Synthesis of Derivatives of Pyrazino[1,2-*a*]pyrimidin-4-ones

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3-Alkoxy-2-aminopyrazines have been condensed with ethyl ethoxymethylenemalonate and isopropylidene methoxymethylenemalonate to afford 9-alkoxypyrazino[1,2-*a*]pyrimidin-4-ones substituted in the first case by an ethoxycarbonyl group at 3 position.

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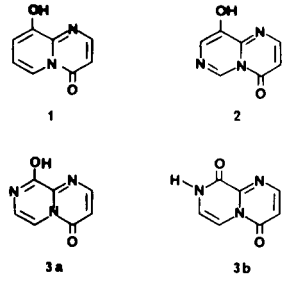
Introduction.

We have been involved for several years in the chemistry of *N*-bridgehead heterocyclic compounds [1] owing to their interesting properties both in fundamental, synthetic or biological fields [2]. The synthesis of hydroxy derivatives of these fused heterocycles has more particularly retained our attention. So, our interest has been lately directed towards the synthesis of structures **1** and **2** [3] in which a pyrimidin-4-one is annelated either to a 3-hydroxypyridine or to a 5-hydroxypyrimidine (Scheme 1). We have now planned the synthesis of structures **3** in which a hydroxypyrazine (or pyrazinone) would be annelated to a pyrimidin-4-one according to a [1-2*a*] ring fusion mode.

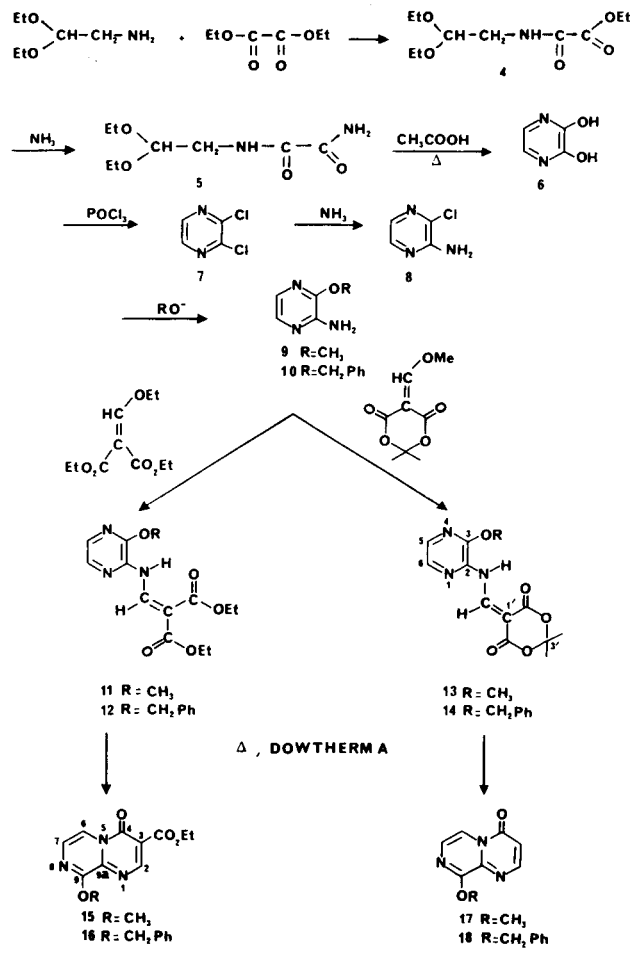
Scheme 1



This paper describes the preliminary results that we have this field, more particularly the synthesis of the methoxy and benzyloxy ethers **17** and **18** which can be regarded as potential precursors of these structures as well as model compounds needed for the study of the expected tautomerism **3a** ⇌ **3b**.

It is noted that the literature does not mention any synthesis of pyrazino[1,2-*a*]pyrimidine-4-one, if one excepts the synthesis of alkyl substituted derivatives obtained by heating alkylaminopyrazines with diethyl ethoxymethylenemalonate [4]. Extension of this condensation to 3-alkoxy-2-aminopyrazines appeared as a promising way to obtain the 3-ethoxycarbonyl derivatives **15** and **16**. But, as we have shown in the case of 3-ethoxycarbonyl-9-alkoxypyrido[1,2-*a*]pyrimidin-4-one, this kind of compound cannot be saponified and decarboxylated; a retrocondensation took place instead reverting to the starting 3-alkoxy-2-aminopyridine **5**. Therefore, in order to prepare the desired 9-alkoxypyrazino[1,2-*a*]pyrimidin-4-one **17** and **18**, we have extended to 3-alkoxy-2-aminopyrazines the condensation with isopropylidene methoxymethylenemalonate that we have successfully used in the previous series **1** and **2** [3,5,6].

Scheme II



Results and Discussion.

The preparation of the required 3-alkoxy-2-aminopyrazines was made according to the methods reported by Palamidessi *et al.* [7,8,9] as described in Scheme 2; thus, the condensation of diethylacetalaminoacetaldehyde with diethyl oxalate furnished ethyl *N*-(2-diethoxyethyl)oxamate

Table 1

^{1}H NMR Chemical Shifts (δ, ppm) in Hexadeuterodimethyl Sulfoxide Downfield From Tetramethylsilane as the Internal Reference

Compounds	H-5	H-6	NH	CH	OCH_3	OCH_2Ph	Ph	CH_2	CH_3	^{J}H-5,H-6 in Hz	^{J}NH-CH in Hz
11	7.90 or	7.92	10.97	8.87	4.01	-	-	4.22 and 4.14	1.25	2.9	12.6
12	7.52 or	7.11	11.21	8.68	-	5.13	7.32	4.21 and 4.14	1.24	4.5	12.5
13	8.05 or	8.00	11.21	8.96	4.03	-	-	-	1.70	2.8	13.2
14	7.68 or	7.21	11.55	8.83	-	5.16	7.33	-	1.5	43	13.7

Table 2

^{1}H NMR Chemical Shifts (δ, ppm) in Hexadeuterodimethyl Sulfoxide Downfield From Tetramethylsilane as the Internal Reference

Compounds	H-2	H-3	H-6	H-7	Ph	OCH_3	OCH_2Ph	CH_2	CH_3	^{J}H-2,H6 in Hz	^{J}H-6, H-7 in Hz
15	8.83	-	8.40	7.87	-	4.66	-	4.28	2.59	-	4.7
16	8.73	-	7.65	7.46	7.33	-	5.10	4.27	1.28	-	6.2
17	8.30	6.63	8.26	7.68	-	4.03	-	-	-	6.4	4.8
18	8.20	6.63	7.57	7.32		-	5.08	-	-	6.4	6.3

Table 3

^{13}C NMR Chemical Shifts (δ, ppm) in Hexadeuterodimethyl Sulfoxide Downfield From Tetramethylsilane as the Internal Reference

Compounds	C-3	C-2	C-5 and C-6	NH-*C*H	$C(CO_2C_2H_5)_2$	CH_2	CH_3	C=O	C_1'	C-3'	OCH_3	OCH_2Ph	
11	146.3	149.2	135.1, 138.8	97.5	146.5	60.3 and 59.9	14.1 and 14.0	167.0 and 164.0	-	-	54.1	-	-
12	145.2	150.4	124.9, 120.6	98.6	144.7	60.3 and 59.9	14.14 and 14.0	166.4 and 164.0	-	-	-	51.4	*i*, 135.6 *o*, 127.8 *m*, 128.6 *p*, 127.9
13	149.0	149.7	137.4, 134.1	105.0	-	-	26.5	164.2 and 162.0	135.6	90.2	54.4	-	-
14	148.3	150.4	127.1, 120.8	105.0	-	-	26.6	163.9 and 162.1	143.9	91.0	-	51.7	*i*, 135.5 *o*, 127.1 *m*, 128.6 *p*, 128.0

Table 4

^{13}C NMR Chemical Shifts (δ, ppm) in Hexadeuterodimethyl Sulfoxide Downfield From Tetramethylsilane as the Internal Reference

Compounds	C-2	C-3	C-4	C-9	C-6,C-7	C-9a	$CO_2C_2H_5$	CH_2-CH_3	CH_2-CH_3	OCH_3	OCH_2Ph	
15	157.3	109.8	158.3	153.1	129.7 or 112.5	140.7	163.3	60.6	14.1	55.2	-	-
16	156.3	113.3	154.7 or 153.9		122.6 or 103.0	148.2	163.1	60.8	14.2	-	51.3	*i*, 135.7 *o*, 127.8 *m*, 128.5 *p*, 127.8
17	153.6	109.6	158.3	156.1	127.7 or 111.7	139.3	-	-	-	54.9	-	-
18	152.8	112.6	156.8	154.7	121.7 or 102.7	145.7	-	-	-	-	51.0	*i*, 135.8 *o*, 127.6 *m*, 128.4 *p*, 127.7

(**4**). The yield of 70% reported by Palamidessi has been improved to 82% by employing two equivalents of diethyl oxalate and performing the reaction at 40°. When **4** was treated with an ammonia solution, the reaction furnished *N*-(2-diethoxyethyl)oxamide which afforded **6** upon cyclization in boiling acetic acid. Compound **6** and phosphorus oxychloride furnished 2,3-dichloropyrazine (**7**). Due to its instability, this compound was immediately treated with an ammonia solution in order to obtain 2-amino-3-chloropyrazine (**8**). Compound **8** was then allowed to react with sodium methylate to give 2-amino-3-methoxypyrazine (**9**). By reaction of **8** with sodium benzylate, a non repeatable reaction was observed. In several cases, 2-amino-3-benzyloxypyrazine (**10**) was obtained in a good yield but in other cases, a mixture of this latter with 2-benzylamino-3-benzyloxypyrazine was produced. A similar phenomenon was observed by Kaminski [10] who obtained these compounds as "a mixture of a solid and an oil" having a large melting point range (68-74°). In our case we were able to characterize the two components of respective melting point 183-184° and 109-110°. The rest of the synthesis consisted of classical transformations similar to those that we have described in the previous series [3,5,6] and which are summarized in the Scheme 2.

All the products showed the expected spectral properties in ir, nmr and mass spectrometry studies; their structures were clearly established as follows. In the ir, the absorption of the secondary amino group for the uncyclized compounds appeared as a large band centered at 3300 cm^{-1}; this finding was indicative of a chelation resulting from the s-*trans* structure of our compounds **11-14**. This band disappeared for the cyclized compounds for which we noticed a band at 1680 cm^{-1} attributed to the CO heterocyclic group. For the ethoxycarbonyl substituted derivatives a second band characteristic of the ester group occurred at 1740 cm^{-1}. In the ^1H nmr, the structure of the intermediates **11-14** was established by the doublets at about 8.8 and 11 ppm (J = 12.5 to 13.7 Hz) assigned respectively to the ethylenic C-H and amino N-H protons. By exchange with deuterium oxide the second signal disappeared while the first one was changed to a singlet. The pyrazine protons H-5 and H-6 appeared as doublets between 7 and 8 ppm (J = 2.8 and 4.5 Hz). In the cyclized compounds **15**, **16**, the proton H-2 suffered a deshielding effect of the ethoxycarbonyl group at the 3 position ($\Delta\delta$ = 0.5 ppm). For the compounds **17**, **18**, the protons H-2 and H-3 appeared as doublets (J = 6.4 Hz). We noticed in these cases a deshielding effect of the carbonyl group at the peri position on the signal of H-6 which appeared at 7.57-8.40 ppm, while the proton H-7 gave rise to a signal at 7.32-7.87 ppm. In the ^{13}C nmr, the assignments were made with respect to those already described in the pyrimido-[1,6-*a*]pyrimidin-4-one and pyrido[1,2-*a*]pyrimidin-4-one series and with the aid of the increments values observed for identical groups [12]. The assignments were achieved by comparison with the observed spectra of the starting compounds **6-10**. The relative intensity was extensively used in order to distinguish the signals of the carbon atoms located in a position adjacent to a heteroatom or a non-protonated carbon atom. All the results appear in Tables 1-4.

Conclusion.

In conclusion, this work presents the first synthetic approach of the desired 9-hydroxypyrazino[1,2-*a*]pyrimidin-4-one and its 3-ethoxycarbonyl derivative. Further studies including improvement of the synthesis of the benzyloxy derivatives and cleavage of the ethers **15-18** are presently under investigation.

EXPERIMENTAL

Ethyl *N*-(2-Diethoxyethyl)oxamate (**4**).

This compound was synthesized according to the procedure described by Palamidessi *et al.* [7] with the following modifications: aminoacetaldehyde diethyl acetal was added to two equivalents of diethyl oxalate in alcoholic medium. After one hour at ambient temperature the solution was warmed to 40° for three hours. After evaporation of the solvent, the residue was distilled yielding the expected compound **4** in 82% yield (lit 70%), bp 104-105° 0.2 mm Hg (lit [7] bp 146-152° 0.4 mm Hg); ir (liquid film): ν cm^{-1} 3400-3300 (NH, amide), 2980 (CH, CH_3), 1700 (CO, amide); ^1H nmr (deuteriochloroform): δ ppm 1.20 (m, 9H, CH_2-CH_3), 3.46 (m, 6H, CH_2-CH_3), 4.33 (m, 3H, C*H*-CH_2 and CH-CH_2), 7.26 (1H, CH_2-N*H*); ms: m/e (relative abundance) 188 (100), 103 (100).

N-(2-Diethoxyethyl)oxamide (**5**).

This compound was prepared from **4** according to the procedure described by Palamedissi *et al.* [7] in 90% yield, mp 139-140° (lit [7] mp 138-140°); ir (potassium bromide): ν cm^{-1} 3320 (NH, amine), 1700 (CO, amide); ^1H nmr (hexadeuteriodimethyl sulfoxide): δ ppm 1.10 (t, 6H, CH_2-CH_3), 3.53 (m, 6H, CH-CH_2-NH and CH_2-CH_3), 4.60 (t, 1H, C*H*-CH_2), 8.10 (s large, 2H, NH_2), 8.52 (t large, 1H, CH_2-N*H*); ms: m/e (relative abundance) 159 (30), 103 (79), 47 (100).

2,3-Dihydroxypyrazine (**6**).

This compound was prepared from **5** according to the procedure described by Palamedissi *et al.* [7] in 68% yield, mp 350° (lit [7] mp 270°); ir (potassium bromide): ν cm^{-1} 3550-3500 (OH), 1650 (C=C and C=N pyrazine); ^1H nmr (hexadeuteriodimethyl sulfoxide): δ ppm 6.26 (d, 2H, H ring), 10.94 (s, large, 2H, OH); ms: m/e (relative abundance) 112 (100), 84 (27).

2,3-Dichloropyrazine (**7**).

This compound was prepared from **6** according to the procedure described by Bernardi *et al.* [8] with a yield of 84%. Due to its instability, this compound was used without purification for the following synthese.

2-Amino-3-chloropyrazine (**8**).

This compound was prepared from **7** according to the procedure described by Palamedissi *et al.* [7] in 78% yield, mp 168-169° (lit [7] mp 165°); ir (potasssium bromide): ν cm^{-1} = 3400, 3300 (NH, amine), 1640 (C=C and C=N); ^1H nmr (hexadeuteriodimethyl sulfoxide): δ ppm 6.78 (s, large, 2H, NH_2), 7.56 (d, 1H, H ring), 7.92 (d, 1H, H ring); ms: m/e (relative abundance) 129 (67), 94 (53), 67 (100).

2-Amino-3-methoxypyrazine (**9**).

This compound was prepared from **8** according to the procedure described by Camerino *et al.* [9] in 84% yield, mp 86-87° (lit [9] mp 85°); ir (potassium bromide): ν cm^{-1} 3400 (NH, amine), 2980 (CH, OMe), 1650 (C=C and C=N); ^1H nmr (hexadeuteriodimethyl sulfoxide): δ ppm 3.8 (s, 3H, OCH_3), 7.22 (d, 1H, H cycle), 7.40 (d, 1H, H ring cycle); ms: m/e (relative abundance) 125 (48), 65 (100).

2-Amino-3-benzyloxypyrazine (**10**).

To 20 ml of benzyl alcohol, 0.5 g of sodium was added in small pieces. To this solution thus obtained, 3 g (0.023 mole) of 2-amino-3-chloropyrazine was added and the resulting mixture was warmed during 72 hours. After cooling, the sodium salt was precipitated by addition of ethyl ether. After filtration and evaporation, a yellow solid was obtained (2.7 g, 58%), mp (ethanol) 183-184° (lit [10] mp 68-74°); ir (potassium bromide): ν cm^{-1} 3400 (NH, amine), 1650 (C=C and C=N); ^1H nmr (hexadeuteriodimethyl sulfoxide): δ ppm 5.02 (s, 2H, O-CH_2-Ph), 7.17 (d, 1H, H ring), 7.37 (d, 1H, H ring), 7.87 (s, 5H, phenyl); ms: m/e (relative abundance) 201 (38), 91 (100), 65 (27).

During some preparations (see theoretical part), in place of the normal product **10**, a mixture was obtained leading after several recrystallizations to 2-benzylamino-3-benzyloxypyrazine which was characterized by the following methods: mp (acétonitrile) 109-110°; ir (potassium bromide): ν cm^{-1} 3400 (NH, amine), 1600 (C=C and C=N); ^1H nmr (deuteriochloroform): δ ppm 4.64 (d, 2H, NH-CH_2-Ph), 5.05 (s, 2H, O-CH_2-Ph), 6.65 (d, 1H, H cycle), 6.88 (d, 1H, H ring), 7.29 (m, 11H, phenyl and N*H*-CH_2-Ph); ms: m/e (relative abundance): 291 (19), 200 (100), 91 (100).

Anal. Calcd. for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.87; N, 14.42. Found: C, 74.39; H, 5.79; N, 14.45.

Diethyl *N*-(3-Methoxy-2-pyrazinyl)aminomethylenemalonate (**11**).

The following mixture was warmed with stirring to 110° for a period of 40 minutes: 1 g (0.008 mole) of 2-amino-3-methoxypyrazine in 4 ml of diethyl ethoxymethylene malonate. After cooling and filtration, compound **11** was obtained as a yellow solid in 75% yield, mp (ethanol) 187-188°; ir (potassium bromide): ν cm^{-1} 3240 (NH, amine), 2980 (CH methyl); ^1H and ^{13}C nmr see theoretical part; ms m/e (relative abundance) 294 (24.8), 222 (100).

Anal. Calcd. for $C_{13}H_{17}N_3O_5$: C, 52.88; H, 5.79; N, 14.23. Found: C, 53.06; H, 5.72; N, 14.27.

Diethyl *N*-(3-Benzyloxy-2-pyrazinyl)aminomethylenemalonate (**12**).

The following mixture was warmed with stirring to 110° for a period of 2 hours: 1 g (0.005 mole) of 2-amino-3-benzyloxypyrazine in 4 ml of diethyl ethoxymethylene malonate. After cooling to ambient temperature then to −20° and filtration, compound **12** was obtained as a yellow solid in 60% yield, mp (ethanol) 74-75°; ir (potassium bromide): ν cm^{-1} 1680 (CO); ^1H and ^{13}C see the theoretical part; ms: m/e (relative abundance): 371 (55.3), 298 (37.2), 91 (100).

Anal. Calcd. for $C_{19}H_{21}N_3O_5$: C, 61.44; H, 5.69; N, 11.31. Found: C, 61.20; H, 5.56; N, 11.46.

Isopropylidene *N*-(3-Methoxy-2-pyrazinyl)aminomethylenemalonate (**13**).

The following mixture was warmed with stirring under inert atmosphere to 80-90° for a period of three hours: 1 g (0.008 mole) of 2-amino-3-methoxypyrazine, 2 g (0.0010 mole) of isopropylidene methoxymethylenemalonate in 10 ml of methyl orthoformate. After cooling, filtration and recrystallization the compound **13** was obtained as a white solid in 82% yield, mp (ethanol) 177-178°; ir (potassium bromide): ν cm^{-1} 3280 (NH), 1720 (CO), 1630, 1550 (C=C and C=N); ^1H and ^{13}C nmr see theoretical part; ms: m/e (relative abundance) 279 (16.1), 221 (38.1), 177 (32.4), 149 (100).

Anal. Calcd. for $C_{12}H_{13}N_3O_5$: C, 51.11; H, 4.69; N, 15.04. Found: C, 51.54; H, 4.84; N, 15.12.

Isopropylidene (*N*-(3-Benzyloxy-2-pyrazinyl)aminomethylenemalonate (**14**).

By the same procedure that had led to the compound **13**, the derivative **14** was obtained from **10** as a white solid in 71% yield, mp (ethanol) 209-210°; ir (potassium bromide): ν cm^{-1} 1730 (CO), 1640, 1570 (C=C and C=N), 1270 (CO benzylic ether); ^1H and ^{13}C nmr see theoretical part; ms: m/e (relative abundance) 355 (5.3), 297 (48.1), 253 (25.7), 43 (100).

Anal. Calcd. for $C_{18}H_{17}N_3O_5$: C, 60.83; H, 4.82; N, 11.82. Found: C, 60.63; H, 4.85; N, 11.66.

3-Ethoxycarbonyl-9-methoxypyrazino[1,2-*a*]pyrimidin-4-one (**15**).

To 10 ml of Dowtherm A warmed to 250°, 1 g (0.034 mole) of compound **11** was added. The heating was maintained for a period of 15 minutes. After cooling to 50°, addition of hexane caused the precipitation of compound **15** which was separated by filtration. After recrystallization, compound **15** was obtained in 63% yield, mp (ethanol) 137-138°; ir (potassium bromide): ν cm^{-1} 2980 (CH, OMe), 1740 (CO, ester), 1680 (CO, heterocycle); ^1H and ^{13}C nmr see theoretical part; ms: m/e (relative abundance) 249 (14.3), 177 (100).

Anal. Calcd. for $C_{11}H_{11}N_3O_4 \cdot ½\ H_2O$: C, 51.16; H, 4.64; N, 16.27. Found: C, 51.60; H, 4.49; N, 16.38.

3-Ethoxycarbonyl-9-benzyloxypyrazino[1,2-*a*]pyrimidin-4-one (**16**).

Under the conditions described above for the synthesis of the compound **15**, the derivative **16** was obtained from **12** in 68% yield as a white solid, mp (ethanol) 139-140°; ir (potasium bromide): ν cm^{-1} 1740 (CO, ester), 1680 (CO, heterocycle); ^1H and ^{13}C nmr see theoretical part; ms: m/e (relative abundance) 325 (10.4), 91 (100).

Anal. Calcd. for $C_{17}H_{16}N_3O_4$: C, 62.76; H, 4.64; N, 12.91. Found: C, 62.82; H, 4.63; N, 12.97.

9-Methoxypyrazino[1,2-*a*]pyrimidin-4-one (**17**).

Starting from **13** and using the same procedure that had led to compound **15**, compound **17** was obtained as a solid in 73% yield, mp (ethanol) 137-138°; ir (potassium bromide): ν cm^{-1} 2980 (CH, OCH_3), 1620 (CO); ^1H and ^{13}C nmr see theoretical part; ms: m/e (relative abundance) 177 (49.7), 148 (100).

Anal. Calcd. for $C_8H_7N_3O_2$: C, 54.23; H, 3.98; N, 23.71. Found:

C, 53.97; H, 4.02; N, 23.73.

9-Benzyloxypyrazino[1,2-*a*]pyrimidin-4-one (**18**).

Starting from **14** and using the same procedure that has been described for the synthesis of compound **16**, compound **18** was obtained as a solid in 72% yield, mp (ethanol) 239-240°; ir (potassium bromide): ν cm^{-1} 1690 (CO); ^1H and **13**C nmr see theoretical part; ms: m/e (relative abundance) 254 (4.7), 91 (100).

Anal. Calcd. for $C_{14}H_{12}N_3O_2 \cdot \frac{1}{2} H_2O$: C, 63.87; H, 4.94; N, 5.96. Found: C, 63.45; H, 4.44; N, 15.96.

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