Synthesis of New Heterocyclic Phenols: 9-Hydroxypyrido[1,2-*a*]pyrimidin-4-one and Derivatives

F. Dennin, D. Blondeau and H. Sliwa*

Laboratoire de Chimie Organique, Université des Sciences et Techniques de Lille Flandres Artois, F 59655 Villeneuve d'Ascq Cedex, France

Received November 30, 1990

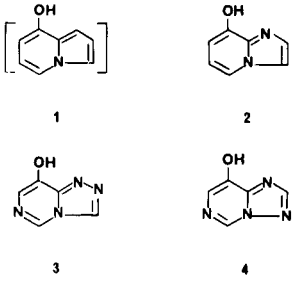
9-Hydroxypyrido[1,2-*a*]pyrimidin-4-one (**5**) was prepared by condensation of 2-amino-3-hydroxypyridine with isopropylidene aminomethylenemalonate. The reaction first led to an enaminoester intermediate which underwent cyclization by heating at 250° affording the new heterocyclic phenol **5**. A similar condensation performed on 2-amino-3-benzyloxypyridine yielded the corresponding benzylic ether which can be easily debenzylated to **5** by hydrogenolysis. Furthermore 2-amino-3-benzyloxypyridine condensed with diethyl ethoxymethylenemalonate gave 9-benzyloxy-3-ethoxycarbonylpyrido[1,2-*a*]pyrimidin-4-one which was also debenzylated to the corresponding free phenol.

J. Heterocyclic Chem., **28**, 1287 (1991).

Introduction.

The *N*-bridgehead heterocyclic compounds, more especially those derived from a six membered ring annelated either to a five or six membered heterocycle have raised up numerous studies [1,2]. In this field we have been more particularly interested by the synthesis of the new heterocyclic phenols **1-4** in which the fused heterocycles indolizine **1** [3], imidazo[1,2-*a*]pyridine **2** [4], triazolo-[4,3-*c*] and [1,5-*c*]pyrimidines **3**, **4** [5] bear an hydroxyl group at the 8 position (Scheme 1).

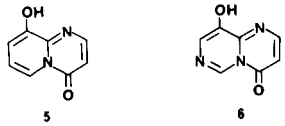
Scheme 1



We have now extended our studies to the case of 9-hydroxypyrido[1,2-*a*]pyrimidin-4-one (**5**) and 9-hydroxypyrimido[1,6-*a*]pyrimidin-4-one (**6**) [6], which have been the subject of a preliminary communication [7]. The present article deals more particularly which the synthesis of the new "phenol" **5** and some of its derivatives.

Independently of the potential pharmacologic activities that one can expect for derivatives of these structures [8,9] the heterocyclic phenols should also exhibit some interesting complexing properties [10].

Scheme 2

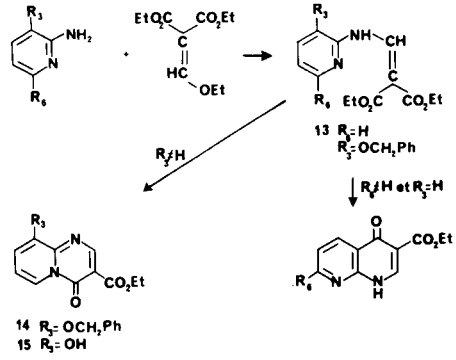


Methods of Synthesis.

The usual method for the synthesis of these fused heterocycles consists of the condensation of 2-aminopyridine with a 1,3-dicarbonyl derivatives (β-diketones or their diketals, β-ketoesters, malonic acid esters or alkoxymethylenemalonic esters).

The synthesis described by Lappin [11] has more particularly captured our attention. In this method the condensation of 2-aminopyridine with diethyl ethoxymethylenemalonate is followed by the cyclization of the resulting product upon heating at 250° in a high boiling solvent (Dowtherm A: mixture of diphenyl and diphenyl ether) as it is described in Scheme 3.

Scheme 3



This reaction is related to the Goulds-Jacobs reaction [12] which consists of the condensation of aniline and its derivatives with the ethyl ester of ethoxymethylenemalonic acid. In this case, derivatives of quinolin-4-one are obtained. Concerning the reaction described by Lappin, when the intermediate bears no substituent at the 6-position, the resulting products are pyrido[1,2-*a*]pyrimidin-4-ones. By constrast, if the heterocycle is substituted at the 6-position and unsubstituted at the 3-position, 1,8-naphthyridines are obtained. A steric effect of the 6-substituent was postulated by Lappin to explain the observed results. In fact,

further studies developed by Hermecz [13] have demonstrated that the cyclization of the intermediates occurred first on the *N*-pyridine atom and the ultimate rearrangment to naphthyridine structures is closely dependent upon the position and the nature of the substituents present on the heterocycle.

Results and Discussion.

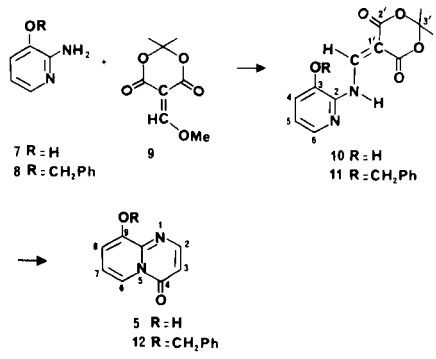
In the case of 2-amino-3-hydroxypyridine, Yale *et al.* [14,15] have shown that the Goulds-Jacobs reaction (performed on diethyl ethoxymethylenemalonate, ethyl acetoacetate or benzyl benzoylacetate) begins by *N*-alkylation followed by a regioselective cyclization in accordance with the greater nucleophilicity of the heterocyclic *N*-atom as compared to the *O*-atom of the phenolic group. This author has noted that if the condensation was realized with the *ortho*-bromobenzylic ether of 2-amino-3 hydroxypyridine and acetylacetic ester the corresponding products were obtained with a poor yield due to the unfavourable steric effect of the 3-*ortho*-bromobenzyloxy substitutent.

It was useful to reexamine this reaction from 2-amino-3-benzyloxypyridine and isopropylidene methoxymethylenemalonate and diethyl ethoxymethylenemalonate. In fact, if 2-amino-3-hydroxypyridine is commercially available, it is not the case for 4-amino-5-hydroxypyrimidine which is the starting compound for the synthesis of products such as **6**. The synthesis needs the preparation of ether derivatives as intermediates. For these reasons, a complete study of the condensation of 2-amino-3-hydroxypyridine and its benzylic ether was investigated.

Synthesis of 9-Hydroxypyrido[1,2-*a*]pyrimidin-4-one (**5**) and Derivatives.

The condensation of 2-amino-3-hydroxypyridine (**7**) with isopropylidene methoxymethylenemalonate (prepared by interaction of Meldrum's acid, 2,2-dimethyl-1,3-dioxane-4,6-dione, with trimethyl orthoformate) for 3 hours afforded isopropylidene *N*-(3-hydroxy-2-pyridyl)aminomethylenemalonate (**10**). Heating this latter at 250° in Dowtherm A for a few minutes, furnished 9-hydroxypyrido[1,2-*a*]pyrimidin-4-one (**5**) (Scheme 4). Starting from 2-amino-3-benzyloxypyridine (**8**) a similar reaction afforded 9-benzyloxypyrido[1,2-*a*]pyrimidin-4-one (**12**). The condensation of diethyl ethoxymethylenemalonate (EMME) with 2-amino-3-benzyloxypyridine could be realized in homogeneous medium, either in methylene chloride or by utilizing EMME in excess. We observed a complete reaction by refluxing the solution for 3 hours in methylene chloride and the spontaneous precipitation of diethyl *N*-(3-benzyloxy-2-pyridyl)aminomethylenemalonate (**13**). The cyclization was performed at 250° in Dowtherm A and afforded 3-ethoxycarbonyl-9-benzyloxypyrido[1,2-*a*]pyrimidin-4-one (**14**).

Scheme 4



One can notice that compound **5** could not be obtained by saponification of **14** and subsequent decarboxylation of the resulting product. Attempted saponification realized in either concentrated or diluted basic medium did not afford the expected compound but reverted to the starting material 2-amino-3-benzyloxypyridine. The hydrogenolysis of **12** and **14** was achieved by the action of palladium hydroxide ($Pd(OH)_2$) in refluxing cyclohexene in good yields (80%); the classical method (pH_2 = 1 atmosphere Pd/C) furnished the same compounds but in much lower yields (from 25 to 30%).

Structural Study.

All the condensation products **10**, **11** and **13** showed in the ir, beyond 3120 cm^{-1}, a unique band of absorption centered at 3240 cm^{-1} which was attributed to the N-H group. The presence of the ester function was confirmed by two bands located at 1730 and 1680 cm^{-1}. This latter was assigned to the CO vibration of a chelated ester through hydrogen bonding [16]. After cyclization, the fused heterocycles showed a CO absorption centered at 1680 cm^{-1} corresponding to the conjugated heterocyclic amide group. These values are in good agreement with these reported by Yale, *et al.* for some 9-alkoxypyrido-[1,2-*a*]pyrimidin-4-ones obtained by alkylation of the corresponding phenol **15**. The phenols were characterized by a large absorption band which extended from 3200 cm^{-1} to 2200 cm^{-1} due to the associated hydroxyl group.

The ^1H nmr spectra confirmed the enamine structure of intermediates **10**, **11** and **13**. The presence of two doublets, attributed respectively to the N-H proton and to the ethylenic hydrogen as well as the disappearance of the former signal and the change of the latter to a singlet when exchange was made with deuterium oxide clearly demonstrated this structure.

According to the literature [17] concerning 2-(2-pyridylaminomethylene) succinates and glutarates, the deshielding of N-H hydrogen ($11.46 < \delta < 11.83$ ppm) and the high values of the associated coupling constants (13.7 Hz < J < 14 Hz) were indicative of a chelated *S-trans* structure. In addition one can notice the low field shift of

the ethylenic hydrogen (9.1 to 9.5 ppm) which lies also in the anisotropic deshielding cone of one of the ester carbonyl groups. This structure causes a non-equivalence for the ester functions as shown by the different observed chemical shifts of the CH_2 groups. The bicyclic structure of the cyclized compounds was characterized by the low field shift of the H-6 proton which was deshielded by the carbonyl group in the peri position. The corresponding signal constituted the X part of an ABX system, the AB part of which relative to H-7 and H-8 appeared between 7 and 7.50 ppm. The H-2 and H-3 protons gave rise to two doublets. The transformation of the benzylic ether to the free phenolic OH group was characterized by the disappearance of the phenyl and methylene signals and by the exchangeable broad singlet at 7.38 ppm assigned to the phenolic hydrogen. The whole attribution was in good agreement with the data described by Yale for 9-hydroxy-3-ethoxycarbonylpyrido[1,2-*a*]pyrimidin-4-one [15]. All the ^{13}C shifts for the intermediates and also for the fused heterocycles were characteristic of the expected structures. The total attribution was made by the classical methods: relative intensity, deshielding effect due to the proximity of one or more heteroatoms, homodecoupling and by analogy with previous shifts described in the literature [2]. Comparison of data concerning compounds **14**, **15** and **12**, **5** showed that the disappearance of the ester function did not affect the shift of the C-3 carbon but induced a shielding effect on the C-2 carbon. This observation and the high value of the corresponding shift was already noticed for a similar compound: tetrahydropyrido[1,2-*a*]pyrimidin-4-one [18]. The transformation of the benzylic ethers **14** and **12** to the free phenols **15** and **5** did not induce significant changes in the heterocyclic carbons shifts.

Conclusion.

The synthesis of the new heterocyclic phenol, 9-hydroxypyrido[1,2-*a*]pyrimidin-4-one and its 3-ethoxycarbonyl derivative have been achieved by two methods in good yields, starting either from 2-amino-3-hydroxypyridine or from its benzylic ether. If the literature mentions a satisfactorily yield for the synthesis of 3-ethoxycarbonyl-9-hydroxypyrido[1,2-*a*]pyrimidin-4-one by the direct reaction, the condensation realized by Yale starting from ethers of this phenol afforded the cyclized products with very poor yields [19]. This was also the case for the intermediate enaminoesters when these could be isolated. For our part, we were able to isolate the intermediate enaminoesters and the resulting fused heterocycles in good yields whatever was the starting product. This result constituted the first challenge of our studies that will be extended to the synthesis of pyrimido[1,6-*a*]pyrimidin-4-ones substituted by an hydroxy group at the 9-position.

EXPERIMENTAL

Melting points were determinated in capillary tubes on a Büchi SMP 20 apparatus and are uncorrected. Infrared spectra were obtained in potassium bromide pellets on a Perkin-Elmer Model 1420 spectrophotometer. Proton and carbon nmr spectra were recorded in deuteriochloroform on a Bruker WP 80 spectrometer; chemical shifts are reported in parts per million (δ) downfield from an internal TMS reference. Mass spectra were taken on a R-10-10 Riber spectrometer under 70 eV. Microanalyses were performed by the Centre National de la Recherche Scientifique.

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

This compound was prepared according to the procedure described by Rydzkowski [20] in 45% yield, mp 93-94°; ir (potassium bromide): ν cm^{-1} 3460-3280 (NH, amine), 3120 (CH aromatic), 1630, 1560, 1490 (C=C and C=N aromatic), 1210, 1050, 1020 (C-O, benzylic ether); ^1H nmr (deuteriochloroform): δ ppm 4.76 (s, 2H, NH_2), 5.06 (s, 2H, phenyl-CH_2-O), 6.51 (dd, 1H, H-5, $J_{H4\text{-}H5}$ = 7.2 Hz, $J_{H5\text{-}H6}$ = 5.0 Hz), 7.00 (dd, 1H, H-5, $J_{H4\text{-}H5}$ = 7.2 Hz, $J_{H4\text{-}H6}$ = 1.5 Hz), 7.40 (s, 5H, phenyl), 7.22 (dd, 1H, H-6, $J_{H4\text{-}H6}$ = 1.5 Hz, $J_{H5\text{-}H6}$ = 5.0 Hz); ^{13}C nmr (deuteriochloroform): δ ppm 70.2 (O-*C*H_2-phenyl), 113.5 (C-5), 116.8 (C-4), 127.5, 128.2, 128.6 (C *ortho, meta, para* of phenyl group), 136.3 (C *ipso* of phenyl group), 139.2 (C-6), 141.5 (C-3), 150.3 (C-2); ms: m/z (relative abundance) 200 (21), 91 (100).

Isopropylidene *N*-(3-Benzyloxy-2-pyridyl)aminomethylenemalonate (**11**).

The following mixture was refluxed with stirring for a period of 3 hours: 8 g (0.040 mole) of **11**, 6.5 g (0.045 mole) of Meldrum's acid, 8 ml of ethyl orthoformate in 20 ml of methylene chloride. After cooling and filtration, compound **11** was obtained in 69% yield, mp (acetonitrile) 149-150°: ir (potassium bromide): ν cm^{-1} 3080 (CH aromatic), 1630, 1560, 1490 (C=C and C=N aromatic), 1730 (C=O); ^1H nmr (deuteriochloroform): δ ppm 7.99 (dd, 1H, H_6), 7.08 (dd, 1H, H_5), 7.34 (m, 6H, H_4 and phenyl), 1.83 (d, 1H, NH), 9.45 (d, 1H, CH), 5.24 (s, 2H, O-CH_2-phenyl), 1.74 (s, 6H, CH_3), $J_{H6\text{-}H5}$ = 4.8 Hz, $J_{H6\text{-}H4}$ = 1.7 Hz, $J_{H5\text{-}H4}$ = 8.3 Hz, $J_{NH\text{-}CH}$ = 13.9 Hz; ^{13}C nmr (deuteriochloroform): δ ppm 150.4 (C-2), 143.3 (C-3), 121.4 and 120.2 (C-4 and C-5), 140.1 and 139.9 (C-6 and C-1'), 165.2 and 163.2 (C-2'), 89.1 (C-3'), 70.8 (O-*C*H_2-phenyl), 135.1, 126.9, 128.8, 128.4 (C *ipso*, *ortho*, *meta*, *para* of phenyl group), 27.1 (CH_3), 104.8 (CH); ms: m/z (relative abundance) 354 (3.2), 296 (17), 252 (10.5), 91 (100), 65 (50.2).

Anal. Calcd. for $C_{19}H_{18}N_2O_2$: C, 64.40; H, 5.11; N, 7.90. Found: C, 64.12; H, 5.10; N, 7.91.

Isopropylidene Methoxymethylenemalonate (**9**).

According to the procedure described by Bihlmayer *et al.* [21], this compound was obtained in 71% yield, mp 120-121° (Lit [21] mp 136-137°); ir (potassium bromide): ν cm^{-1} 1680 (CO); ^1H nmr (deuteriochloroform): δ ppm 1.69 (s, 6H, CH_3), 4.22 (s, 3H, CH_3-O), 8.11 (s, 1H, H ethylenic); ms: (relative abundance), 186 (25.3), 171 (74-75), 129 (82).

Diethyl *N*-(3-Benzyloxy-2-pyridyl)aminomethylenemalonate (**13**).

First Method.

The following mixture was warmed until white fumes appeared (10 minutes): 2 g (0.01 mole) of 2-amino-3-benzyloxypyridine (**8**) in

3 ml of diethyl ethoxymethylenemalonate. After cooling to ambient temperature and filtration, the resulting solid was recrystallized. Compound **13** was obtained in 78% yield, mp (absolute ethanol) 84-85°; ir (potassium bromide): ν cm^{-1} 3220 (NH), 1700 (CO), 1620 (C=C conjugated); ^1H nmr (deuteriochloroform): δ ppm 7.93 (dd, 1H, H_6), 6.90 (dd, 1H, H_5), 7.43 (m, 6H, H_4 and phenyl), 11.46 (d, 1H, NH), 9.23 (d, 1H, CH), 5.20 (s, 1H, O-CH_2-phenyl), 4.32 and 4.21 (2q, 4H, CH_2), 1.32 (s, 6H, CH_3), J_{H6-H5} = 4.6 Hz, J_{H6-H4} = 1.4 Hz, J_{H5-H4} = 8.0 Hz, J_{NH-CH} = 13.6 Hz; ^{13}C nmr (deuteriochloroform): δ ppm 148.3 (C-2), 142.0 and 142.8 (C-3 and *C*-$(CO_2C_2H_5)_2$), 119.4 and 119.1 (C-4 and C-5), 139.6 (C-6 and C-1'), 70.6 (O-*C*H_2-phenyl), 135.7, 127.0, 128.7, 128.3 (C *ipso, ortho, meta, para* of phenyl group), 60.4 and 60.1 (CH_2), 14.5 and 14.3 (CH_3), 96.3 (CH); ms: m/z (relative abundance) 370 (2.0), 297 (7.2), 91 (100), 65 (17.3).

Anal. Calcd. for $C_{20}H_{22}N_2O_5$: C, 64.85; H, 5.95; N, 7.46. Found: C, 64.93; H, 5.98; N, 7.56.

Second Method.

The following mixture was refluxed for a period of 3 hours: 6 g (0.03 mole) of 2-amino-3-benzyloxypyridine, (**8**), 6 ml of diethyl ethoxymethylenemalonate and 100 ml of methylene chloride. After cooling, the solvent was evaporated under reduced pressure. The resulting product **13** was obtained after recrystallization in absolute ethanol in 97% yield. It had the same physicochemical data that were observed for the compound obtained by the first method.

Isopropylidene *N*-(3-Hydroxy-2-pyridyl)aminomethylene (**10**).

The following mixture was refluxed for a period of 5 minutes: 1 g (0.01 mole) of 2-amino-3-hydroxypyridine, 2 g, (0.01 mole) of isopropylidene methoxymethylenemalonate (**2**) and 10 ml of methyl orthoformate. After cooling, the resulting solid was separated by filtration and recrystallized. Compound **10** was obtained in 83% yield, mp (absolute ethanol) 210-211°; ir (potassium bromide): ν cm^{-1} 2500-3200 (OH phenolic), 1630-1560 (C=C and C=N aromatic), 1680 (CO); ^1H nmr (deuteriochloroform): δ ppm 7.95 (dd, 1H, H_6), 7.27 (m, 2H, H_5, H_4), 11.49 (d, 1H, NH), 9.16 (d, 1H, CH), 1.70 (s, 6H, CH_3), J_{H6-H5} = 4.7 Hz, J_{H6-H4} = 1.8 Hz, J_{H5-H4} = 8.0 Hz, J_{NH-CH} = 14.0 Hz, ^{13}C nmr (deuteriochloroform): δ ppm 149.1 (C-2), 142.2 (C-3), 122.1 and 123.3 (C-4 and C-5), 138.4 (C-6 and C-1'), 164.4 and 162.5 (C-2'), 88.1 (C-3'), 26.5 (CH_3), 104.5 (CH); ms: m/z (relative abundance) 264 (10), 206 (100), 162 (57.5).

Anal. Calcd. for $C_{12}H_{12}N_2O_5$: C, 54.54; H, 4.57; N, 10.60. Found: C, 54.66; H, 4.70; N, 10.39.

3-Ethoxycarbonyl-9-benzyloxypyrido[1,2-*a*]pyrimidin-4-one (**14**).

The following mixture was warmed at 250°, under an inert atmosphere for a period of 45 minutes: 5 g (0.0135 mole) of diethyl *N*-(3-benzyloxy-2-pyridyl)aminomethylenemalonate in 60 ml of Dowtherm A. After cooling, the precipitated product was filtered and recyrstallized. The compound was obtained in 85% yield, mp (absolute ethanol) 165°; ir (potassium bromide): ν cm^{-1} 1745 (CO ester), 1630-1490 (C=C and C=N aromatic); ^1H nmr (deuteriochloroform): δ ppm 9.11 (s, 1H, H_2), 8.89 (dd, 1H, H_6), 7.18 (dd, 1H, H_7), 7.42 (m, OH, H_8 and phenyl), 5.40 (s, 2H, O-CH_2-phenyl), 4.43 (q, 2H, CH_2), 1.42 (t, 3H, CH_3), J_{H6-H7} = 5.6 Hz, J_{H7-H8} = 3.4 Hz, J_{H6-H8} = 2.4 Hz; ^{13}C nmr (deuteriochloroform): δ ppm 158.1 (C-2, C-4), 106.2 (C-3), 120.6 (C-6), 116.9 and 116.2 (C-7 and C-8), 147.5 (C-9a), 151.8 (C-9), 72.1 (O-*C*H_2-phenyl), 134.9, 127.4, 129.1, 128.7 (C *ipso, ortho, meta, para* of phenyl group), 164.7 (CO_2), 61.2 (CH_2), 14.5 (CH_3); ms: m/z (relative abundance) 324 (1.4), 91 (100), 65 (11.7).

Anal. Calcd. for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.96; N, 8.63. C, 66.93; H, 5.06; N, 8.58.

9-Benzyloxypyrido[1,2-*a*]pyrimidin-4-one (**12**).

Compound **11** (3 g, 0.0084 mole) was added to 60 ml of Dowtherm A warmed at 250°. After vigorous stirring for a period of 5 minutes, the resulting mixture was cooled to 50° and then poured into 60 ml of petroleum ether. After extraction with a diluted solution of hydrochloric acid (20%, 3 x 30 ml) and neutralization with a sodium carbonate solution (20%), the aqueous layer was extracted with chloroform. The organic phases were dried over magnesium sulfate, filtrated and evaporated under reduced pressure. The resulting crude product was recrystallized from absolute ethanol yielding **12** in 67% yield, mp (absolute ethanol) 131-132°; ir (potassium bromide): ν cm^{-1} 3100 (CH aromatic), 1680 (CO); ^1H nmr (deuteriochloroform): δ ppm 8.38 (d, 1H, H_2), 6.50 (d, 1H, H_3), 8.71 (m, 1H, H_6), 7.01 (m, 1H, H_7), 7.42 (m, 6H, H_8 and phenyl), 5.39 (s, 2H, O-CH_2-phenyl), J_{H2-H3} = 6.9 Hz, J_{H7-H8} = 3.9 Hz, J_{H6-H7} = 5.1 Hz, J_{H6-H8} = 2.8 Hz; ^{13}C nmr (deuteriochloroform): δ ppm 153.6 (C-2), 157.7 (C-4), 105.6 (C-3), 119.3 (C-6), 114.5 and 113.3 (C-7 and C-8), 146.3 (C-9a), 151.1 (C-9), 71.6 (CH_2), 135.2, 127.2, 128.8, 128.4 (C *ipso, ortho, meta, para* phenyl group); ms: m/z (relative abundance) 252 (15.4), 91 (100), 65 (8.4).

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.71; H, 4.89; N, 11.00.

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

First Method.

The following mixture was introduced in an autoclave heated to 45° and shaken under a hydrogen pressure of 3 atmospheres for a period of 8 hours: 1 g (0.003 mole) of 3-ethoxycarbonyl-9-benzyloxypyrido[1,2-*a*]pyrimidin-4-one (**14**), 0.35 g of catalyst (Pd/C, 10%) and 60 ml of absolute methanol. The methanolic suspension was filtered and evaporated under reduced pressure. The yellow residual product was recrystallized yielding compound **15** in 25% yield, mp (absolute ethanol) 165°; ir (potassium bromide): ν cm^{-1} 2800-3500 (OH phenolic), 1690 (C=O ester), 1630, 1585 (C=C and C=N aromatic), 1150 (C-O ester); ^1H nmr (deuteriochloroform): δ ppm 9.01 (s, 1H, H_2), 8.81 (dd, 1H, H_6), 6.53 (s, 1H, OH), 7.38 (m, 2H, H_7 and H_8), 4.45 (q, 2H, CH_2), 1.42 (t, 3H, CH_3), J_{H6-H7} = 6.1 Hz, J_{H7-H8} = 3.4 Hz, J_{H6-H8} = 2.2 Hz; ^{13}C nmr (deuteriochloroform): δ ppm 156.8 (C-2), 154.4 (C-4), 105.7 (C-3), 119.4 (C-6), 117.2 and 117.5 (C-7 and C-8), 147.5 (C-9a), 164.5 (CO_2), 61.1 (CH_2), 14.3 (CH_3); ms: m/z (relative abundance 234 (100), 162 (42.1).

Second Method.

The following mixture was refluxed for a period of 2 hours: 1 g (0.003 mole) of 3-ethoxycarbonyl-9-benzyloxypyrido[1,2-*a*]pyrimidin-4-one (**14**), 0.3 g of palladium hydroxide at 10%, 40 ml of absolute ethanol and 20 ml of cyclohexene. After cooling, the resulting suspension was filtered over celite and evaporated under reduce pressure. The crude product was filtered and recrystallized. Compound **15** was obtained in 78% yield and showed the same physicochemical data that those noticed for the product **14** obtained by the first method.

9-Hydroxypyrido[1,2-*a*]pyrimidin-4-one (**5**).

1. From 9-Benzyloxypyrido[1,2-*a*]pyrimidin-4-one (**12**).

First Method.

The following mixture was introduced into an autoclave: 0.8 g (0.0031 mole) of 9-hydroxypyrido[1,2-*a*]pyrimidin-4-one (**12**), 60 ml of absolute ethanol and 0.35 g of 10% palladium on carbon. This suspension was shaken at 45° for a period of 8 hours under a hydrogen pressure of 3 atmospheres. The resulting mixture was cooled and filtered on celite. After evaporation under reduced pressure, recrystallization of the residue afforded compound **5** in 30% yield, F(absolute ethanol): 222-223; ir (potassium bromide): ν cm^{-1} 3500-2800 (OH phenolic), 1730 (C=O), 1640, 1580, 1545 (C=C and C=N aromatic); ^1H nmr (deuteriochloroform): δ ppm 8.35 (d, 1H, H_2), 6.45 (d, 1H, H_3), 8.55 (dd, 1H, H_6), 7.38 (m, 3H, OH, H_7b H_8), J_{H2-H3} = 6.1 Hz, J_{H6-H7} = 5.4 Hz, J_{H6-H8} = 2.7 Hz; ^{13}C nmr (deuteriochloroform): δ ppm 152.5 (C-2), 156.8 (C-4), 103.6 (C-3), 117.2 (C-6), 116.4 and 115.4 (C-7 and C-8), 145.4 (C-9a), 150.3 (C-9); ms: m/z (relative abundance) 162 (100), 134 (38.3).

Anal. Calcd. for $C_8H_6N_2O_2$: C, 59.26; H, 3.72; N, 17.27. Found: C, 59.30; H, 4.17; N, 17.57.

Second Method.

The following mixture was refluxed for a period of 2 hours: 1.2 g (0.0047 mole) of 9-benzyloxypyrido[1,2-*a*]pyrimidin-4-one (**12**), 20 ml of absolute ethanol, 20 ml of cyclohexene and 0.3 g of 10% palladium hydroxide. After cooling, the resulting suspension was filtered on celite and concentrated under reduced pressure. After filtration and recrystallization of the crude product, the compound **5** was obtained in 78% yield. It was characterized by the same physicochemical data that were recorded for the product obtained by the first method.

2. From Isopropylidene *N*-(3-Hydroxy-2-pyridyl)aminomethylenemalonate.

To 10 ml of Dowtherm A warmed at 250°, 1 g (0.0038 mole) of **10** was added in one portion and the mixture was vigorously shaken for a period of 10 minutes at this temperature. The resulting solution was cooled to 50° and poured into 40 ml of hexane. The precipitated compound was separated by filtration and recrystallized from absolute ethanol. Compound **5** was obtained in 81% yield and showed the same physicochemical data as that obtained for the preceeding product by the previous procedures.

REFERENCES AND NOTES

[1] L. W. Mosby, The Chemistry of Heterocyclic Compounds, in Heterocyclic Systems with Bridgehead Nitrogen Atoms, Interscience Publishers, New York, London, 1961.

[2] A. R. Katritzky, Handbook of Heterocyclic Chemistry, Pergamon Press, Oxford, 1985, p 495.

[3] D. Blondeau and H. Sliwa, *Tetrahedron Letters*, 933 (1976).

[4] R. Rydzkowski, D. Blondeau and H. Sliwa, *Tetrahedron Letters*, 1591 (1985).

[5] O. Rousseaux, D. Blondeau and H. Sliwa, *Tetrahedron Letters*, **27**, 3127 (1986).

[6] F. Dennin, D. Blondeau and H. Sliwa, *J. Heterocyclic Chem.*, **27**, 1963 (1990).

[7] F. Dennin, D. Blondeau and H. Sliwa, *Tetrahedron Letters*, **30**, 1529 (1989).

[8] I. Hermecz, T. Breining, Z. Meszaros, J. Kökösi, L. Meszaros, F. Dessy and C. De Vos, *J. Med. Chem.*, **26**, 1126 (1983).

[9] I. Hermecz, L. Vasvari-Debreczy, A. Horvath, M. Balogh, J. Kökösi, C. De Vos and L. Rodriguez, *J. Med. Chem.*, **30**, 1543 (1987).

[10] P. Decock, B. Dubois, D. Blondeau, H. Sliwa and H. Kozlowski, *J. Coor. Chem.*, **20**, 1 (1988).

[11] G. R. Lappin, *J. Am. Chem. Soc.*, **70**, 3348 (1948).

[12a] L. A. Paquette, Principles of Modern Heterocyclic Chemistry, W. A. Benjamin, Inc., New York, Amsterdam, 1968, p 280; [b] C. C. Price and R. M. Roberts, *J. Am. Chem. Soc.*, **68**, 1204 (1946).

[13] I. Hermecz, Z. Meszaros, L. Vasvari-Debreczy, A. Horvath, G. Horvath and M. Pongor-Csakvari, *J. Chem. Soc., Perkin Trans. 1*, 789 (1977).

[14] H. L. Yale, *J. Heterocyclic Chem.*, **11**, 739 (1974).

[15] H. L. Yale, *J. Heterocyclic Chem.*, **12**, 427 (1975).

[16] G. B. B. Sutherland, *Discuss. Farad. Soc.*, **9**, 114 (1950).

[17] L. Vasvari-Debreczy, I. Hermecz, Z. Meszaros, A. Horvath and P. Simon-Parkanyi, *J. Chem. Soc., Perkin Trans. 1*, 795 (1978).

[18] G. Toth, C. de la Cruz, I. Bitter, I. Hermecz, B. Pete and Z. Meszaros, *Org. Magn. Reson.*, **20**, 229 (1982).

[19] H. L. Yale and J. T. Sheehan, *J. Heterocyclic Chem.*, **10**, 143 (1973).

[20] R. Rydzkowski, D. Blondeau and H. Sliwa, *J. Chem. Res., S*, 404; M, 3368 (1986).

[21] G. A. Bihlmayer, G. Derflinger, J. Derkosch and O. E. Polansky, *Monatsch. Chem.*, **98**, 564 (1967).