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# PURINES, PYRIMIDINES, AND CONDENSED SYSTEMS BASED ON THEM. 18*. REACTION OF 6,8-DIMETHYLPYRIMIDO-[4,5-*c*]PYRIDAZINE-5,7(6H,8H)-DIONE $N_{(2)}$-OXIDE WITH ALKYLAMINES

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*Heating 6,8-dimethylpyrimido[4,5-c]pyridazine-5,7(6H,8H)-dione $N_{(2)}$-oxide (**2**) with piperidine or morpholine gave a moderate yield of 3-piperidino- and 3-morpholino-6,8-dimethylpyrimido[4,5-c]-pyridazine-5,7(6H,8H)-diones (**3a,b**). Reaction of N-oxide (**2**) with ammonia and alkylamines in the presence of an oxidant led to formation of the 3-amino derivatives of **2** and the corresponding desoxy products **3**. The latter were also obtained by an independent method by heating 3-chloro-6,8-dimethylpyrimido[4,5-c]pyridazine-5,7(6H,8H)-dione with alkylamines in butanol.*

**Keywords:** azine N-oxides, 3-alkylamino-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6H,8H)-diones, 6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6H,8H)-dione, nucleophilic addition, oxidative amination.

We have shown recently that 4-amino derivatives are formed from 6,8-dimethylpyrimido[4,5-*c*]-pyridazine-5,7(6H,8H)-dione (**1**) under the influence of primary alkylamines or ammonia in the presence of oxidizing agents [2]. In the case of secondary amines oxidative amination occurs with difficulty to form only 3-amino derivatives in poor yield [2]. We proposed that the yield of the latter might be increased if 6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6H,8H)-dione $N_{(2)}$-oxide (**2**) was used as starting material since quantum-chemical calculations (MOKh method) showed that in this molecule the positive charge on $C_{(3)}$ atom (+0.252) is considerably greater than on the $C_{(4)}$ atom (+0.094). The present paper is concerned with investigation of this question.

We have found that N-oxide **2** does not react with alkylamines at room temperature. However 3-piperidino- and 3-morpholino-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6H,8H)-diones (**3a,b**) were formed in 42 and 36% yields respectively when the compound **2** was boiled for a long time (55-66 h) in excess of piperidine or morpholine. It is known that nucleophilic substitution of hydrogen atom in azine N-oxides is accelerated by the addition of an oxidant [3] and it is possible to retain the N-oxide function in this case [4-6]. The reaction of N-oxide **2** with alkylamines in the presence of an oxidant ($KMnO_4$, $AgPy_2MnO_4$) does not occur cleanly and leads to the formation of a mixture of 3-amino derivatives **3** and **4** (overall yield 50-68%) which is difficult to separate. The $^1$H NMR spectrum of the mixture contains two sets of signals of different intensity, each of which corresponds to substitution of the hydrogen atom at position 3 by alkylamino group. The less soluble N-oxides **4a,c-e,g-i** were isolated successfully by column chromatography and fractional crystallization from carbon tetrachloride.

* For part 17 see [1].

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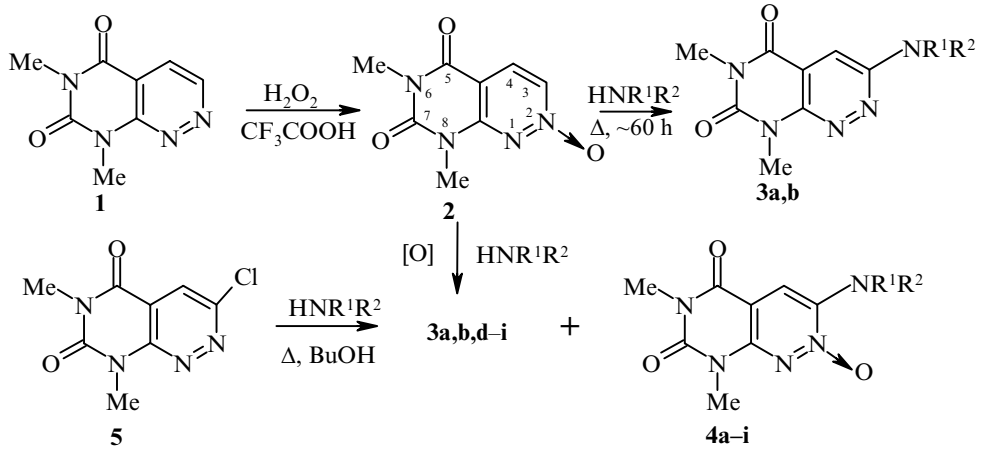
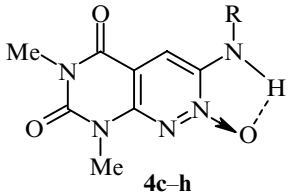
The desoxy amines **3** were not isolated in pure form, but compounds **3a,b,d-i** were prepared by an independent synthesis by heating 3-chloro-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6H,8H)-dione (**5**) with alkylamines in butanol (yield 50-77%). The physicochemical characteristics of compounds **3** and **4** are given in Tables 1 and 2.




**3,4 a** $NR^1R^2$ = piperidino, **b** $NR^1R^2$ = morphplino, **c** $R^1 = R^2 = H$, **d** $R^1$ = Me, $R^2$ = H;
**e** $R^1$ = Et, $R^2$= H; **f** $R^1$ = Pr, $R^2$ = H; **g** $R^1+R^2$ = cyclo-$C_6H_{11}$; **h** $R^1 = CH_2Ph$, $R^2$ = H; **i** $R^1$,$R^2$ = Me

Amines **3** are bright yellow substances ($\lambda_{max}$ 400-430 nm) with a singlet for the 4-H aromatic proton in the 7.28-7.60 ppm region of their $^1$H NMR spectra. The NH proton of the alkylamino group in compounds **3d-h** appears as a broad signal at 4.79-6.12 ppm. A characteristic of the $^1$H NMR spectra of N-oxides **4** in comparison with the spectra of amines **3** is a small high-field shift of the 8-Me signals (~0.2 ppm*), while the NH proton appears at 3-4 ppm to weaker field. It is probable that this is due to formation of an intramolecular hydrogen bond between the oxygen atom of the N-oxide group and the hydrogen atom of the alkylamino group. The lack of color of N-oxides **4c-g** ($\lambda_{max}$ 340-360 nm), in the molecules of which the amino group is removed from conjugation with the heteroaromatic ring, also supports this idea. It should also be noted that the UV spectra of amines **4c-g** contain an additional absorption maximum at ~320 nm, characteristic for heteroaromatic N-oxides*[2] [7].




**4c–h**

Compounds **4a** and **4i**, which contain moieties of secondary amines, are bright yellow substances with $\lambda_{max}$ 430-436 nm.

On the basis of the successful assignment of the signals in the $^1$H NMR spectra we conclude that in most cases the predominant product from the oxidative amination of compounds **2** are 3-amino derivatives **4** with retention of the N-oxide function. The ratios of components **3**:**4** (in %) in the mixtures are as follows: **a** 37:63, **b** 40:60, **c** 0:100, **d** 61:39, **e** 33:67, **f** 13:87, **g** 25:75, **h** 37.63, and **i** 0:100.

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* A similar shift was observed in the spectrum of N-oxide **2** in comparison with that of the spectrum of compound **1**.

*[2] An additional absorption band at 280 nm was observed in the UV spectrum of N-oxide **2** in comparison with the spectrum of compound **1**.

TABLE 1. Physicochemical Characteristics of the Compounds Synthesized

| Compound | mp, °C | $^1$H NMR spectrum ($CDCl_3$), δ, ppm, *J*, Hz | | | | | IR spectrum, ν, $cm^{-1}$ | | | UV spectrum (methanol), $\lambda_{max}$, nm (lg ε) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 8-Me | 6-Me | 4-H | NH | $NR^1R^2$ | ring | CO | NH | |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| **3a** | 156-159 | 3.49 | 3.81 | 7.60 | — | 1.71 (6H, m, β- and γ-$CH_2$ piperidino); 3.70 (4H, m, α-$CH_2$ piperidino) | 1443, 1460, 1479 | 1665, 1713 | — | 252 shoulder (4.33) 273 (4.38) 421 (3.26) |
| **3b** | 211-214 | 3.46 | 3.78 | 7.60 | — | 3.62 (4H, t, *J* = 5.2, $N(CH_2)_2$); 3.86 (4H, t, *J* = 5.2, $O(CH_2)_2$) | 1442, 1476 | 1669, 1714 | | 218 (4.58) 240 shoulder (4.20) 425 (3.76) |
| **3d** | 226-228 | 3.46 | 3.77 | 7.34 | 4.92 d *J* = 4.51 | 3.08 (3H, d, *J* = 5.14, NH<u>Me</u>) | 1473, 1529, 1655 | 1675, 1714 | 3380 | 252 (4.31) 265 shoulder (4.17) 420 (3.31) |
| **3e** | 211-213 | 3.45 | 3.60 | 7.55 | 6.12 | 1.35 (3H, t, *J* = 7.33, C–Me); 3.27 (2H, m, NH–<u>$CH_2$</u>) | 1470, 1525, 1655 | 1671, 1710 | 3385 | 251 (4.18) 268 shoulder (4.06) 420 (3.46) |
| **3f** | 161-162 | 3.45 | 3.76 | 7.33 | 5.04 t *J* =5.36 | 1.00 (3H, t, *J* = 7.33, C–Me); 1.70 (2H, m, C–$CH_2$); 3.4 (2H, m, N–$CH_2$) | 1466, 1521, 1654 | 1668, 1709 | 3396 | 250 (4.35) 265 shoulder (4.29) 423 (3.36) |
| **3g** | 210-211 | 3.45 | 3.76 | 7.28 | 4.79 d *J* =7.74 | 1.38 (4H. m), 1.61 (2H, m); 1.77 (2H, m); 1.97 (2H, m); 3.31 (1H, m, –<u>CH</u>NH cyclohexyl) | 1444, 1466, 1518 | 1663, 1709 | 3398 | 249 (4.39) 263 shoulder (4.31) |
| **3h** | 249-250 | 3.41 3.25* | 3.76 3.55 | 7.37 7.43 | 5.33 t *J* = 5.72 7.60 t *J* =5.68 | 4.65 (2H, t, *J* = 5.72, NH–<u>$CH_2$</u>); 7.26-7.36 (5H, m, $C_6H_5$); 4.64 (2H, t, NH–<u>$CH_2$</u>, *J* = 5.68); 7.23-7.38 (5H, m, $C_6H_5$) | 1452, 1476, 1518 | 1662, 1712 | 3389 | 245 (4.66) 264 shoulder (4.56) 404 (3.59) |

TABLE 1 (continued)

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|---|---|---|---|---|---|---|---|---|---|---|
| **3i** | 158-160 | 3.50 | 3.77 | 7.60 | — | 3.21 (6H, s, $NMe_2$) | 1600 | 1660, 1700 | — | 249 (4.11)<br>269 shoulder (4.12)<br>423 (3.14) |
| **4a** | 172-175 dec. | 3.44 | 3.60 | 7.80 | — | 1.65 (2H, m, γ-$CH_2$ piperidino);<br>1.75 (4H, m, β-$CH_2$);<br>3.19 (4H, m, α-$CH_2$) | 1620 | 1675, 1725 | — | 233 (4.22)<br>287 (4.20)<br>430 (3.61) |
| **4c** | 310-312 dec. | 3.39<br>3.24* | 3.58<br>3.37 | 7.52<br>7.64 | 8.05 | | 1620 | 1665, 1720 | 3200,<br>3260,<br>3390 | 249 (4.30)<br>317 (4.24)<br>340 shoulder (3.74) |
| **4d** | 294-296 dec. | 3.38 | 3.57 | 7.58 | 9.01 | 2.99 (3H, d, *J* = 5.25, NH<u>Me</u>) | 1610 | 1670, 1720 | 3320 | 250 (4.30)<br>319 (3.85)<br>360 (3.57) |
| **4e** | 222-224 dec. | 3.37 | 3.54 | 7.60 | 9.00 | 1.32 (3H, t, *J* = 7.32, C–Me);<br>3.27 (2H, m, NH–<u>$CH_2$</u>); | 1600 | 1675, 1720 | 3315 | 250 (4.30)<br>320 (3.90) |
| | | 3.20* | 3.33 | 7.32 | 8.96 | 1.16 (3H, t, *J* = 7.04, C–Me);<br>3.33 (2H, m, NH–<u>$CH_2$</u>) | | | | 360 (3.65) |
| **4g** | 242–245 dec. | 3.37 | 3.56 | 7.60 | 9.13 d<br>*J* =7.32 | 1.38 (4H, m); 1.61 (2H, m);<br>1.76 (2H, m);<br>1.97 (2H, m); 3.31 (1H, m, NH–<u>CH</u> cyclohexyl) | 1590, 1635 | 1655, 1710 | 3290,<br>3330 | 250 (4.14)<br>325 (3.59)<br>360 (3.42) |
| **4h** | 151-152 dec. | 3.20* | 3.37 | 7.43 | 7.96 | 4.57 (2H, t, *J* = 6.59, NH–<u>$CH_2$</u>);<br>7.2-7.35 (5H, m, $C_6H_5$) | 1600, 1625 | 1665, 1715 | 3270,<br>3325 | 230 (4.54)<br>276 (4.42)<br>450 (3.70) |
| **4i** | 165-168 dec. | 3.44 | 3.60 | 7.80 | — | 2.97 (6H, s, $NMe_2$) | 1620 | 1674, 1714 | — | 233 (3.86)<br>285 (4.05)<br>436 (2.35) |

* For solution in DMSO-$d_6$.

TABLE 2. Elemental Analysis Results for the Compounds Synthesized

| Compound | Empirical formula | Found, % / Calculated, % | | |
|---|---|---|---|---|
| | | C | N | H |
| **3a** | $C_{13}H_{17}N_5O_2$ | 56.5 / 56.7 | 6.3 / 6.2 | 25.6 / 25.5 |
| **3b** | $C_{12}H_{15}N_5O_3$ | 52.2 / 52.0 | 5.4 / 5.4 | 25.1 / 25.3 |
| **3d** | $C_9H_{11}N_5O_2$ | 48.7 / 48.9 | 5.3 / 5.0 | 31.8 / 31.7 |
| **3e** | $C_{10}H_{13}N_5O_2$ | 51.0 / 51.1 | 5.2 / 5.5 | 30.0 / 29.8 |
| **3f** | $C_{11}H_{15}N_5O_2$ | 53.2 / 53.0 | 5.9 / 6.0 | 28.3 / 28.1 |
| **3g** | $C_{14}H_{19}N_5O_2$ | 58.0 / 58.1 | 6.6 / 6.6 | 24.2 / 24.2 |
| **3h** | $C_{15}H_{15}N_5O_2$ | 60.8 / 60.6 | 5.4 / 5.1 | 23.8 / 23.6 |
| **3i** | $C_{10}H_{13}N_5O_2$ | 51.3 / 51.1 | 5.3 / 5.5 | 29.7 / 29.8 |
| **4a** | $C_{13}H_{17}N_5O_3$ | 53.8 / 53.6 | 5.7 / 5.8 | 24.3 / 24.1 |
| **4c** | $C_8H_9N_5O_3$ | 43.1 / 43.1 | 4.2 / 4.0 | 31.1 / 31.4 |
| **4d** | $C_9H_{11}N_5O_3$ | 45.8 / 45.6 | 4.4 / 4.6 | 29.3 / 29.5 |
| **4e** | $C_{10}H_{13}N_5O_3$ | 48.0 / 47.8 | 5.2 / 5.2 | 28.1 / 27.9 |
| **4g** | $C_{14}H_{19}N_5O_3$ | 55.2 / 55.1 | 6.2 / 6.2 | 23.0 / 22.9 |
| **4h** | $C_{15}H_{15}N_5O_3$ | 57.3 / 57.5 | 4.7 / 4.8 | 22.5 / 22.4 |
| **4i** | $C_{10}H_{13}N_5O_3$ | 47.9 / 47.8 | 5.0 / 5.2 | 27.7 / 27.9 |

## EXPERIMENTAL

IR spectra of nujol mulls (compounds **3**) were recorded with a Specord IR-71 apparatus and those of KBr disks (compounds **4**) – with a Perkin Elmer ST/IR - Spectrum 1000 instrument. $^1$H NMR spectra were recorded with a Bruker-250 (250 MHz) apparatus. UV spectra of methanol solutions were recorded with a Specord M-40 spectrometer. Melting points were measured with a PTP apparatus in sealed capillaries without correction. The progress of reactions and the purity of products were monitored by TLC on $Al_2O_3$ (Brockman activity grade 3-4) with chloroform as eluent and development with iodine vapor.

The physicochemical characteristics of the compounds synthesized are given in Table 1 and results of their elemental analyses – in Table 2.

**6,8-Dimethylpyrimido[4,5-*c*]pyridazine-5,7(6H,8H)dione $N_{(2)}$-Oxide (2)**. Hydrogen peroxide (30%, 1 ml) was added to solution of compound **1** [8] (300 mg, 1.6 mmol) in trifluoroacetic acid (5 ml) and the solution was heated for 1 h at 40-45°C (at higher temperatures vigorous oxidation of the starting material occurred!). The reaction mixture was evaporated to dryness in air. The residue was neutralized with aqueous ammonia and extracted with chloroform (3 × 10 ml). Purification was made by chromatography on $Al_2O_3$ column (eluent chloroform), the first colorless fraction being collected. Yield 290 mg (90%). Colorless needles, mp 167-168°C (ethanol) which corresponds to literature data [9]. The method of synthesis of N-oxide **2** described in [9], in which a mixture of formic acid and hydrogen peroxide was used as the oxidant, is less effective (yield, 65%, duration 12 h).

**Synthesis of 3-Alkylamino-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6H,8H)-diones (3) and Their $N_{(2)}$-Oxides (4) (General Method).** Solution of N-oxide **2** (0.21 g, 1 mmol) in alkylamine (30 ml) was stirred for 20 min at 18-20°C (-25°C for $MeNH_2$, -10°C for $EtNH_2$) and $AgPy_2MnO_4$ (0.77 g, 2 mmol) was added in portions.

The reaction mixture was stirred at the same temperature for 1 h (in the case of benzylamine, cyclohexylamine, and secondary amines for one day with the addition of more $AgPy_2MnO_4$ (2 mmol) in portions). The reaction mixture was evaporated to dryness in air and the residue extracted with boiling chloroform (50 ml). The extract was concentrated to about 5 ml and passed through $Al_2O_3$ column (1 × 40 cm, eluent chloroform). The bright yellow fluorescent fraction, containing amines **3** and **4** was collected (overall yield 50-68%). To isolate the pure compound **4** the mixture was again passed through $Al_2O_3$ column (1 × 40 cm, eluent 10:1 $CHCl_3$–$CCl_4$). Multiple fractional crystallization from $CCl_4$ gave pure N-oxides **4**. The physicochemical characteristics of compounds **4** are given in Tables 1 and 2.

**Ammonolysis of 3-Chloro-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6H,8H)-dione (5) (General Method).** Solution of compound **5** [9] (0.23 g, 1 mmol) and alkylamine (3 mmol) in butanol (5 ml) was boiled for 12-60 h (depending on the rate of disappearance of the spot of the starting material on TLC). The reaction mixture was evaporated to dryness in air. The residue was dissolved in the minimum amount of $CHCl_3$ and passed through $Al_2O_3$ column (eluent $CHCl_3$). The clear yellow fraction was collected. Yield 50-77%. Physicochemical characteristics of compounds **3** are given in Tables 1 and 2.

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