NITROGEN BRIDGEHEAD COMPOUNDS PART 47[1]. SYNTHESIS AND SOME REACTIONS OF 4H,10H-PYRIMIDO[1,2-a]AZEPIN-4-ONES

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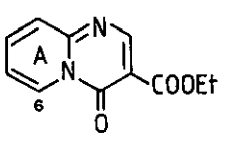
Abstract — 4-Oxo-4H,10H-pyrimido[1,2-a]azepine-3-carboxylate (3) was prepared from 2-amino-3H-azepine (4) and diethyl ethoxymethylenemalonate (5). The compound (3) was transformed into the isomeric 4H,6H-pyrimido[1,2-a]azepine-3-carboxylate (8) by proton migration, in a symmetry-allowed [1,5]-sigmatropic shift. The isomers (3) and (8) were characterized by their UV, IR, ^{1}H NMR and ^{13}C NMR spectra. From the ester (3) the 3-carboxylic acid (9), the amide (10) and the hydrazide (11) were prepared.

Of the nitrogen bridgehead compounds, pyrido[1,2-a]pyrimidines are remarkable because of their analgetic, antiinflammatory, antiatherogenic and antiasthmatic activities[2,3]. Above all, the 6-methyl-substituted pyridopyrimidine derivatives excel with their favourable biological properties[4]. However, the pharmacological activities can often not be utilized, as the 6-methyl substituent causes instability of the ring system[5]. This is the case, for instance, with the analgetic[4a] ethyl 6-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxylate[6], which easily suffers ring opening and gives rise to toxic 2-amino-6-methylpyridine derivatives[7].



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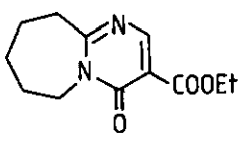

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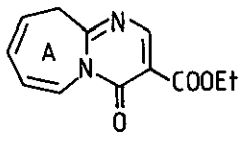

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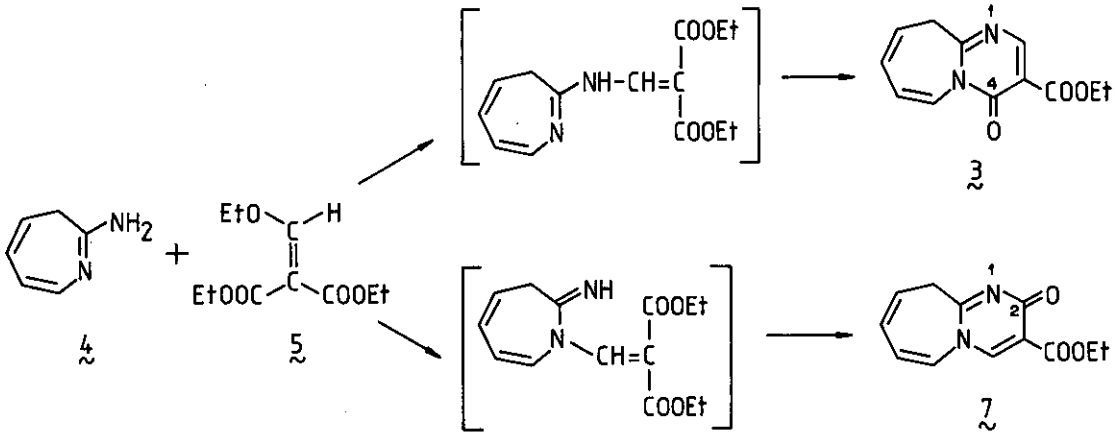
The pyrimido[1,2-a]azepine-3-carboxylates (2) were recently reported to exhibit analgetic activity[8]. In a search for new analogues which contain an unsaturated A ring and are still not inclined to ring opening, it seemed attractive to us to extend our studies to 4H,10H-pyrimido[1,2-a]azepine derivatives of type (3). The pyrido[1,2-a]azepine (3) is a ring homologue of the pyrido[1,2-a]pyrimidine (1), but it can also be considered as an isomer of 6-methyl substituted (1). In the synthesis of compound (3) we started from 2-amino-3H-azepine (4)[10] and diethyl ethoxymethylenemalonate (EMME) (5).

In view of earlier results relating to the reaction of EMME with 2-amino-4,5,6,7-tetrahydro-3H-azepine, and considering the presence of two reactive nitrogen atoms in the unsaturated aemicyclic amidine (4), we expected the formation of the isomeric 4-oxo- and 2-oxopyrimido[1,2-a]azepines, (3) and (7), respectively.

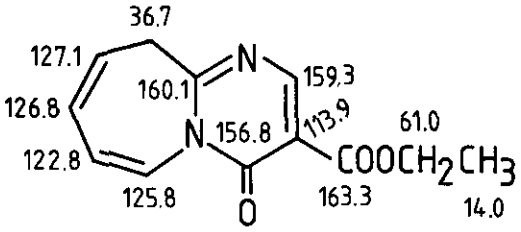


4 5 3 7

Scheme 1

The reaction of the amidine (4) and EMME (5) was achieved in refluxing butanol. The condensation proceeded at ambient temperature, but cyclization required thermal activation. As indicated by TLC, cyclization was accomplished within 1 h and gave rise to two products. After evaporation of the butanolic solution in vacuo, the residue was crystallized from a mixture of diethyl ether and ligroin. The product with the higher Rf value (~0.6) was obtained as pure material, (3) (mp 92-94 °C), in a yield of 50%, whereas that with the lower Rf value (~0.45) accumulated in the mother liquor and was obtained as crystals after separation by preparative HPLC, (8) (mp 102-104 °C). This difference between the mps of the products (10 °C) was too small for the expected isomeric 2-oxo (7) and 4-oxo (3) compounds. In the previously investigated[11] 6,7,8,9-tetrahydro series, the tetrahydro derivative of (7) had a mp 70 °C higher than that of (2). Spectral,

Scheme 2. Spectral data on ethyl pyrimido[1,2-a]azepine-3-carboxylates (3) and (8).



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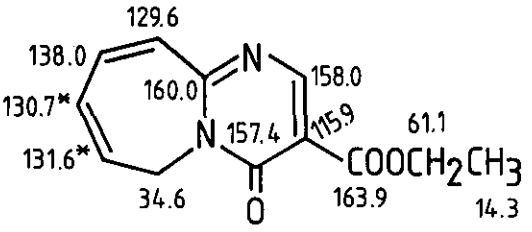
mp 92-94 °C



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mp 102-104 °C

UV	λ_{max} 325 (log ε 4.06); 243 (3.72);	340 (4.03); 255nm (3.73)
IR	$\nu_{3\text{-CO}}$ 1756; $\nu_{C(4)O}$ 1675; $\nu_{C=C}$ 1632	$\nu_{3\text{-CO}}$ 1736; $\nu_{C(4)O}$ 1668; $\nu_{C=C}$ 1634cm^{-1}
^{1}H NMR	1.34t, $OCH_2\underline{CH_3}$; 3.29d, H_2-10; 4.29 q, OCH_2; 5.90dt, H-9; 6.23dd, H-7; 6.47dd, H-8; 7.59dd, H-6; 8.44s, H-2.	1.36t, $OCH_2\underline{CH_3}$; 4.43q, OCH_2; 4.49d, H_2-6; 6.27dtt, H-7; 6.51ddd, H-8; 6.85-6.96m, H-9 and H-10; 8.51s, H-2.
Coupling constants (Hz)	$J_{6,7}$= 9.3; $J_{7,8}$= 4.9; $J_{8,9}$= 9.3; $J_{9,10}$= 6.6 and $^4J_{6,8} \approx 0.5$.	$J_{6,7}$= 6.6; $J_{7,8}$= 9.8; $J_{8,9}$= 3.2; $^4J_{7,9} \approx {}^5J_{7,10} \approx 1.0$; $^4J_{8,10}$= 2.8.

^{13}C NMR $J_{C,H}$ coupling constants (Hz)

$^1J_{C,H}$	$J_{2,H-2}$	$J_{6,H-6}$	$J_{7,H-7}$	$J_{8,H-8}$	$J_{9,H-9}$	$J_{10,H-10}$
(3)	183.1	188.6	161.7	168.0	168.6	134.0
(8)	183.1	143.4	164.6	167.2	161.1	168.5

$^2J_{C,H}$	$J_{3,H-2}$	$J_{6,H-7}$	$J^*_{7,H-6}$	$J^*_{7,H-8}$	$J_{10,H-9}$
(3)	4.3	6.1	3.6	2.4	8.5
(8)	4.9	8.5			

$^3J_{C,H}$	$J_{4,H-2}$	$J_{4,H-6}$	$J_{6,H-8}$	$J_{7,H-9}$	$J_{10,H-8}$	$J_{COO,H-2}$	J_{COO,CH_2}
(3)	7.3	1.8	6.1	9.8	8.5	3.1	3.1
(8)	7.9	3.0	8.5	$J_{9,H-7}$ 10.4	$J_{10,H-8}$ 7.3	3.1	3.1

* may be reversed

and primarily ^{1}H NMR characteristics, supported our assumption that the product melting at 92-94 °C was the expected 4H,10H-pyrimido[1,2-a]azepine (3), while

that melting at 102-104 °C was the 4H,6H-pyrimido[1,2-a]azepine (8).

Hydrogenation experiments confirmed that the two structures differ only in the position of the CH_2 group, for on catalytic hydrogenation over Pd/C a 2:1 mixture of compounds (3) and (8) gave one, chromatographically pure product, which was identified as the azepinopyrimidine (2)[11].

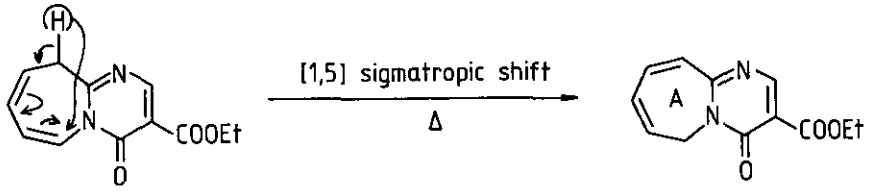
Assignment of the ^1H NMR spectra to the individual isomers was based mainly on the chemical shifts of the protons at positions 6 and 10. Due to the anisotropic effect of the neighbouring C(4)=O group[12], the 6-CH_2 protons of compound (8) suffer a downfield shift and appear at δ=4.43 ppm (d); the chemical shift of the 10-CH_2 protons of compound (3) is δ=3.29 ppm (d). On the other hand, the 6-CH proton of (3) appears at lower field, δ=7.59 ppm (dd), than the 10-CH proton of 8, δ=6.85-6.96 ppm (m). The doublet of the CH_2 signals in the two isomers points to rapid conformational movements of the A rings, causing averaging of the signals of the quasi-axial and quasi-equatorial protons.

The ^{13}C NMR spectra provided further evidence for structures (3) and (8). Assignment of the signals was solved by a series of single-frequency off-resonance decouplings. The chemical shifts of the carbon atoms, and the coupling constants $J_{C,H}$, are shown is Scheme 2. The high value of the coupling constant $^1J_{6CH}$=188.6 Hz in the spectrum of 3, due to the effect[13] of the electronegative neighbouring atom, N(5), is further evidence in favour of structure (3). Because of similar reason the CH_2 group of compound (8) has a $^1J_{C,H}$ coupling constant 9.4 Hz higher than that of compound (3).

Characteristic differences are to be found between the UV and IR spectra of compounds (3) and (8). Although conjugation occurs in both structures, over the double bonds of the pyrimidone and the A rings, this interaction is more favourable in structure (8), through the C=N double bond, than in structure (3), through the N(5) atom. This is shown by the UV spectra, where there is a difference of 15 nm between the longest wavelength absorption maxima [325 nm in (3) and 340 nm in (8)]. The stretching vibrational band of the ester carbonyl appears at a higher frequency (1752 cm^{-1}) for (3) than for (8) (1736 cm^{-1}), which is also related with the more extended conjugation in (8).

The 4H,6H-pyrimidoazepine (8) arises from the primarily formed 4H,10H-pyrimidoazepine (3) by means of proton migration, in a symmetry-allowed [1,5]-sigmatropic shift[14]. As indicated by TLC, compound (3), on heating in butanol, is gradually transformed into compound (8). The butanolic solution was evaporated in

vacuo at room temperature, and the ratio of the isomers (3) and (8) was measured by ^{1}H NMR in $CDCl_3$. From the intensities in the ^{1}H NMR spectra, the isomer ratio was 67:33 after 12 h, 45:55 after 30 h and 40:60 after 60 h of heating. Addition of quinoline as an acid scavenger or addition of hydroquinone as a radical scavenger or degassing (in the presence or absence of oxygen) did not change the yield. The driving force of the proton migration is the more extended conjugation in isomer (8).



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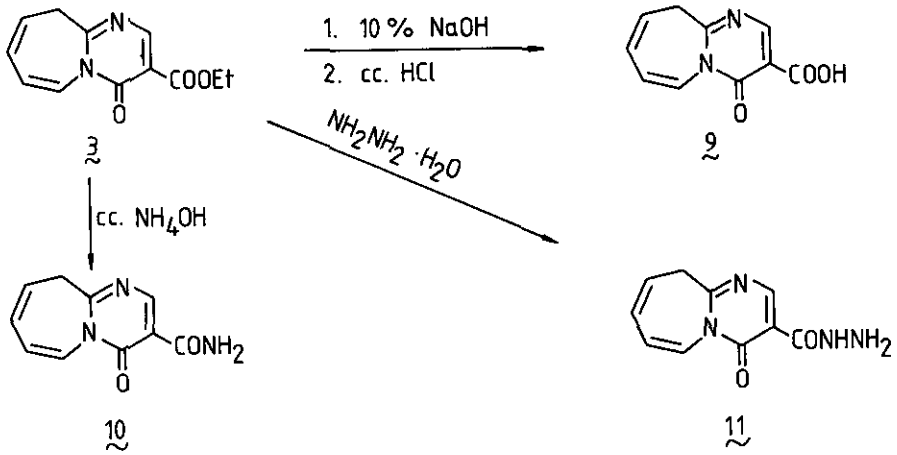
The ester (3) can easily be converted by alkaline hydrolysis into the carboxylic acid (9), by treatment with ammonium hydroxide into the 3-carboxamide (10), and by reaction with hydrazine hydrate into the 3-carbohydrazide (11) (see Scheme 3). In the course of these transformations the bicycle proved stable, ring opening not being observed.



3 9 10 11

Scheme 3

The pyrimido[1,2-a]azepine-3-carboxylate (3) exhibited significant analgetic activity in the rat hot-plate test (iv ED_{50} ~ 45 mg/kg), but this increased activity was accompanied by a considerable toxicity in rat (iv LD_{50} ~ 270 mg/kg)[15].

EXPERIMENTAL

All melting points are uncorrected. Ultraviolet (UV) spectra were obtained in ethanol on a UNICAM SP 800 spectrophotometer. Infrared (IR) spectra were determined with KBr disks on a ZEISS UR 20 spectrophotometer, The ^{1}H and ^{13}C NMR spectra were recorded on a JEOL FX-100 instrument using $SiMe_4$ as an internal standard, in $CDCl_3$ solution.

Reaction of 2-Amino-3H-azepine with Diethyl Ethoxymethylenemalonate

A solution of 2-amino-3H-azepine[10] (4) (10.7 g, 10 mmol) and diethyl ethoxymethylenemalonate (5) (21,6 g, 10 mmol) in butanol (50 ml) was refluxed for 1 h, then the solvent was evaporated in vacuo. The residue was dissolved in benzene (150 ml) and the organic phase was extracted with water (2x40 ml). The dried (Na_2SO_4) organic layer was evaporated to dryness. The residue was recrystallized from a mixture of diethyl ether-ligroin to give ethyl 4-oxo-4H,10H-pyrimido-[1,2-a]azepine-3-carboxylate (3) (11.6 g, 50%). Mp 92-94 °C (from water). Anal. Calcd. for $C_{12}H_{12}N_2O_3$ (232.240): C, 62.06; M, 5.21; N, 12.06. Found: C, 62.02; H 5.26; N 11.95%.

The ethereal mother liquid was evaporated to dryness, and the residue (8.8 g, mp 72-77 °C) was separated on a Prep-500 Silica (Waters) column by a Waters preparative liquid chromatograph instrument with an i-propanol:dichloromethane:ligroin = 2:2:1 eluent, to give another fraction of compound (3) (4.2 g, 18%, mp 92-94 °C) and ethyl 4H,6H-pyrimido[1,2-a]azepine-3-carboxylate (8) (2.6 g, 11.2%, mp 102-104 °C). Anal. of compound (8). Calcd. for $C_{12}H_{12}N_2O_3$ (232.240): C, 62.06; H, 5.21; N, 12.06. Found: C, 61.97; H, 5.21; N 12.15%.

Ethyl 4-Oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-a]azepine-3-carboxylate (2)

A 2:1 mixture of ethyl pyrimido[1,2-a]azepine-3-carboxylates (3 and 8) (2.32 g, 10 mmol) in ethanol (30 ml) was hydrogenated at atmospheric pressure over 10% Pd-C (0.5 g). After absorption of the theoretical amount of hydrogen (20 mmol) the catalyst was filtered off. The filtrate was evaporated in vacuo to dryness to give hexahydropyrimido[1,2-a]azepine-3-carboxylate (2) (1.92 g, 81%). Mp 82-84 °C (from ethyl acetate). Lit. mp[16] 80-82 °C.

4-Oxo-4H,10H-pyrimido[1,2-a]azepine-3-carboxylic acid (9)

A mixture of ethyl 4-oxo-4H,10H-pyrimido[1,2-a]azepine-3-carboxylate (3) in 10% aqueous sodium hydroxide solution was stirred at ambient temperature for 24 h. The pH of the clear solution was adjusted to 3.5 with concentrated hydrochloric acid. The precipitated acid (9) (1.12 g, 54%) was filtered off, washed with wa-

ter, and dried. Mp 179 °C (decomp.). Anal. Calcd. for $C_{10}H_8N_2O_3$ (204.187): C, 58.83; H, 3.95; N, 13.72. Found: C, 59.01; H, 4.00; N, 13.66%. UV 332 (log ε 3.90); 280 nm (3.88).

4-Oxo-4H,10H-pyrimido[1,2-a]azepine-3-carboxamide (10)

A mixture of ethyl 4-oxo-4H,10H-pyrimido[1,2-a]azepine-3-carboxylate (3) (2.32 g, 10 mmol) in concentrated ammonium hydroxide (23 ml) was stirred at ambient temperature for 1 h. The precipitated crystals were filtered off, washed with water, dried and recrystallized from ethanol to give the carboxamide (10) (1.6 g, 78%). Mp 226-227 °C. Anal. Calcd. for $C_{10}H_9N_3O_2$ (203.202): C, 59.11; H, 4.46; N, 20.68. Found: C, 58.97; H, 4.52; N, 20.82%. UV 323 (log 3.99); 245 inflexion nm (3.72).

4-Oxo-4H,10H-pyrimido[1,2-a]azepine-3-carbohydrazide (11)

A mixture of ethyl 4-oxo-4H,10H-pyrimido[1,2-a]azepine-3-carboxylate (3) (2.32 g 10 mmol) and 98% hydrazine hydrate (10 ml) was left to stand at ambient temperature for 24 h. The precipitated crystals were filtered off, washed with water, dried to give the carbohydrazide (11) (1.5 g, 68%). Mp 151-152 °C (from ethanol). Anal. Calcd. for $C_{10}H_{10}N_4O_2$ (218.216): C, 55.04; H, 4.62; N, 25.67. Found: C, 54.97; H, 4.70; N, 25.81%.

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