# Nitrogen Bridgehead Compounds. Part 51 [1]. Autoxidation of 9-Aminotetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones. Synthesis and Stereochemistry of 9-Amino- and 9-Hydroxy-6,7-dihydro-4*H*-pyrido[1,2-*a*]-pyrimidin-4-ones



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Received November 28, 1984

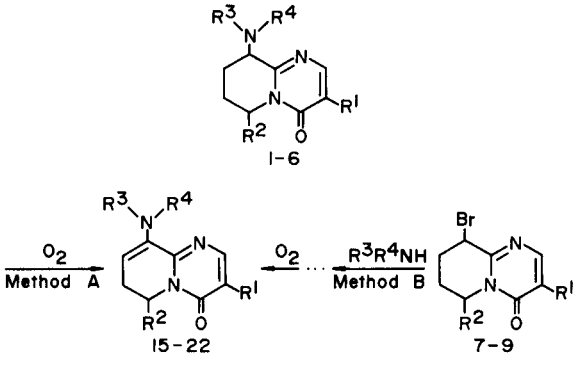
In solution the 9-phenylaminotetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **1-5** were oxidized into the 9-aminodihydro compounds **15-19** by atmospheric oxygen at ambient temperature. Autoxidation is most probably a free-radical chain process, which takes place with ground-state triplet oxygen *via* the radical cation of the enamine form. The 9-aminodihydro derivatives were also prepared from 9,9-dibromo compounds **10** and **11** and from 9-hydroxydihydro compounds **12-14**. The 9-hydroxydihydro derivatives, obtained from the 9-amino compounds **16**, **19** and **21** by acidic hydrolysis, showed a solvent-dependent and $R^1$ substituent-dependent oxo-enol tautomerism. The enol form was stabilized by electron-withdrawing $R^1$ groups and a polar solvent. However, for the 9-aminodihydropyrido[1,2-*a*]pyrimidines **15-26** only the enamine tautomer (*E*) could be identified independently of the substituent and the solvent. The chemical structures of the synthesized products were studied by uv, ir, $^1$H- and $^{13}$C-nmr spectroscopy.

*J. Heterocyclic Chem.*, **22**, 1253 (1985).

## Introduction.

The active 9-methylene group of 6,7,8,9-tetrahydropyrido[1,2-*a*]pyrimidinones [2] allowed us to synthesize 9-substituted derivatives with high biological potency [3-5]. Among these the 9-amino-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones exert antiallergic-antiasthmatic activities [4,5].

In this paper we discuss the synthetic possibilities of the 9-amino-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidines and investigate the structures of the products by uv, ir, $^1$H- and $^{13}$C-nmr spectroscopy.




| | | | | | |
|---|---|---|---|---|---|
| 1, | 15: | $R^1$=COOH, | $R^2$=H, | $R^3$=H, | $R^4$=Ph |
| 2, | 16: | $R^1$=COOH, | $R^2$=Me, | $R^3$=H, | $R^4$=Ph |
| 3, | 17: | $R^1$=COOEt, | $R^2$=Me, | $R^3$=Me, | $R^4$=Ph |
| 4, | 18: | $R^1$=H, | $R^2$=H, | $R^3$=H, | $R^4$=Ph |
| 5, | 19: | $R^1$=H, | $R^2$=Me, | $R^3$=H, | $R^4$=Ph |
| 6: | | $R^1$=H, | $R^2$=Me, | $R^3$=Me, | $R^4$=Ph |
| 7, | 20: | $R^1$=COOH, | $R^2$=Me, | $R^3$=H, | $R^4$=Bu |
| 8, | 21: | $R^1$=COOEt, | $R^2$=Me, | $R^3$=H, | $R^4$=Ph |
| 9, | 22: | $R^1$=COOEt, | $R^2$=H, | $R^3$=Me, | $R^4$=Ph |

Scheme I

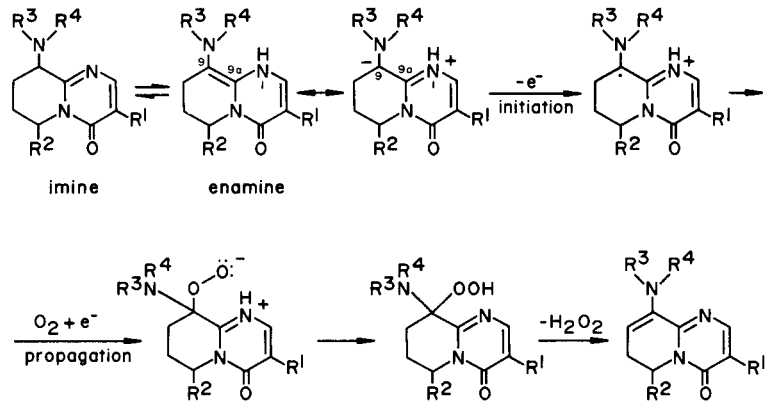
## Oxidation of 9-Amino-4-oxotetrahydropyrido[1,2-*a*]pyrimidines.

We observed that the 9-aminotetrahydropyrido[1,2-*a*]-pyrimidines [5,6] are oxidized in air. Thus, when air was bubbled through solutions of compounds **1-5** in water or chloroform, the dihydro compounds **15-19** were formed (Method A) (Scheme 1). Compound **6** however, resisted oxidation under such conditions. Oxidation took place in other solvents too, *e.g.* in methanol, acetonitrile, acetone, dimethyl formamide, dimethyl sulfoxide and nitromethane.

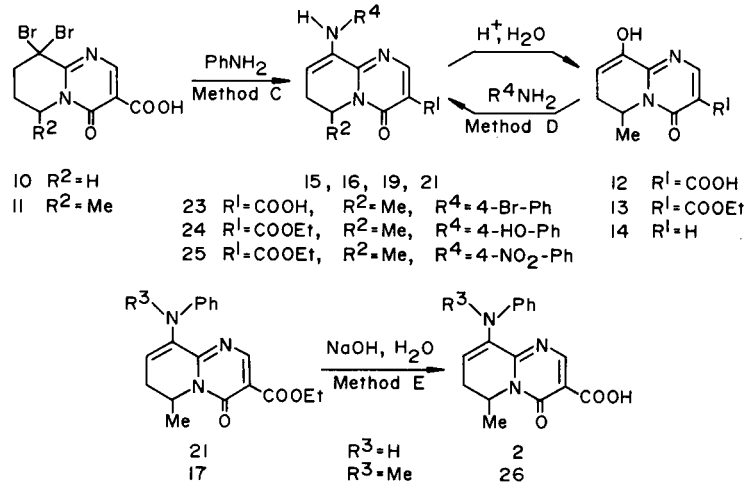
Similarly to the synthesis of the 9-aminotetrahydropyrido[1,2-*a*]pyrimidines **1-6** [5,6] the 9-bromotetrahydropyridopyrimidines **7-9** [7,8] were reacted with butylamine, aniline and *N*-methylaniline. Even under an argon blanket, only the dihydro derivatives **20-22** could be isolated (Method B), presumably due to oxidation of the primary products during work-up.

The oxidation of 9-aminotetrahydropyrido[1,2-*a*]pyrimidines also proceeds in the dark and without any catalyst, which excludes the involvement of excited-state singlet oxygen and suggests a radical mechanism.

It is known, that the 9-aminotetrahydropyrido[1,2-*a*]pyrimidines (**1-6**) show imine-enamine tautomerism [6] (Scheme 2). The oxidation is much faster for the carboxylic acid **2** which contains a higher proportion of the enamine tautomer, than for **5**, which lacks a carboxylic acid function and for which the presence of the enamine form could be detected only indirectly [6]. The difference be-




Scheme 2







Scheme 3

tween the ester **3** and its decarboxylated analogue **6** is even more striking. Compound **3**, which exists partly in the enamine form, is amenable to oxidation, whereas compound **6**, in which the enamine form could not be detected, reacts not at all, or only very slowly, with oxygen under the same conditions. All these facts suggest that oxidation proceeds through the enamine form.

On the basis of the results of our experiments and the literature data [9], the autoxidation of the amines **1-6** can be envisaged as a free radical electron-transfer process involving triplet oxygen (Scheme 2). The first, and at the same time rate-determining step is electron abstraction from the enamine. This is followed by a fast attack of triplet oxygen on the C(9)-carbon of the enamine, the uptake of one electron and the formation of a hydroperoxide, from which, in our case, the dihydro compound is formed by the elimination of hydrogen peroxide.

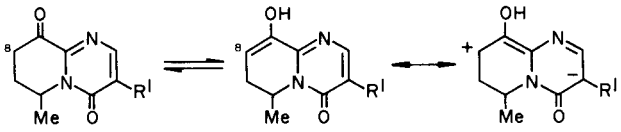
As pointed out earlier in the discussion of the uv spectra of the tetrahydropyrido[1,2-*a*]pyrimidines **1-6** [6] the N(1)H-C(9a)=C(9) sequence should be regarded as the enamine moiety and peroxidation should therefore involve C(9).

Further Synthesis of 4-Oxo-6,7-dihydro-4*H*-pyrido[1,2-*a*]-pyrimidines.

Besides the oxidation described above, the following methods have been developed for the preparation of 6,7-dihydropyrido[1,2-*a*]pyrimidines (Scheme 3). Reaction of the dibromo compounds **10** and **11** [7] with three molar equivalents of aniline in dimethyl sulfoxide at room temperature yielded the 9-anilino-6,7-dihydropyrido[1,2-*a*]pyrimidine-3-carboxylic acids **15** and **16** (Method C). On acidic hydrolysis, the 9-amino derivatives **16**, **19** and **21** provided the 9-hydroxy compounds **12-14**. Reaction of the 9-hydroxy derivatives **12** and **13** with anilines in boiling ethanol yielded the 9-arylamino-6,7-dihydropyridopyrimidines **21**, **23-25** (Method D). Hydrolysis of the ethyl 9-amino-6,7-dihydropyrido[1,2-*a*]pyrimidine-3-carboxylates **17** and **21** with aqueous sodium hydroxide at 60-70° gave the corresponding acids **2** and **26** (Method E).

Tautomerism of 9-Hydroxy-4-oxo-6,7-dihydro-4*H*-pyrido-[1,2-*a*]pyrimidines.

The hydroxy compounds **12-14** may be involved in oxo-enol tautomerism (Scheme 4).




Scheme 4

The ir spectra, taken in potassium bromide pellets, show sharp peaks at about 3400 $cm^{-1}$ refering to the presence of the enol form in the solid phase.

The uv spectra of these derivatives, recorded in ethanol and chloroform, contain the highest wavelength maxima in the range of 300-335 nm. The intensities decreased in time which could be catalysed by acids. The most distinct change was observed for compound **14** in chloroform (Figure 1). In the presence of catalytic amount of trifluoroacetic acid the tautomer equilibrium involved within two hours and resulted in a decrease of the intensity of the band at 305 nm from $\epsilon$ = 6370 to 3470. A conjugated system, containing two double bonds in *s-trans* position, gives more intensive band than that of the *s-cis* rotamer. With compounds **12-14**, in the enol form the C(8)=C(9) double bond assumes an *s-trans*, and in the oxo form the C(9)=O double bond assumes an *s-cis* position, as compared to the C(9a)=N(1) double bond. The maxima gradually decreased refer to the enol → oxo transformation.

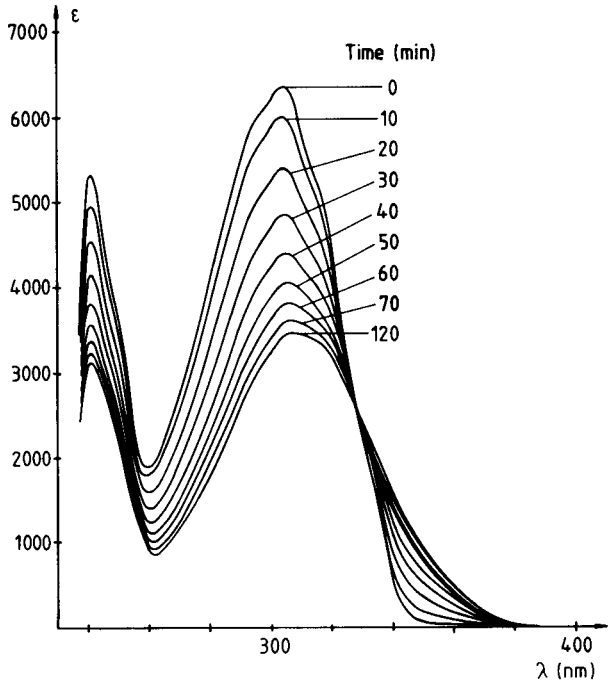



Figure 1

Immediately after dissolution, the nmr spectra show only the presence of the enol tautomer, but signals of the oxo form gradually emerge on standing. The tautomers can best be distinguished by means of the 8-H and C(8) signals. Thus, for the ester **13** in the enol form the vinyl

Table 1

Characteristic $^1$H-NMR Data on 6,7-Dihydropyrido[1,2-*a*]pyrimidin-4-ones in Deuteriochloroform

| Compound | Tautomer | 2-H | 6-H$_e$ | $J_{6,7}$ (Hz) | $^4J_{6,8}$ (Hz) | 7-H$_e$ | 7-H$_a$ | $^2J_7$ (Hz) | $J_{7,8}$ (Hz) | 8-H | 6-C$H_3$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **12** | Enol | 8.87 s | 5.22 m | 1.3, 7.1 | 1.2 | 2.43 ddd | 2.91 ddd | 17.8 | 7.0, 3.0 | 5.77 ddd | 1.40 d |
| | Oxo | 9.07 s | [a] | | | [a] | [a] | | | [a] | 1.58 d |
| **13** | Enol | 8.57 s | 5.22 m | 1.3, 7.1 | 1.3 | 2.43 ddd | 2.91 ddd | 17.8 | 7.0, 3.0 | 5.77 ddd | 1.39 d |
| | Oxo | 8.72 s | 5.25 m | | | 2.10-2.45 m | | | | 2.95 m | 1.53 d |
| **14** | Enol | 7.80 d | 5.12 m | 1.2, 6.9 | 0.8 | 2.30 ddd | 2.85 ddd | 17.9 | 6.9, 2.6 | 5.61 ddd | 1.32 d |
| | Oxo | 8.08 d | 5.12 m | | | 2.00-2.60 m | | | | 2.90 m | 1.52 d |
| **15** | Enamine | 8.61 s | 4.16 t [b] | 7.6 | | 2.55 m | | | 4.9 | 6.30 t | |
| **16** | Enamine | 8.87 s | 5.20 m | 1.5, 6.9 | 1.1 | 2.50 ddd | 2.93 ddd | 18.4 | 7.3, 3.2 | 6.04 ddd | 1.45 d |
| **17** | Enamine | 8.47 s | 5.30 m | 1.4, 7.0 | 1.4 | 2.46 ddd | 2.91 ddd | 18.3 | 7.1, 2.8 | 6.40 ddd | 1.47 d |
| **18** | Enamine | 7.88 d | 4.20 t [b] | 7.1 | | 2.53 td | | | 5.0 | 6.03 t | |
| **19** | Enamine | 7.81 d | 5.10 m | 1.5, 6.8 | 1.0 | 2.34 ddd | 2.80 ddd | 17.8 | 7.3, 2.9 | 5.85 ddd | 1.35 d |
| **20** | Enamine | 8.85 s | 5.23 m | 1.5, 6.6 | | 2.42 ddd | 2.91 ddd | 18.1 | 7.1, 3.3 | 5.08 ddd | 1.38 d |
| **21** | Enamine | 8.62 s | 5.29 m | 1.7, 6.9 | 1.0 | 2.40 ddd | 2.85 ddd | 18.1 | 7.1, 3.2 | 5.96 ddd | 1.39 d |
| **22** | Enamine | 8.55 s | 4.31 t [b] | 7.3 | | 2.66 td | | | 4.9 | 6.57 t | |
| **23** | Enamine | 8.90 s | 5.30 m | 1.7, 6.8 | 1.0 | 2.50 ddd | 2.95 ddd | 18.5 | 7.2, 3.3 | 6.00 ddd | 1.45 d |
| **24** | Enamine | 8.66 s | 5.27 m | 1.5, 6.6 | 1.1 | 2.32 ddd | 2.78 ddd | 18.1 | 7.3, 3.1 | 5.62 ddd | 1.36 d |
| **25** | Enamine | 8.60 s | 5.33 m | 1.7, 6.5 | 1.0 | 2.60 ddd | 2.99 ddd | 18.6 | 6.9, 3.2 | 6.28 ddd | 1.43 d |
| **26** | Enamine | 8.75 s | 5.32 m | 1.5, 6.9 | 1.3 | 2.53 ddd | 3.03 ddd | 18.5 | 7.2, 2.9 | 6.48 ddd | 1.51 d |

[a] Could not be assigned because of overlap. [b] 6-C$H_2$ signal.

Table 2

Characteristic $^{13}$C-NMR Shifts of 6,7-Dihydropyrido[1,2-*a*]pyrimidin-4-ones in Deuteriochloroform

| Compound | Tautomer | C(2) | C(3) | C(4) | C(6) | C(7) | C(8) | C(9) | C(9a) | 6-$CH_3$ | C(1') | C(2') | C(3') | C(4') |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **12** | Enol | 158.2 | 113.6 | 163.1 | 46.7 | 26.6 | 107.2 | 141.4 | 153.0 | 18.2 | | | | |
| | Oxo | 159.0 | 116.5 | 162.9 | 48.9 | 25.7 | 31.6 | 187.5 | 149.9 | 18.0 | | | | |
| **13** | Enol | 156.4 | 116.3 | 157.2 | 45.4 | 26.7 | 105.7 | 141.6 | 153.1 | 18.1 | | | | |
| | Oxo | 156.8 | 119.6 | 157.1 | 47.6 | 25.8 | 31.7 | 188.9 | 150.7 | 18.0 | | | | |
| **14** | Enol | 150.9 | 115.0 | 160.5 | 45.2 | 26.6 | 102.9 | 141.6 | 150.6 | 18.4 | | | | |
| | Oxo | 152.4 | 118.5 | 160.2 | 46.8 | 25.9 | 32.0 | 189.3 | 148.9 | 18.1 | | | | |
| **15** | Enamine | 156.7 | 113.5 | 160.7 | 38.6 | 20.2 | 112.3 | 131.3 | 154.5 | | 142.5 | 117.8 | 128.9 | 120.1 |
| **16** | Enamine | 158.2 | 112.9 | 163.1 | 46.0 | 26.9 | 104.0 | 131.1 | 153.2 | 17.7 | 141.0 | 119.8 | 129.4 | 122.4 |
| **17** | Enamine | 157.4 | 115.0 | 157.2 | 43.9 | 27.8 | 129.6 | 139.3 | 154.2 | 17.2 | 148.5 | 115.3 | 128.6 | 118.9 |
| **18** | Enamine | 151.4 | 114.4 | 161.2 | 38.6 | 20.9 | 104.1 | 132.2 | 151.9 | | 142.0 | 119.6 | 129.4 | 121.8 |
| **19** | Enamine | 151.3 | 114.4 | 160.9 | 44.5 | 27.0 | 101.5 | 131.1 | 150.7 | 17.9 | 141.9 | 119.3 | 129.3 | 121.6 |
| **20** | Enamine | 158.3 | 112.6 | 163.3 | 43.6 | 27.0 | 98.4 | 135.2 | 153.6 | 17.5 | 46.4 | 30.9 | 20.4 | 13.9 |
| **21** | Enamine | 156.8 | 115.9 | 157.5 | 44.9 | 27.3 | 103.6 | 131.4 | 153.7 | 17.6 | 141.9 | 119.5 | 129.4 | 121.9 |
| **23** [a] | Enamine | 156.8 | 112.8 | 160.3 | 44.9 | 26.6 | 111.0 | 130.5 | 153.4 | 17.0 | 142.6 | 119.4 | 131.7 | 114.2 |
| **24** | Enamine | 157.3 | 115.8 | 158.0 | 45.3 | 27.2 | 101.0 | 133.4 | 153.8 | 17.7 | 134.2 | 123.8 | 116.5 | 152.6 |
| **25** | Enamine | 156.6 | 116.6 | 157.2 | 44.7 | 27.7 | 110.8 | 129.4 | 152.9 | 17.9 | 148.1 | 116.0 | 126.1 | 121.0 |
| **26** | Enamine | 159.1 | 112.8 | 163.3 | 45.5 | 28.1 | 131.0 | 139.7 | 154.7 | 17.6 | 148.8 | 116.0 | 129.1 | 119.7 |

[a] Spectrum taken in DMSO-$d_6$ due to poor solubility in deuteriochloroform.

signal for 8-H appears at 5.77 ppm and the C(8) signal at 105.7 ppm, while for the oxo form the corresponding values are 2.95 and 31.7 ppm respectively (Tables 1 and 2). Differences are also reflected in the position of the C(9) signal, which is at 141.6 ppm in the enol form and at 188.9 ppm in the keto form.

The tautomeric equilibrium is established within a few hours at ambient temperature. Equilibrium ratios are shown in Table 3. In deuteriochloroform solutions the proportion of the enol form is lower than in DMSO-$d_6$, for in

Table 3

Equilibrium Ratios of 9-Hydroxy-6,7-dihydro- and 9-Oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]pyrimidin-4-one Tautomers

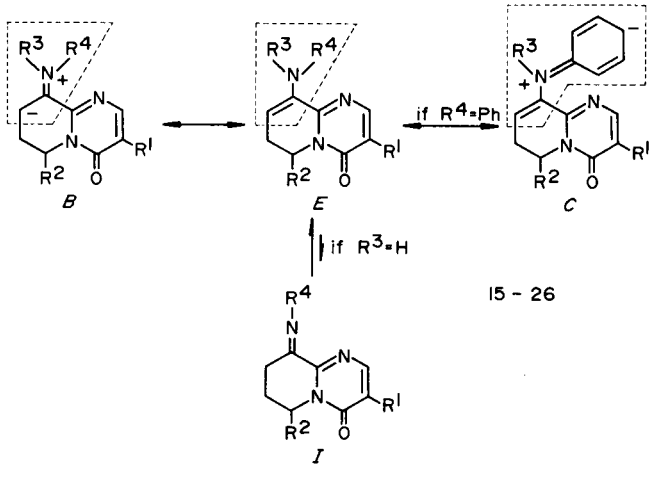
| Compound | in deuteriochloroform | | in DMSO-$d_6$ | |
|---|---|---|---|---|
| | Enol form (%) | Oxo | Enol form (%) | Oxo |
| **12** | 78 | 22 | 73 | 27 |
| **13** | 45 | 55 | 71 | 29 |
| **14** | 27 | 73 | 60 | 40 |

the latter the more polar enol form is stabilized not only by the higher polarity of the solvent, but also by hydrogen-bonding. An exception is the carboxylic acid **12**, for which the tautomeric equilibrium is unaffected by a change of solvent. The dominant factor in this case seems to be not the solvent polarity, but the acidity of the carbonyl group.

The ratio of the tautomers also depends on the substitution at C(3). In compounds **12** and **13** the strongly electron-attracting carboxyl and ester groups increase the ratio of the enol form in comparison with the unsubstituted compound **14**. This can be explained by considering the mesomeric structure *A*. (Scheme 4).

Tautomerism of 9-Amino-4-oxo-6,7-dihydro-4*H*-pyrido-[1,2-*a*]pyrimidines.

The title compounds **15-26** are capable of imine-enamine tautomerism (Scheme 5). The ir spectra of these compounds taken in solid phase exhibit strong absorption




Scheme 5

bands in the range of 3400-3330 $cm^{-1}$ which refer to the presence of the enamine form. Our structural studies were aided by an X-ray investigation on one of the enantiomers of the 4-bromophenyl compound **23** [10], which demonstrated that only the enamine form (*E* in Scheme 5) is present in the solid phase. The planes of the pyrido[1,2-*a*]pyrimidine skeleton and of the phenyl ring are twisted by

Table 4

UV Data on Substituted 9-Amino-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones in Ethanol

| Compound | λ max (ε) | | | |
|---|---|---|---|---|
| **15** | 251 (16030) | 311 (11210) | 387 ( 2830) | 407 (2590) |
| **16** | 261 (16850) | 324 (11400) | 402 ( 1900) | |
| **17** | 247 (18110) | 325 (10860) | 400 infl ( 1020) | |
| **18** | 254 (12300) | 295 ( 7310) | 380 infl ( 2330) | |
| **19** | 255 (17820) | 295 ( 9680) | 350 infl ( 2300) | |
| **20** | 286 infl ( 4920) | 320 ( 7600) | 380 infl ( 2240) | |
| **21** | 259 (17410) | 322 (11960) | 380 infl ( 2290) | |
| **22** | 259 (16490) | 325 (10410) | 380 infl ( 1190) | |
| **23** | 267 (16730) | 318 (11120) | 390 infl ( 1460) | |
| **24** | 258 (10730) | 322 (10610) | 390 infl ( 1340) | |
| **25** | | 357 (19560) | 380 infl (17930) | |
| **26** | 247 (16140) | 325 (10730) | 400 ( 690) | |

about 30°, which decreases the conjugation of the two chromophores.

Similar conclusions can be reached from inspection of the uv spectra. In the 6,7,8,9-tetrahydro derivatives unsubstituted at C(9) carbon atom the highest wavelength maximum is at 280 and 300 nm, respectively [6,8,10,11]. This is shifted by 20 nm to longer wavelengths in compounds **15-26** (Table 4), indicating that the conjugated system is extended by an additional double bond.

On the basis of earlier data on similar compounds [12], a larger bathochromic shift would be expected if the imine tautomer is dominant, since this would involve more extended conjugation with the aryl group attached to the exocyclic double bond.

Accordingly, compounds **15-26** are mainly in the enamine form in ethanolic solution too. It should be mentioned that uv absorption vanishes only at about 500 nm, and an inflection (sometimes a weak maximum) can be observed at 380-400 nm. This phenomenon is a sign of a weak interaction between the electronic system of the pyrido[1,2-*a*]-pyrimidine skeleton and the non-bonding pair of electrons at the amino-nitrogen, and through the latter with the electrons of the phenyl group too. There is a marked difference between the 9-anilino **16** and 9-(*N*-methylanilino) **25** derivatives as concerns the intensity of the band at around 400 nm ($\epsilon$ = 1900 and 690, respectively). This may be explained by assuming that the more bulky *N*-methyl-*N*-phenylamino group is less coplanar with the rest of the molecule than is the *N*-phenyl group, which results in a further weakening of the conjugation.

The $^1$H- and $^{13}$C-nmr spectra of the 9-amino-dihydro compounds comprise only one set of signals and this can be assigned to the enamine tautomer (Tables 1 and 2). The imine tautomer could not be detected even on change of the solvent, or on variation of the substitution at C(3) or C(9).

Shifts of the 8-H and C(8) signals are sensitive indicators of the electron distribution in the enamine form. The relatively high-field position (5.08 ppm) of the 8-H signal in the butylamino derivative **20** indicates that conjugation of the non-bonding electron pair at the nitrogen with the C(8)=C(9) double bond increases the contribution of mesomeric structure *B* (Scheme 5). Replacement of the butyl group by phenyl **16** results in a downfield shift of this signal by almost 1 ppm (to 6.04 ppm). In accord with literature data for *N*-phenyl enamines [13], this suggests that the non-bonding pair is now more conjugated, rather with the $\pi$-electrons of the phenyl group than with the C(8)=C(9) double bond, the importance of mesomer *C* being increased. Accordingly, the shift of 8-H is higher (6.28 ppm) in the *p*-nitrophenyl analogue **25** and lower (5.62 ppm) in the *p*-hydroxyphenyl analogue **24** than in the unsubstituted compound **21** (5.96 ppm). The highest shifts for 8-H were observed in the *N*-methyl-*N*-phenylamino compounds **17** and **26** (6.48 and 6.40 ppm respectively). Here, the bulky substituent turns out of the plane of the molecule, thus further increasing the contribution of mesomer *C*. This is supported by upfield shifts of the $^{13}$C signals for the ortho and para carbons of the phenyl group in compounds **17** and **36** as compared with those in **16** and **21** (Table 2).

If an electron-attracting group is present at C(3), the electron density at C(8) is further reduced relative to that in the unsubstituted compound (*e.g* 6.04 ppm for **16** and 5.85 ppm for **19**).

Variation of the $^{13}$C shift of C(8) in the dihydro derivatives **15-26** follows the regularities observed in the $^1$H-nmr spectra, but the effects are even more pronounced (Table 2).

Due to the allylic strain [14] in both the hydroxy compounds **12-14** and the amino compounds **15-26** an envelope conformer containing the 6-methyl group in a quasi-axial orientation is dominant. This is supported both by the shift of 6-H (Table 1) and by the long-range coupling of 1.0-1.4 Hz between 6-H and 8-H, which are in a nearly coplanar W-shaped arrangement in this particular confor-

mer. The coupling between 6-H and the 7-$H_2$ protons is 1.3-1.7 Hz and 6.5-7.1 Hz, respectively, which confirms the quasi-equatorial disposition of 6-H and thereby the quasi-axial orientation of the 6-methyl group.

## EXPERIMENTAL

Melting points are uncorrected. Yields were not optimized. The uv spectra were recorded in ethanol with a UNICAM SP-800, the ir spectra in potassium bromide pellets with a ZEISS UR-20 spectrophotometer. The $^1$H- and $^{13}$C-nmr spectra were taken on a Brucker WP-80 instrument at 80 and 20.1 MHz, respectively, $^1$H-nmr spectra in 5-10% solutions, $^{13}$C-nmr spectra in saturated solutions with tetramethylsilane internal standards. Tautomer ratios were determined by integration of the $^1$H-nmr spectra.

Ethyl 9-bromo-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (**9**).

A mixture of ethyl 4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate [15] (1.0 g, 4.5 mmoles) and *N*-bromosuccinimide (0.9 g, 4.95 mmoles) in carbon tetrachloride (10 ml) was refluxed for 4 hours. After filtration of the reaction mixture, the filtrate was evaporated *in vacuo* to dryness. The oily residue was crystallized from ethanol giving 1.1 g (81%) of white crystals, mp 110-111°; uv (ethanol): λ max 314 nm (ε 8120), 232 nm (ε 3960); ir (potassium bromide): 1740, 1665 cm$^{-1}$ (C=O); nmr (deuteriochloroform): δ 1.38 (t, $CH_3$, 3H), 2.00-2.60 (m, 7-$CH_2$, 8-$CH_2$, 4H), 3.50-4.03 (m, 6-$H_{ax}$, 1H), 4.30 (m, 6-$H_{eq}$, 1H), 4.35 (q, $OCH_2$, 2H), 5.20 (dd, CHBr, 1H, J = 2.7, 3.7 Hz), 8.55 (s, NCH, 1H).

*Anal.* Calcd. for $C_{11}H_{13}BrN_2O_3$: C, 43.87; H, 4.35; Br, 26.53; N, 9.30. Found: C, 43.94; H, 4.32; Br, 27.00; N, 9.16.

9-Hydroxy-6-methyl-4-oxo-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic Acid (**12**).

See ref [5].

Ethyl 9-hydroxy-6-methyl-4-oxo-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (**13**).

A suspension of ethyl 6-methyl-4-oxo-9-phenylamino-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (**21**) (5.0 g, 15.4 mmoles) in 10% hydrochloric acid (50 ml) was stirred at ambient temperature for 2 days. The precipitated crystals were filtered off. The crystals were stirred in a mixture of water (10 ml) and chloroform (10 ml) and the aqueous phase was neutralized with 5% aqueous sodium hydroxide solution. After separation of the aqueous and organic phase the aqueous layer was extracted twice with chloroform (2 × 10 ml). The organic phase was combined and dried over anhydrous sodium sulfate and was evaporated *in vacuo*. The residue was recrystallized from ethanol giving 1.5 g (39%) of **13**, mp 119-120°; uv (ethanol): λ max 332 nm (ε 12300), 235 nm infl. (ε 5370); ir (potassium bromide): 3390 cm$^{-1}$ (O-H), 1742, 1675 cm$^{-1}$ (C=O).

*Anal.* Calcd. for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.66; H, 5.53; N, 11.33.

9-Hydroxy-6-methyl-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**14**).

A solution of 6-methyl-9-phenylamino-6,7-dihydro-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one (**9**) (1.0 g, 4.0 mmoles) in 10% hydrochloric acid (10 ml) was left to stand at ambient temperature for 2 days. The solution was neutralized with sodium bicarbonate, and was extracted with chloroform (4 × 3 ml). The organic phase was combined and dried over anhydrous sodium sulfate, and was evaporated *in vacuo*. The resulting residue was recrystallized from diethyl ether giving 0.5 g (70%) of **14**, mp 144-146°; uv (ethanol): λ max 310 nm infl (ε 7220), 303 nm (ε 7600), 238 nm (ε 5860), 228 nm (ε 5810); ir (potassium bromide): 3370 cm$^{-1}$ (O-H), 1665 cm$^{-1}$

Table 5

Physical and Analytical Data of Substituted 9-Aminopyrido[1,2-*a*]pyrimidines

| Compound [a] | Mp (°C) solvent | Formula | Analysis % Calcd./Found C | H | N | Method | Yield % |
|---|---|---|---|---|---|---|---|
| **15** | 197-198 acetonitrile | $C_{15}H_{13}N_3O_3$ | 63.60<br>63.35 | 4.63<br>4.43 | 14.83<br>14.74 | A(1)<br>C | 62<br>66 |
| **16** | 172-173 acetonitrile | | | [b] | | A(1)<br>C<br>E | 71<br>75<br>82 |
| **17** | 140-142 ethanol | | | [b] | | A(2) | 58 |
| **18** | 155-156 methanol | $C_{14}H_{13}N_3O$ | 70.28<br>70.25 | 5.48<br>5.39 | 17.56<br>17.52 | A(2) | 71 |
| **19** | 80-81 methanol | $C_{15}H_{15}N_3O$ | 71.13<br>70.83 | 5.97<br>5.97 | 16.59<br>16.76 | A(2) | 40 |
| **20** | 135-137 methanol | $C_{14}H_{19}N_3O_3$ | 60.63<br>60.72 | 6.91<br>7.00 | 15.15<br>15.11 | B(1) | 31 |
| **21** | 119-120 ethanol | $C_{18}H_{19}N_3O_3$ | 66.45<br>66.30 | 5.89<br>5.80 | 12.91<br>12.82 | B(2)<br>D | 59<br>47 |
| **22** | 145-147 hexane | $C_{18}H_{19}N_3O_3$ | 66.45<br>66.51 | 5.89<br>5.90 | 12.91<br>12.93 | B(2) | 25 |
| **23** [c] | 210-212 nitromethane | $C_{16}H_{14}BrN_3O_3$ | 51.08<br>51.15 | 3.75<br>3.90 | 11.17<br>10.90 | D | 78 |
| **24** | 196-197 acetonitrile | $C_{18}H_{19}N_3O_4$ | 63.33<br>63.09 | 5.61<br>5.63 | 12.31<br>12.07 | D | 74 |
| **25** | 235-236 acetonitrile | $C_{16}H_{18}N_4O_5$ | 58.37<br>58.16 | 4.89<br>4.82 | 15.13<br>15.20 | D | 95 |
| **26** | 175-176 methanol | | | [b] | | E | 89 |

[a] Substituents for specific compounds are given in Scheme 1 and 3. [b] Known compounds, see ref [5]. [c] Analysis for bromine: calculated 21.24%; found 21.21%.

(C = O).

*Anal.* Calcd. for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.54; H, 5.63; N, 15.69.

Substituted 9-amino-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **15-26**. See Table 5.

Method A(1).

Air was bubbled through a stirred solution of 9-anilinotetrahydropyrido[1,2-*a*]pyrimidine-3-carboxylic acid **1** or **2** [5,6] (1.0 g) in 2% aqueous sodium hydroxide solution (10 ml) at ambient temperature for 4 hours. The reaction mixture was acidified with a few drops of acetic acid and the precipitated crystals (**15** or **16**) were filtered off, washed with water and dried.

Method A(2).

Air was bubbled through a stirred solution of 9-aminotetrahydropyrido[1,2-*a*]pyrimidin-4-one **3**, **4** or **5** [6] (2.0 g) in chloroform (20 ml) at ambient temperature for 3 days. The reaction mixture was evaporated *in vacuo* to dryness to give 9-aminodihydropyrido[1,2-*a*]pyrimidin-4-one **17**, **18** or **19**.

Method B(1).

A solution of 9-bromo-6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido-[1,2-*a*]pyrimidine-3-carboxylic acid [7] (14.35 g, 50 mmoles) and butylamine (15 ml, 150 mmoles) in chloroform (100 ml) was left to stand at ambient temperature for 3 days in an open reaction vessel. To the reaction mixture water (70 ml) was added, the *p*H of the aqueous phase was adjusted to 2 with 10% hydrochloric acid and the organic and acidic aqueous phases were intensively shaken. The separated aqueous phase was extracted twice with chloroform (2 × 50 ml). The combined organic phase was dried over anhydrous sodium sulfate, and was evaporated *in vacuo* to dryness to give 9-butylamino-6-methyl-4-oxo-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid (**20**).

Method B(2).

A solution of ethyl 9-bromotetrahydropyrido[1,2-*a*]pyrimidine-3-carboxylate (**8**) [8], (or **9**) (10 mmoles) and aniline or *N*-methylaniline (22 mmoles, respectively) in acetonitrile (5 ml) was left to stand at ambient temperature for a week in an open reaction vessel. The reaction mixture was then evaporated *in vacuo* to dryness. The residue was dissolved in 5% hydrochloric acid (20 ml). The acidic solution was extracted with benzene (3 × 7 ml). The combined organic phase was dried over anhydrous sodium sulfate, and was evaporated *in vacuo* to dryness to give the 9-aminodihydropyrido[1,2-*a*]pyrimidine derivative **21** or **22**. Compound **21** was crystallized, while compound **22** was isolated by thin layer chromatography using Kieselgel 60 $PF_{254+366}$ plate and benzene:methenol = 7:1 as the developing system. The product **22** was eluted from the adsorbent with a mixture of methanol and dichloromethane 1:10.

Method C.

A solutin of 9,9-dibromotetrahydropyrido[1,2-*a*]pyrimidine-3-carboxylic acid [7] **10** or **11** (10 mmoles) and aniline (3 ml, 33 mmoles) in dimethyl sulfoxide (5 ml) was left to stand at ambient temperature for 3 days. The reaction mixture was poured onto water (20 ml) and the precipitated crystals **15** or **16** were filtered off, washed with water, dried.

Method D.

A solution of 9-hydroxypyrido[1,2-*a*]pyrimidin-4-one **12** or **13** (5 mmoles) and the requisite aniline (5.5 mmoles) in ethanol (10 ml) was refluxed for 3 hours. (With the preparation of a nitro derivative **25** a drop of concentrated hydrochloric acid was added to the ethanolic solution). After the reaction mixture had been cooled to 0° the precipitated crystals **21** or **23-25** were filtered off, washed with ethanol and dried.

Method E.

A mixture of ethyl 9-aminodihydropyrido[1,2-*a*]pyrimidine-3-carboxylate **17** or **21** (2.0 g) in 4% aqueous sodium hydroxide solution (10 ml) was stirred at 60-70° for 4-15 hours. After the clear solution had been cooled to ambient temperature the reaction mixture was neutralized with 10% hydrochloric acid, and decolourized with activated carbon. The *p*H of the filtrate was adjusted to 2 with 10% hydrochloric acid. The precipitated crystals **2** or **26** were filtered off, washed with water, dried.

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