# Nitrogen Bridgehead Compounds. Part 73.[1] Ring Transformation of Nitrogen Bridgehead Ring Systems†

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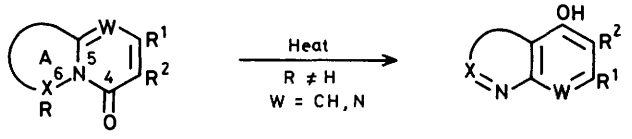
In an investigation of the role of the substituents in position 3 in the ring-transformation reactions of 6-substituted nitrogen bridgehead condensed pyrimidinones (**1**) it was revealed that the resonance effect of the substituent in position 3 may play a more significant role than its field contribution. *X*-Ray crystallographic analysis confirms the structures of pyrido[1,2-*a*]pyrimidine-3-acetates (**7**) and (**8**). While the bicycle of 6-unsubstituted (**7**) is nearly planar, that of 6-methyl-substituted (**8**) is twisted around the C(4)–N(5) bond; the consequence of a 1—3 interaction of the substituents in *peri* positions 4 and 6.

It has been established that bi- or poly-cyclic nitrogen bridgehead compounds of type (**1**) (where A is an unsaturated five- or six-membered ring, X = C or –N= and R ≠ H) may undergo thermal rearrangement into the condensed pyridine derivatives (**2**).[3,4]

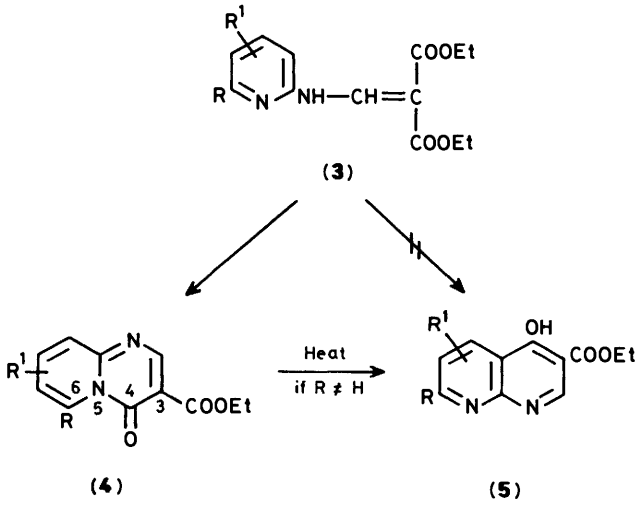



(**1**) (**2**)

**Scheme 1.**

Ring transformation is the essential reaction involved in the synthesis of nalidixic acid and related antibacterial agents[5] starting from α-aza-arylaminomethylenemalonates. For the thermal cyclization of 2-(2-pyridylaminomethylene)malonates (**3**), it was pointed out by Lappin that the 6-unsubstituted derivatives (**3**; R = H) afforded 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**4**; R = H), but the 6-substituted ones (**3**; R ≠ H) gave 1,8-naphthyridines (**5**).[6] [Compound (**5**; R = Me, $R^1$ = H) is the key intermediate of nalidixic acid.[7]]

It was later found that the 6-substituted malonates (**3**; R ≠ H), also gave 6-substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**4**; R ≠ H) as primary products, but these can rearrange to 1,8-naphthyridines (**5**) under the conditions of the cyclization reaction.[3,8] It was assumed that the driving force of the ring transformation of the pyrido[1,2-*a*]pyrimidines (**4**; R ≠ H) [and in general the nitrogen bridgehead compounds (**1**; R ≠ H)] is the unfavourable steric interaction occurring between the adjacent coplanar C(4)=O and the R group. As a consequence of this interaction, the C(4)–N(5) bond becomes the weakest bond of the molecule, which may split to yield an iminoketene intermediate[9] on the input of sufficient energy.[4]

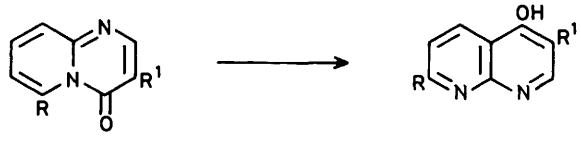



(**3**) (**4**) (**5**)

**Scheme 2.**

Our earlier experimental data on the rearrangement of 6-substituted pyrido[1,2-*a*]pyrimidines into 1,8-naphthyridines indicated that, besides the fundamental role of the 6-substituent (R), the substituent at the position 3 also influences the ring transformation.[3]

We have now investigated the structures and the ring-transformation abilities of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones with various $R^1$ substituents at position 3. The present study involved the ethyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (**6**),[10] the 3-acetates (**7**)[9] and (**8**)[9] and the 3-nitrile (**9**).[3]




(**6**) R = Me ; $R^1$ = COOEt (**10**)
(**7**) R = H ; $R^1$ = $CH_2COOEt$ (**11**)
(**8**) R = Me ; $R^1$ = $CH_2COOEt$ (**12**)
(**9**) R = Me ; $R^1$ = CN (**13**)

**Scheme 3.**

The structures of the 3-acetates (**7**) and (**8**) were analysed by *X*-ray diffraction in the solid state, and their characteristic data were compared with those for the pyridopyrimidinecarboxylate (**6**) and its hydrochloride salt (see Table 1). Molecular diagrams of compounds (**7**) and (**8**) are depicted in the Figure.

The unit cell of the 6-methylpyridopyrimidin-4-one (**6**) contains two independent molecules (A and B) with relatively

† This paper is also regarded as Part 13 of the series 'Ring Transformations.' Part 12 is ref. 2.

**Table 1.** Some *X*-ray diffraction data on 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines (**6**)—(**8**)

| Compound | Dihedral angle O=C(4)···C(6)–R/°[b] | Distance between O(17) and (C81)/ pm[a] | C(4)–N(5) bond distance/pm | N(5)–C(6) bond distance/pm | Ref. |
|---|---|---|---|---|---|
| (**6**)[c] A | 29(1) | 262.8(7) | 146.9(7) | 141.6(7) | 11 |
| B | 19(1) | 260.6(7) | 147.4(7) | 140.4(7) | 11 |
| (**6**·HCl) | 12(1) | 258.9(8) | 151.5(8) | 140.6(8) | 12 |
| (**7**) | 3(2) | 236.4(6)[d] | 143.4(4) | 139.1(4) | |
| (**8**) | 40.4(1) | 265.7(7) | 144.2(3) | 140.7(4) | |

[a] Distance between the geometric centres of substituents on C(4) and C(6) atoms. [b] E.s.d.s are given in parentheses. [c] Two independent molecules are present in the unit cell. [d] Atom C(6) bears a hydrogen atom.

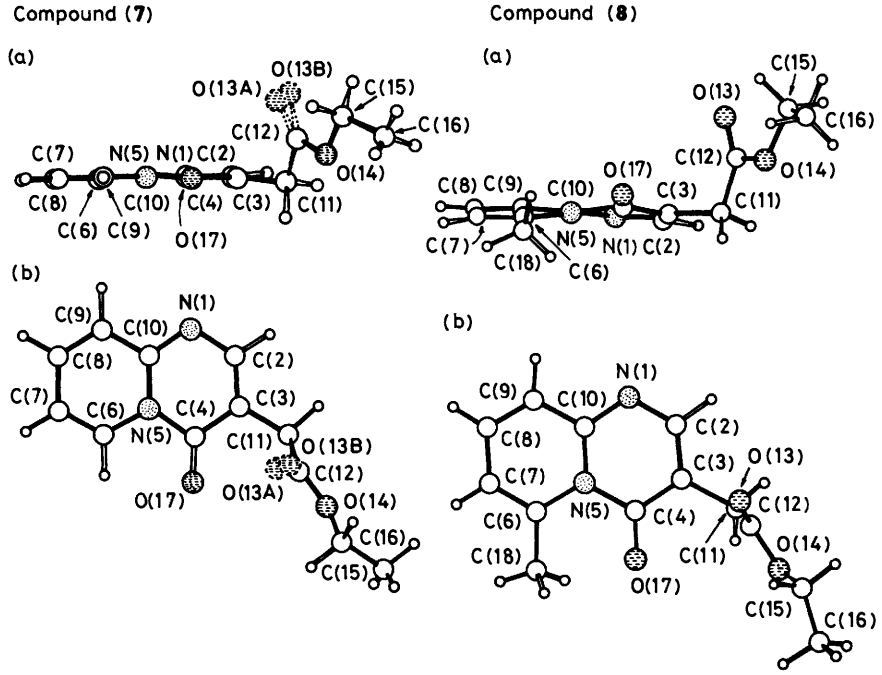



**Figure.** Molecular diagrams for compounds (**7**) and (**8**) with crystallographic atomic numbering. (a) The N(5)–C(10) bond is perpendicular to the plane of the drawing; (b) Atoms C(3), N(5), and C(10) are in the plane of the drawing

long C(4)–N(5) bonds (146.9 and 147.4 pm, respectively). The shorter C(4)–N(5) bond in molecule A is associated with a larger dihedral angle (29°) between the 6-Me group and the oxygen atom of the 4-carbonyl group, O(17)–C(4)···C(6)–C(18), than that in molecule **B** (19°).[11] It is noteworthy that in the protonated species (**6**·HCl), in which the positive charge is dispersed between the N(1) and N(5) atoms, the C(4)–N(5) bond is even longer (151.5 pm),[12] and the dihedral angle decreases to 12°. Compound (**6**) readily undergoes ring transformation at 250 °C, to give the 1,8-naphthyridine (**10**) (see Table 2).

Compared with the 3-carboxylate (**6**), the pyridopyrimidine-3-acetates (**7**; R = H) and (**8**; R = Me) contain much shorter C(4)–N(5) bonds (143.4 and 144.2 pm, respectively).

This is in agreement with the experimental observation that the 3-acetate (**8**; R = Me) requires a higher temperature (300 °C) for the ring transformation than its homologue (**6**; R = Me). The 3-acetate (**7**; R = H), however, does not undergo ring transformation; it decomposes at 350 °C. This enormous difference between the reactivities of the 3-acetates (**7**) and (**8**) cannot be attributed to the small difference in their C(4)–N(5) bond lengths, but can be explained on the basis of the dihedral angles; the 6-unsubstituted compound (**7**) is nearly planar (see the Figure), whereas the 6-methyl-substituted derivative (**8**) has a dihedral angle of 40.4°, which is the largest among the investigated compounds [(**6**)—(**8**) and (**6**·HCl)].

The results of the present *X*-ray investigations supplement our earlier conclusion on the structure and the ring transformation; the ring transformation (ring-opening at the amide bond) of pyrido[1,2-*a*]pyrimidines is dependent on both the C(4)–N(5) amide bond length and the dihedral angle, and these are primarily determined by substituent R in position 6, but are also influenced by substituent $R^1$ at position 3. The presence of an electron-withdrawing group at position 3 [*i.e.* the ester group in compound (**6**)] makes a more planar arrangement of the molecule preferable but it decreases the thermal stability. The introduction of a methylene entity between the pyrido-pyrimidine ring and the ester group [in compound (**8**)] diminishes the conjugation and allows a more flexible conformation. When the C(6) methyl group is replaced by a hydrogen atom [compound (**7**)], a nearly planar arrangement becomes possible, with a relatively short C(4)–N(5) bond.

The above data indicate that the substituent in position 3 influences the ring-transformation of the 6-substituted pyrido[1,2-*a*]pyrimidin-4-ones (**4**; R ≠ H) through its effect on the strength of the C(4)–N(5) bond. Comparison of the results

**Table 2.** Ring transformation of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines (**6**)–(**9**)

| Compound no. | Reaction temperature (°C) | Reaction time (min) | Yield (%) | Ref. |
|---|---|---|---|---|
| (**6**) ⟶ (**10**) | 250[a] | 30 | 80 | 3 |
| (**7**) ⟶ (**11**) | 250[a] | 30 | No reaction | 10 |
| | 300[b] | 30 | | 10 |
| (**8**) ⟶ (**12**) | 250[a] | 30 | 0 | 10 |
| | 300[b] | 30 | 25 | 10 |
| | 350[b] | 5 | 65 | 10 |
| (**9**) ⟶ (**13**) | 250[a] | 30 | 12 | 13 |

[a] In Dowtherm. A. [b] In paraffin oil.

**Table 3.** Crystallographic data on compounds (**7**) and (**8**)

| Data | Compound (**7**) | Compound (**8**) |
|---|---|---|
| Formula | $C_{12}H_{12}N_2O_3$ | $C_{13}H_{14}N_2O_3$ |
| $M$ | 232.2 | 246.2 |
| $a$/pm | 680.1(1) | 2 551.2(7) |
| $b$/pm | 1 287.7(1) | 951.5(5) |
| $c$/pm | 2 567.1(1) | 1 508.2(4) |
| β/° | | 127.09(3) |
| Space group | *Pbca* | *C2/c* |
| $Z$ | 8 | 8 |
| $D_c$/g cm$^{-3}$ | 1.371 | 1.328 |
| μ/cm$^{-1}$ | 8.44 (Cu-$K_\alpha$) | 1.04 (Mo-$K_\alpha$) |
| Number of reflections [$I > 3\sigma(I)$] | 1 913 | 1 448 |
| $R$ | 0.058 | 0.054 |
| $R_w$ | 0.060 | 0.082 |

obtained in the ring-transformation of the 6-methylpyrido-pyrimidine-3-carboxylate (**6**) with those for the 6-methyl-pyridopyrimidine-3-carbonitrile (**9**) (see Table 2) suggests that, with respect to the C(4)–N(5) bond strength, the resonance effect[14] of the substituent in position 3 is more significant than its field contribution.

## Experimental

Suitable single crystals were grown by recrystallization from ethanol. *X*-Ray data on (**7**) and (**8**) were collected on an Enraf–Nonius CAD-4 diffractometer at the Central Research Institute for Chemistry of the Hungarian Academy of Sciences, Budapest. The structures were solved by routine application of the direct methods. All calculations were carried out on a PDP 11/34 minicomputer by means of the Enraf–Nonius SDP program package, with local modifications. Hydrogen-atom positions were found from a difference Fourier map, and they were refined isotropically in the final stages of the anisotropic refinement for the non-hydrogen atoms only in the case of (**8**), as two different positions for atom O(13) denoted by A and B, respectively were found, with an approximate occupancy factor of 0.5 each in structure (**7**).*

* *Supplementary data* (see section 5.6.3 of Instructions for Authors in the January issue). Lists of fractional atomic co-ordinates, bond lengths, and bond angles, hydrogen-atom co-ordinates, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

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