinyl)sulfanilamide respectively as represented in Chart 3, because of their solubility in dilute aqueous alkali and the method of preparation.

The second product (XVI), insoluble in dilute sodium hydroxide solution, gave 4-amino-6-methoxy-3(2\(H\))pyridazinone (V) and sulfanilic acid (VI) when boiled in water. It follows that the constitution of the product is 4-amino-6-methoxy-3-pyridazinol \(p\)-acetamidobenzenesulfonate, as shown in Chart 3. The ester linkage in XVI seems to be responsible for its susceptibility to hydrolysis.

The sulfonamide (XIV) was investigated bacteriostatically in our laboratory and was found to possess a very high bacteriostatic activity \textit{in vitro} against various microorganisms. These results have already been reported elsewhere.\(^9\)

The 4- and 5-aminopyridazinone derivatives in this and subsequent papers were formulated by amino-3(2\(H\))pyridazinone structures. With respect to the hydroxy group, the oxo formulation was supported by the similarity of the ultraviolet spectra

---


Table I. Ultraviolet Spectral Values

<table>
<thead>
<tr>
<th>Compound (Fig. 3~5)</th>
<th>λ&lt;sub&gt;max&lt;/sub&gt; &lt;sup&gt;SH&lt;/sup&gt; mp (log ε)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) 4-Amino-3(2H)pyridazinone&lt;sup&gt;11&lt;/sup&gt;</td>
<td>290 (4.04)</td>
</tr>
<tr>
<td>(b) 2-Methyl-4-amino-3(2H)pyridazinone&lt;sup&gt;11&lt;/sup&gt;</td>
<td>295 (4.04)</td>
</tr>
<tr>
<td>(c) 3-Methoxy-4-aminopyridazinone&lt;sup&gt;13,14&lt;/sup&gt;</td>
<td>251.5 (3.96), 275 (3.89)</td>
</tr>
<tr>
<td>(d) 4-Amino-6-methyl-3(2H)pyridazinone&lt;sup&gt;13&lt;/sup&gt;</td>
<td>291 (4.02)</td>
</tr>
<tr>
<td>(e) 4-Amino-2,6-dimethyl-3(2H)pyridazinone&lt;sup&gt;15&lt;/sup&gt;</td>
<td>294.5 (4.01)</td>
</tr>
<tr>
<td>(f) 3-Methoxy-4-amino-6-methylpyridazinone&lt;sup&gt;13,16&lt;/sup&gt;</td>
<td>250.5 (3.90), 278 (3.86)</td>
</tr>
<tr>
<td>(g) 5-Amino-3(2H)pyridazinone&lt;sup&gt;13&lt;/sup&gt;</td>
<td>274 (3.72)</td>
</tr>
<tr>
<td>(h) 2-Methyl-5-amino-3(2H)pyridazinone&lt;sup&gt;11&lt;/sup&gt;</td>
<td>277.5 (3.79)</td>
</tr>
</tbody>
</table>

![Figures 3 to 5](image)

Fig. 3. NH₂

Fig. 4. NH₂

Fig. 5. NH₂

of these compounds (a, d, g in Fig. 3~5) to those of 2-methyl-4- and 5-amino-3(2H)pyridazinone derivatives and by the fact that the spectra of (a) and (d) were different from those of 3-methoxy compounds, as shown in Fig. 3~5. For the supposed amino structure there was no investigation made. The amino structure was assumed by analogy with many heterocyclic amino compounds and amino pyrimidinones.<sup>19</sup>

 Experimental

Reaction of 4-Amino-3,6-dichloropyridazine (I) with Potassium Hydroxide—To a solution of 23.8 g. of KOH dissolved in 250 ml. of MeOH 15 g. of I was added and the mixture was heated in an autoclave at 150° for 1.5 hr. The resulting mixture was filtered to remove KCl and the filtrate was evaporated to dryness. The residue was triturated with 20 ml. of water, cooled, and filtered to give 6.35 g. (44.8%) of 4-amino-3,6-dimethoxypyridazine (II), m.p. 175~177°. Recrystallization from water afforded colorless rods, m.p. 177~178°, undepressed on admixture with an authentic specimen.17) Yield, 5.8 g. (41%). The aqueous mother liquor from the crude (II) was neutralized with HCl and the resulting precipitate was filtered, weighing 5.7 g. (43%), m.p. 260~268°.

Ten g. of this solid was dissolved in dilute sodium hydroxide, treated with charcoal and the product fractionally reprecipitated by the addition of HCl in five portions.

<table>
<thead>
<tr>
<th>m.p. (°C)</th>
<th>Beilstein reaction</th>
<th>TLC*7</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. 1 (pH &gt; 12.5)</td>
<td>0.7 g.</td>
<td>274~275</td>
</tr>
<tr>
<td>No. 2 (pH 12.5~12.0)</td>
<td>0.4 g.</td>
<td>274~275</td>
</tr>
<tr>
<td>No. 3 (pH 12.0~11.5)</td>
<td>0.7 g.</td>
<td>264~265</td>
</tr>
<tr>
<td>No. 4 (pH 11.5~11.25)</td>
<td>0.4 g.</td>
<td>279~280</td>
</tr>
<tr>
<td>No. 5 (pH &lt; 11.25)</td>
<td>7.6 g.</td>
<td>278~280</td>
</tr>
</tbody>
</table>

The first two precipitates were combined and recrystallized from MeOH, giving 0.7 g. (3%) of 4-amino-6-methoxy-3(2H)pyridazinone (V), m.p. 276~277°. Anal. Calcd. for C₉H₈O₃N₂: C, 42.55; H, 5.06; N, 28.78. Found: C, 42.50; H, 5.06; N, 28.42. Recrystallization of the last fraction from MeOH gave 6.7 g. (29%) of 4-amino-6-chloro-3(2H)pyridazinone (V) as colorless scales, m.p. 300~301°, undepressed on admixture with a sample prepared by the method of Kurnishi. The IR spectra of the two samples were identical. Anal. Calcd. for C₉H₈O₃N₂Cl: C, 32.99; H, 2.75; N, 28.87. Found: C, 33.02; H, 2.77; N, 28.51.

Reaction of III with Potassium Hydroxide—A solution of 96.5 g. (0.62 mole) of II and 225 g. (3.45 moles) of potassium hydroxide dissolved in 960 ml. of MeOH was heated in an autoclave at 160~165° for 2 hr. The solution was evaporated, and the residue was dissolved in water (500 ml.) and filtered. The filtrate was neutralized with HCl and the precipitate was filtered. Yield, 59.1 g. (67.4%), m.p. 264~273°. The methanolic solution of the crude product was boiled with charcoal, and the charcoal was removed by filtration. Almost all of the solvent was removed from the solution by evaporation, which resulted in the precipitation of 45 g. of colorless prisms, m.p. 277~278°. The melting point of a mixture with the material (V) prepared in the previous experiment was not depressed.

Reaction of III with Acetylsalicylanyl Chloride (ASC)—To a stirred solution of 5.5 g. of III in 30 ml. of pyridine was added with cooling below 10° 7.9 g. (0.95 times of calculated amount) of ASC and the resulting solution was maintained at the same temperature overnight. The reaction mixture was poured into ice water (200 ml.), containing sufficient sodium hydroxide to give pH of 7. The solution was concentrated in vacuo, water (150 ml.) was added and the solution was concentrated to a small volume. The cooled residue was made alkaline with dil. aq. NaOH and filtered. The insoluble solid, 2-p-acetylamino-benzensulfonil-5-amino-6-methoxy-3(2H)pyridazinone (X), weighing 1.37 g. (11.4%), m.p. 200~212°, was purified by dissolving in pyridine and adding water, to give 0.85 g. (7.1%) of colorless prisms of m.p. 215~217° and 0.165 g. (1.4%) of second crop, m.p. 211~212°. Anal. Calcd. for C₁₅H₁₆O₅NS: C, 46.16; H, 4.17; N, 16.56. Found: C, 46.15; H, 4.31; N, 16.32. The alkaline filtrate was adjusted with HCl to pH 3, giving 7.3 g. (58.3%) of crude V-3(3,6-dimethoxy-4-pyridazinyl)-N₄-acetylsulfanilamide (M), m.p. 200° (decomp.). TLC of the product showed the presence of III and K (Fig. 1). This was again dissolved in dil. aq. NaOH solution and conc. HCl was added to the solution until pH 6 was attained. This caused the precipitation of 6.9 g. (55%) of pure III of m.p. 206~207°, which was recrystallized from MeOH to give colorless prisms, m.p. 206~207°, undepressed on admixture with an authentic sample.11) The filtrate from

*6 All melting points are uncorrected. Infrared and ultraviolet spectra were respectively measured with a Shimadzu RS-27 Recording Spectrophotometer.

*7 AcOEt solvent, Silica Gel G plate, detected by I₂ vapor.

the crude (VIII) was made alkaline, evaporated in vacuo, and 1.35 g. (24.6%) of crystals which separated out on cooling were collected. Recrystallization from water formed colorless rhombs, melting at 177~177.5°, underpressed on admixture with starting material. Yield 1.05 g. (18%). The aqueous filtrates from pure VIII and from crude VIII were combined and evaporated in vacuo. The residue was heated with dil. NaOH solution under reflux for 1 hr., 0.3 g. of white powder was precipitated by addition of dil. HCl at pH 3. The product was recrystallized from MeOH yielding 0.05 g. (0.5%) of N'-[3-oxo-6-methoxy-2,3-dihydro-5-pyridazinyl]sulfanilamide (XIII), m.p. 266°. Anal. Calcd. for C_{15}H_{18}O_{7}N_{2}S: C, 44.60; H, 4.08; N, 18.91; S, 10.80. Found: C, 44.52; H, 4.39; N, 19.22; S, 10.48. The methanolic mother liquor was evaporated to dryness and 0.06 g. of XIII recovered by dissolving the residue in dil. NaOH solution and precipitation with HCl.

ii) VIII was reacted with ASC in the same manner as described in i). After evaporation of pyridine and water in vacuo, the residue was digested with 120 ml. of dil. NaOH and filtered. Hydrolysis was effected by refluxing the filtrate for 45 min. The sulfonamide was fractionally precipitated by the addition of dil. HCl. The first fraction, which was precipitated within a pH range 7.5~6.9 and melted at 189~190°, was pure XIII. The second fraction, melting within a range 250~260°, was precipitated within a pH range 6.0~3.0, and filtered after standing for 12 hr. This was purified by recrystallization from MeOH. The starting material was recovered by concentration and cooling the filtrate.

**Table II.**

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Reaction temp. (°C)</th>
<th>Reaction time</th>
<th>ASC (mole ratio)</th>
<th>Yield (%)</th>
<th>XIV</th>
<th>XIII</th>
<th>X</th>
<th>recovered from VIII</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>overnight</td>
<td>0.95</td>
<td>54</td>
<td>1.0</td>
<td>11.4</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>overnight</td>
<td>1.25</td>
<td>64</td>
<td>1.6</td>
<td>6.3</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>overnight</td>
<td>1.44</td>
<td>68</td>
<td>3.2</td>
<td>7.6</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>20~65</td>
<td>0.5 hr.</td>
<td>1.25</td>
<td>52</td>
<td>8.2</td>
<td>9.2</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>room temp.</td>
<td>overnight</td>
<td>1.25</td>
<td>52</td>
<td>8.1</td>
<td>9.0</td>
<td>--</td>
<td></td>
</tr>
</tbody>
</table>

**Reaction of N'-[3,6-Dimethoxy-4-pyridazinyl]sulfanilamide (XII) with Pyridine Hydrochloride**—A solution of 7 g. of XII and 3 g. of pyridine hydrochloride in 30 ml. of pyridine was allowed to stand overnight with ice cooling, and heated at 60~65° for 30 min. After cooling the mixture was poured into sufficient dil. aq. NaOH to give pH of 7 and concentrated in vacuo to remove pyridine. The precipitated product was collected by filtration. This crude product was shown to contain XIII, XIV and XV by thin-layer chromatographic examination according to the procedure represented in Fig. 2. The crude product was dissolved in dil. aq. NaOH, neutralized with HCl to pH 6 to give XIII, 6.65 g. (93.5%), m.p. 190~190.5°. Evaporation of the filtrate to 100 ml., acidification with HCl to pH 2.5 and filtration gave 0.35 g. of crude XIII which was purified by washing with boiling MeOH. Yield, 0.1 g. (1.5%), m.p. 273°.

**Reaction of VIII with Pyridine Hydrochloride**—The treatment of a solution of 7.95 g. of VIII and 3 g. of pyridine hydrochloride in 30 ml. of pyridine in the same manner as described above for the reaction of XII and pyridine hydrochloride and subsequent hydrolysis of the product with 80 ml. of 2N NaOH afforded 6.75 g. (96.3%) of XIII and 0.14 g. (2%) of XIV, m.p. 270°. The presence of VIII, XIII and XV in the crude product from the reaction between XIII and pyridine hydrochloride was proved by thin-layer chromatographic examination according to the procedure represented in Fig. 1.

**Acetylation of XIII**—A slurry of 0.7 g. of XIII in 6 ml. of 75% AcOH was treated with 1.1 ml. of AcOCl. After 30 min. stirring, the mixture was poured into ice water and filtered. There was obtained 0.7 g. of N'-[3-oxo-6-methoxy-2,3-dihydro-5-pyridazinyl]-N' -acetyl sulfanilamide (X), m.p. 274°. Recrystallization from MeOH did not raise the melting point. Anal. Calcd. for C_{15}H_{18}O_{7}N_{2}: C, 46.30; H, 4.29; N, 16.57. Found: C, 46.37; H, 4.27; N, 16.31.

**3-Methoxy-4-amino-6(1H)pyridazine (VI)**—i) From XII. A solution of 0.9 g. of XII in 10 ml. of 2N HCl was refluxed for 15 hr. After cooling, the solution was made alkaline with Na_{2}CO_{3}, and evaporated to dryness. The residue was washed with small quantity of water and filtered, yielding 0.34 g. of VI, m.p. 254~258°. Recrystallization from EtOH gave 0.27 g. (60%) of colorless prisms melting at 266°. Anal. Calcd. for C_{12}H_{18}O_{4}N_{2}: C, 42.55; H, 5.00; N, 29.78. Found: C, 43.19; H, 5.07; N, 29.57. Hydrochloride; m.p. 217~218° (decomp.). Anal. Calcd. for C_{13}H_{18}O_{4}N_{2}·HCl: C, 33.81; H, 4.54; N, 23.66. Found: C, 34.66; H, 4.83; N, 23.60.

ii) From XX. To a stirred solution of 0.7 g. of 3-oxo-6-methoxy-2,3-dihydro-5-pyridazinecarboxamide (XX) in 20 ml. of water containing 1.05 g. of NaOH was added dropwise 0.72 g. of bromine with cooling. After stirring was continued for 45 min., the ice bath was removed and the temperature was raised to room temperature for 1 hr. and then the mixture was heated on the boiling water bath for 10 min. The
cooled solution was neutralized with HCl and concentrated in vacuo to a small volume. The precipitated crystals were recrystallized from EtOH (charcoal treatment) giving 0.3 g. of colorless prisms melting at 268°, and a second crop, 0.1 g., m.p. 268—269°, yield 69%. This product was identified with V prepared from III as described above by mixture melting point and comparison of IR spectra.

Reaction of III with Pyridine Hydrochloride—A solution of 3 g. of III and 3 g. of pyridine hydrochloride in 30 ml. of pyridine was refluxed for 3 hr. The resulting solution was poured into water containing sufficient amount of NaOH to give pH of 7. The solution was concentrated in vacuo to dryness, was added and again the solution was concentrated to dryness. The residue was rinsed with N HCl and filtered. The insoluble material, weighing 0.22 g. (8.2%) and melting at 269—272°, was purified by recrystallization from water. The melting point was raised to 276.5—277.5°. No depression of the melting point was observed when mixed with V described above. The filtrate from crude V was concentrated in vacuo, made alkaline with Na₂CO₃, cooled and filtered, giving 0.98 g. (36%) of colorless prisms, m.p. 260°. Recrystallization from water raised the melting point to 266°. No melting point depression was observed when mixed with V prepared in the previous experiment.

Hydrolysis of XI—A mixture of 2 g. of XI and 20 ml. of 2N NaOH was refluxed for 1.5 hr. The resulting solution was acidified with HCl, then neutralized with Na₂CO₃, concentrated to 5—10 ml., cooled and filtered (mother liquor A). The solid was extracted with boiling EtOH. The EtOH was distilled from the extract, leaving 1.44 g. of crude V which was purified by recrystallization from water. Yield 0.5 g. (60%), m.p. 259—259.5°. Additional recrystallization from MeOH gave 0.48 g. of colorless prisms, identical to a sample prepared from II by mixed melting point and comparison of IR spectra. The insoluble material in boiling EtOH was dissolved in water, and made alkaline with Na₂CO₃. The filtered solution was acidified with HCl to give 0.25 g. (22.1%) of colorless crystals of m.p. >300°, which were identified with an authentic sample of sulfanilic acid by comparison of IR spectra. Acidification to the mother liquor A with HCl, concentration to a small volume, and recrystallization of the precipitate from water gave additional crop (0.12 g.) of sulfanilic acid; total 0.37 g. (33%).

Reaction of V with ASC—To a stirred mixture of 2.8 g. (0.02 mole) of V and 60 ml. of pyridine was added 5.1 g. (0.022 mole) of ASC with cooling. The resulting mixture was stirred at room temperature overnight and then poured into ice water containing 10 ml. of 2N NaOH. The solution was concentrated in vacuo below 40°, water was added, and again the solution was concentrated to a small volume. The residue was made alkaline with NaOH solution with cooling, the insoluble solid was filtered, washed and dried in vacuo, giving 2.9 g. (43.2%) of 4-amino-6-methoxy-3-pyridazinol β-acetaminobenzensulfonate (XVI), m.p. 163—165°. Recrystallization from pyridine—water formed pale brown prisms, m.p. 167—169°. Anal. Calcd. for C₁₃H₁₄O₅N₁₂: C, 46.16; H, 4.17; N, 16.56. Found: C, 46.78; H, 4.46; N, 16.44. From the alkaline mother liquor 2.2 g. (32.8%) of crude N-(3-oxo-6-methoxy-2,3-dihydro-4-pyridazinyl)-N'-acetyl-sulfanilamide (X), m.p. 255—256° was precipitated by the addition of HCl. Recrystallization from MeOH formed colorless needles, m.p. 261° (decomp.). Anal. Calcd. for C₁₄H₁₂O₅N₁₂S: C, 46.16; H, 4.17; N, 16.56. Found: C, 46.28; H, 4.28; N, 16.63.

N-(3-Oxo-6-methoxy-2,3-dihydro-4-pyridazinyl)sulfanilamide (XIV)—A solution of 1 g. of XII in 15 ml. of 2N NaOH was refluxed for 1 hr. Precipitation by acidification with dil. HCl gave 0.75 g. (86%) of XIV, m.p. 252.5°, which was recrystallized from MeOH to give colorless needles, m.p. 248—248.5°. Anal. Calcd. for C₁₃H₁₄O₅N₁₂S: C, 44.60; H, 4.08; N, 18.91. Found: C, 44.60; H, 4.45; N, 18.92.

Hydrolysis of XVI—A mixture of 2 g. of XI and 20 ml. of water was refluxed for 1 hr. The cooled mixture was made alkaline with 10% Na₂CO₃ solution and insoluble V was filtered, giving 0.71 g. (85%), m.p. 280°, depressed when admixed with V obtained above (from I). The IR spectra of the two samples were identical. The filtrate was evaporated and the residue was recrystallized from water, yielding 0.5 g. (50%) of colorless crystals, m.p. >300°, which were identified with a sample of sulfanilic acid by comparison of IR spectra.

3-Oxo-6-methoxy-2,3-dihydro-5-pyrazinedicarboxylic Acid (XVIII)—To a stirred solution of 10 g. of 5-methyl-6-methoxy-3(2H)pyrazinedione (XIII) in 60 ml. of conc. H₂SO₄ was gradually added 27 g. of K₂Cr₂O₇ mixed with 120 ml. of conc. H₂SO₄, the temperature being maintained at 20° with external cooling. Stirring was continued for further 2 hr., then the ice bath was removed and the mixture was allowed to stand overnight. The reaction mixture was poured into 1.2 L. of ice water, and the separated crystals were collected, dissolved inaq. NaHCO₃ solution, treated with charcoal, and filtered. On acidification with HCl there was obtained 3.1 g. (25.6%) of XVIII, m.p. 259° (decomp.), which after recrystallization from water, melted at 261.5° (decomp.). Anal. Calcd. for C₁₃H₁₄O₅N₁₂: C, 42.36; H, 3.56; N, 16.47. Found: C, 42.14; H, 3.53; N, 16.59.

Methyl 3-Oxo-6-methoxy-2,3-dihydro-5-pyrazinedicarboxylate (XIX)—A mixture of 2 g. of XVIII in 50 ml. of MeOH containing 0.2 g. of dry HCl was heated under reflux for 6 hr. The reaction mixture was evaporated to dryness, andaq. NaHCO₃ solution was added to the residue. Extraction with CHCl₃ and evaporation of the extract left 1.9 g. (88%) of XIX, m.p. 175—177°, which formed colorless leaflets melting at 178—179° on recrystallization from MeOH. Anal. Calcd. for C₁₃H₁₄O₅N₁₂: C, 45.65; H, 4.38; N, 15.21. Found: C, 45.92; H, 4.54; N, 15.23.
3-Oxo-6-methoxy-2,3-dihydro-5-pyrazinedicarboxamide (XX)—To a stirred solution of 30 ml. of MeOH saturated with NH₃ at 0° was added with cooling 0.33 g. of XX. The ester dissolved and amide began to deposit. The reaction mixture was stirred and cooled overnight, and evaporated to one-third of the original volume. The filtered crystals were recrystallized from water, giving XX as colorless needles, m.p. 265°-266°. Yield, quantitative. Anal. Calcld. for C₇H₇O₅N₃: C, 42.60; H, 4.17; N, 24.85. Found: C, 42.89; H, 4.31; N, 25.03.

The authors express their deep gratitude to Prof. Emeritus E. Ochiai of the University of Tokyo for his kind encouragements throughout the course of the present work. They are also indebted to Mr. A. Murano for the measurement of infrared and ultraviolet spectra, to Mr. M. Chikada for his cooperation in this work, and to Mr. K. Iwai, Mr. N. Nishimura and Miss M. Fujita for the elementary analysis.

Summary

Reactions of 4-amino-3,6-dichloropyridazine (I) with caustic alkali in methanol and of 4-amino-3,6-dimethoxy-pyridazine (III) with acetyl sulfanil chloride in pyridine were studied. In the former reaction, the reaction sequence to the formation of (III), 4-amino-6-chloro-(V) and 4-amino-6-methoxy-3(2H) pyridazinone (V) was clarified. In the latter condensation reaction, it was found by thin-layer chromatography that 2-p-acetylaminobenzensulfonyl-5-amino-6-methoxy-3(2H)pyridazinone (XI), two demethylated compounds (K and L) of N₁-(3,6-dimethoxy-4-pyridazinyl)-N'-acetyl sulfanilamide (VII) as well as the main product (VII) were produced and their structures were proved. The demethylation reactions of VII and its deacetylated compound (XII) with pyridine hydrochloride were examined.

(Received January 17, 1966)

147. Takenari Nakagome, Akira Kobayashi, and Atsuko Misaki:
Synthesis of Pyrazinedicarboxamide. III, Reaction of Amino-3(2H)pyridazinone Derivatives with Tosyl Chloride.

(Research Department, Pharmaceutical Division, Sumitomo Chemical Co., Ltd.)

In a previous work of this series, 4-amino-3,6-dimethoxy-pyridazine (XV) and 4-amino-6-methoxy-3(2H)pyridazinone (I) was reacted with acetyl sulfanil chloride in pyridine with the object of preparing hitherto unknown N₁'-4-pyridazinylsulfanilamides after subsequent deacetylation. The reaction was not quite simple and, besides desired N₁'-4-pyridazinyl-N'-acetyl sulfanilamides some neutral substances were formed, whose structures, postulated as XIX and XX (Chart 3) have not yet been conclusive. The present work was undertaken in order to obtain further evidences supporting the foregoing assumption and for this purpose the reaction of some pyridazine and pyrazidinone derivatives with tosyl chloride was investigated.

---

*2 Kasugade-cho, Konohana-ku, Osaka (中込孟也, 小林晃, 三島敦子)