1,2-Fused Pyrimidines. III.
Derivatives of 12H-Pyrido[1',2':1,2]pyrimido[4,5-b]quinoline, A Novel Heterocyclic System [1]

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Reactivities of 2-amino-4H-pyrido[1,2-a]pyrimidin-4-ones and 4-amino-2H-pyrido[1,2-a]pyrimidin-2-ones, both N,N-dialkyl and (N-alkyl,N-phenyl)substituted, when treated with the N,N-dimethylformamide/phosphorus oxychloride Vilsmeier-Haack reagent **XII** were compared.

Starting from 2-[(N-alkyl,N-phenyl)amino] compounds **IXa,b**, the expected **XVIa,b** and **XVIIa,b** were obtained, which are derivatives of 12H-pyrido[1',2':1,2]pyrimido[4,5-b]quinoline, a novel heterocyclic system. When 2-(phenylamino) compound **IXc** was used a mixture of 3-formylderivative **XVIII** and 12H-pyrido-[1',2':1,2]pyrimido[4,5-b]quinolin-12-one (**XIX**) resulted from the reaction. On the other hand, 2-(dialkylamino)-4H-pyrido[1,2-a]pyrimidin-4-ones **IIIa-c** plainly afforded high yields of 3-formylderivatives **XIVa-c**.

In contrast, no significant reaction occurred when 4-(dialkylamino) and 4-[(N-alkyl,N-phenyl)amino] compounds **IIa-c** and **VIIIa,b** were treated with the reagent **XII**, under the same as well as more severe conditions. A clear difference in the nucleophilic reactivity of C-3 position between these two classes of isomers is pointed out by the above summarized results.

We recently described [2] the synthesis and spectroscopic properties of 4-(dialkylamino)-2H-pyrido[1,2-a]pyrimidin-2-ones **II**, a new class of pyrido[1,2-a]pyrimidine derivatives. Compounds **II** were obtained from the reaction of 2-aminopyridine with the N,N-dialkylethoxycarbonylacetamide/phosphorus oxychloride reagent **I**, together with lower yields of isomer 2-(dialkylamino)-4H-pyrido[1,2-a]pyrimidin-4-ones **III**.
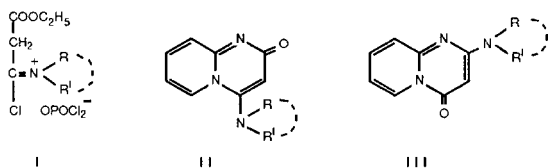
Significant differences between solubilities, melting points, ir and ¹H-nmr spectral data of the isomer compounds **II** and **III** [2] prompted us to compare their chemical behavior.

On the other hand, we previously showed that Vilsmeier-Haack formylation of analogous ß-enaminocarbonylic compounds, *i.e.* N,N-disubstituted 3-amino-1H-naphtho[2,1-b]pyran-1-ones **IV**, led to different results according to the type of 3-amino substituent. Actually, when it was dialkylamino group the simple formation of 2-formylderivatives was achieved [3], while when it was (N-alkyl,-N-phenyl)amino group both 14H-naphtho[1',2':5,6]pyrano-[2,3-b]quinoline and 1H-phenalene derivatives were obtained [4]. Furthermore, when 3-(phenylamino)-1H-naphtho[2,1-b]pyran-1-one (**IV**, R = H, R' = C₆H₅) was used in the reaction, only 14H-naphtho[1',2':5,6]pyrano[2,3-b]quinolin-14-one **V** was yielded [5].
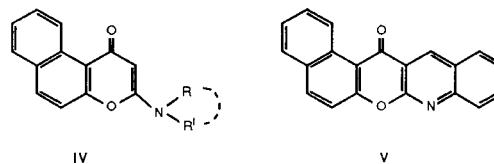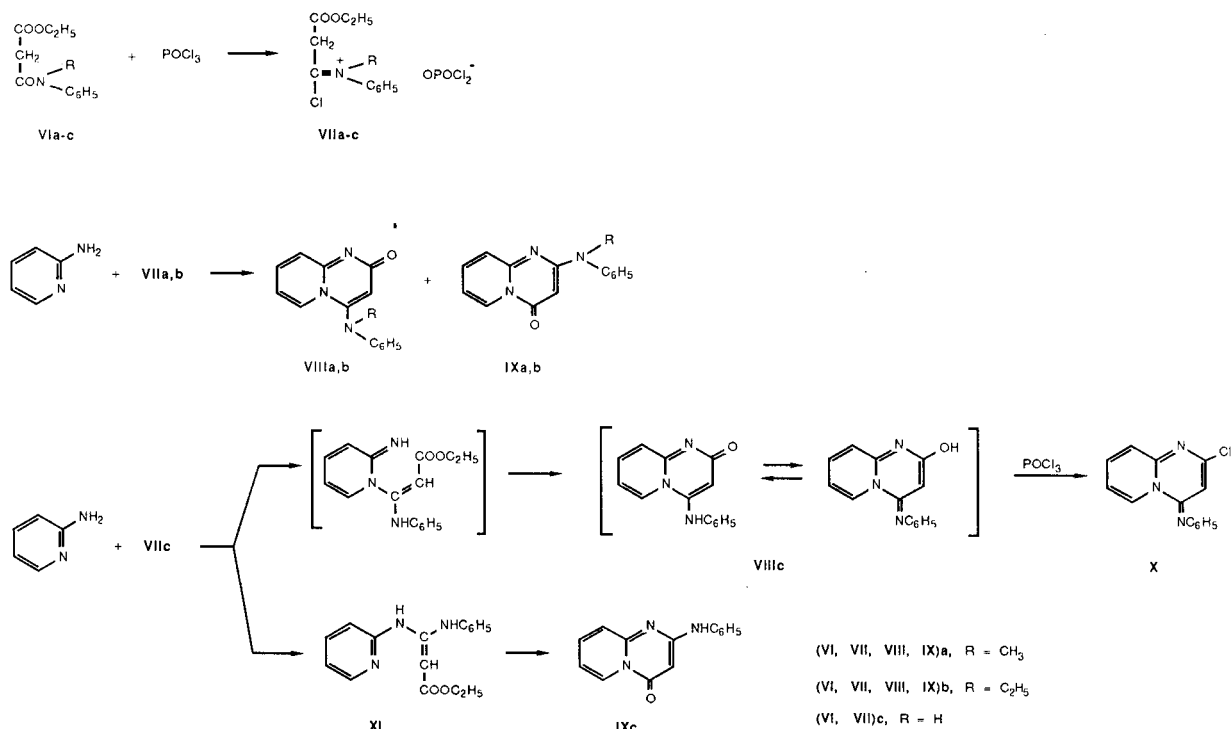

Following these suggestions, we have now studied the behavior of dialkylamino compounds **II** and **III**, as well as of their novel phenylamino analogs **VIII** and **IX**, when treated with the N,N-dimethylformamide/phosphorus oxychloride reagent **XII**. The possible preparation of new pyridopyrimidoquinoline derivatives through the reaction of **XII** with compounds **VIII** or **IX** was an aim of our study.

In this connection, the starting (N-alkyl,N-phenyl)-amino compounds **VIIIa,b** and **IXa,b** were first prepared by treating 2-aminopyridine with the reagent **VIIa,b** in refluxing 1,2-dichloroethane (Chart I).

An interesting result occurred when the same reaction was performed using the reagent **VIIc** (R = H). In this case a mixture of compounds **IXc**, **X** and **XI** was obtained. The formation of 2-chloro derivative **X** may be explained through the action of phosphorus oxychloride on the enolic form **VIIIc** of the unisolated 4-(phenylamino) compound. Furthermore, the presence of the open chain intermediate **XI**, from the cyclization of which the compound **IXc** plainly derived, provides a confirmatory evidence of the pattern we already suggested [2] for this type of reaction.

2-Aminocompounds **III**, **IX** and their 4-aminosubstituted isomers **II**, **VIII** showed quite different behaviors when treated with the reagent **XII** (Chart II).

Chart I

VIa-c   VIIa-c

VIIIa,b   IXa,b

VIIIc   X

XI   IXc

(VI, VII, VIII, IX)a, R = CH$_3$

(VI, VII, VIII, IX)b, R = C$_2$H$_5$

(VI, VII)c, R = H

Indeed 2-(dialkylamino) compounds **IIIa-c** reacted with **XII** to give plainly 2-(dialkylamino)-4-oxo-4*H*-pyrido-[1,2-*a*]pyrimidine-3-carbaldehydes **XIVa-c** in very good yields. Moreover, under the same conditions (95°, 90 minutes, *N*,*N*-dimethylformamide as solvent), the reaction of 2-[(*N*-alkyl,*N*-phenyl)amino] compounds **IXa,b** with **XII** afforded the expected mixture of 5-alkyl-5,13-dihydro-12*H*-pyrido[1′,2′:1,2]pyrimido[4,5-*b*]quinolin-12-ones **XVIa,b** and 5-alkyl-12*H*-pyrido[1′,2′:1,2]pyrimido[4,5-*b*]-quinoline-12,13(5*H*)-diones **XVIIa,b**, while starting from 2-(phenylamino) compound **IXc** a mixture of 2-(phenylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde **XVIII** and 12*H*-pyrido[1′,2′:1,2]pyrimido-[4,5-*b*]quinolin-12-one **XIX** was obtained.

In contrast no significant reaction apparently occurred when 4-amino compounds **IIa-c** and **VIIIa,b** were treated with **XII**, under the above or even more severe conditions (95°, 8 hours or 140°, 90 minutes). In most cases a large amount of starting compound was recovered.

The above described reactivity of compounds **III** and **IX** is in agreement with the behavior of other 2-substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones, the C-3 atom of which readily takes part in electrophilic substitutions [6].

In accordance with our previous suggestions in analogous cases [4,5], the formation of tetracyclic compounds **XVI** and **XVII**, or **XIX**, may be explained through the reaction pattern depicted in Chart II. In this connection

the cyclization of the intermediate **XV**, by intramolecular electrophilic attack of the carbocation on the *N*-phenyl position 2, is a fundamental step of the reaction.
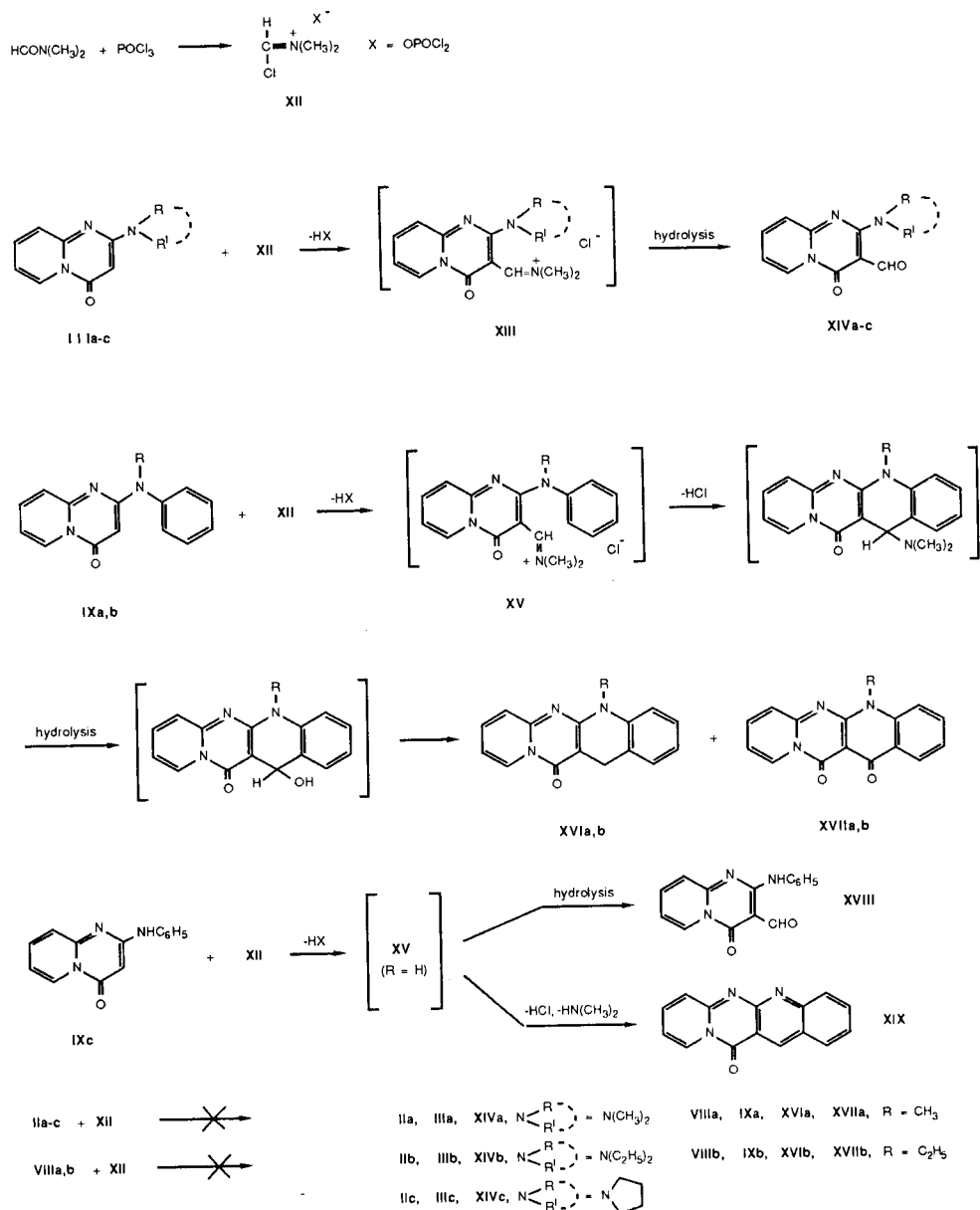
It is interesting to observe that, starting from compound **IXc**, under standard conditions (95°, 90 minutes) the intermediate **XV** (R = H) only partly underwent cyclization, followed by elimination of dimethylamine, to give the tetracyclic compound **XIX**. Actually a small amount of **XV** (R = H) was still present in the final hydrolysis to give formyl derivative **XVIII**, the *N*-phenyl group being not involved in the reaction. That is likely due to insufficient electron density on the *N*-phenyl position 2 when the favourable inductive effect of *N*-alkyl group is absent.

Indeed when the reaction of **IXc** with **XII** was carried out in milder conditions (45°, 90 minutes) only a small amount of compound **XIX** was obtained, the formation of 3-formylderivative **XVIII** largely prevailing (see Experimental). On the contrary, when compound **IXa** was treated with the reagent **XII** at 45° almost the same result as at 95° occurred (*i.e.* high yields of compounds **XVIa** and **XVIIa**) and no formylderivative of **IXa** was obtained from the reaction.

Results of elemental analyses, and ir, [¹H]-nmr and mass spectral data were consistent with the structures attributed to the compounds described in this paper (see Experimental).

The characteristic differences previously observed [2]

Chart 11

$HCON(CH_3)_2 + POCl_3 \longrightarrow$ XII $X = OPOCl_2$

III a-c + XII $\xrightarrow{-HX}$ XIII $\xrightarrow{hydrolysis}$ XIVa-c

IXa,b + XII $\xrightarrow{-HX}$ XV $\xrightarrow{-HCl}$

$\xrightarrow{hydrolysis}$ XVIa,b + XVIIa,b

IXc + XII $\xrightarrow{-HX}$ XV (R = H) $\xrightarrow{hydrolysis}$ XVIII

XV (R = H) $\xrightarrow{-HCl, -HN(CH_3)_2}$ XIX

IIa-c + XII $\longrightarrow\!\!\!\!\times$

VIIIa,b + XII $\longrightarrow\!\!\!\!\times$

IIa, IIIa, XIVa, $N{<}^{R}_{R^1} = N(CH_3)_2$	VIIIa, IXa, XVIa, XVIIa, R = CH_3	
IIb, IIIb, XIVb, $N{<}^{R}_{R^1} = N(C_2H_5)_2$	VIIIb, IXb, XVIb, XVIIb, R = C_2H_5	
IIc, IIIc, XIVc, $N{<}^{R}_{R^1} = N$ (pyrrolidine)		

XI

between both ir and ^{1}H-nmr spectra of (dialkylamino)substituted isomers **II** and **III** were significantly again present between spectra of [(N-alkyl,N-phenyl)amino]-substituted isomers **VIII** and **IX**. In this connection the position of ν CO ir band and of H-3, H-6 ^{1}H-nmr signals were specially meaningful.

The low frequencies, not affected by change of concentration, of ir ν NH and ν CO bands of compound **XI** may be explained by the presence of two intramolecular hydrogen bonds (see below). In accordance, the ^{1}H-nmr NH signals were very downfield.
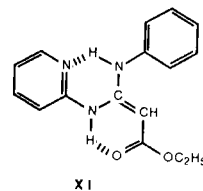
Referring to compound **XVIII**, an intramolecular hydrogen bond seems again to be responsible of ir low stretching frequencies of NH and formyl CO groups, as well as of the low-field position of the ^{1}H-nmr NH signal.

The [1]H-nmr spectra of compounds **XVI, XVII, XIX** were particularly confirmatory of their structures. The downfield position of the H-10 multiplet (corresponding to the like H-6 signal of starting compounds **IXa-c**) confirmed the presence of the 4H-pyrido[1,2-a]pyrimidin-4-one moiety in those tetracyclic structures. Moreover, the 13-CH$_2$ singlet of compounds **XVI** (δ ca. 4.12, deuteriochloroform), the downfield H-1 multiplet of compounds **XVII** (δ 8.78, deuteriotrifluoroacetic acid, deshielding effect of 13-CO) and the downfield H-13 singlet of compound **XIX** (δ = 10.08, deuteriotrifluoroacetic acid, deshielding effect of 12-CO) are very significant as regards the quinoline part of these molecules; positions and shapes of these latter signals well agree with those of the corresponding protons in the quinoline moiety of the analogous 14H-naphtho[1',2':5,6]pyrano[2,3-b]quinoline derivatives (e.g. compound **V**) we previously described [4].

Chemical evidences of the structures attributed to compounds **IXc, XI** and **X** are reported in Chart III.

In fact the reaction of 2-chloro-4H-pyrido[1,2-a]pyrimidin-4-one **XX** [7] with aniline (160°, ethylene glycol) unequivocally [2] afforded 2-(phenylamino)-4H-pyrido[1,2-a]pyrimidin-4-one which was identical (mp, ir) with compound **IXc** (in a like way, starting from N-methylaniline, compound **IXa** was obtained in 68% yield).

On the other hand, 2-(phenylamino) derivative **IXc** was also obtained by heating at high temperature (230°, Dowtherm A) the open chain ester **XI**, confirming the structure of this latter compound.

Finally the acid-catalyzed hydrolysis of 2-chloro-4-iminoderivative **X** significantly yielded a mixture of compounds **XX** and **VIIIc**.

The structure of **VIIIc** in the solid state is most likely zwitterionic (see Chart III), in accordance with the properties of the compound (high melting point, low solubility in nonpolar solvents, ir spectrum pattern) and with previous statements [8-10] about the structure of 2-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one. Actually the ir spectrum (potassium bromide pellet) of compound **VIIIc** shows a broad band at 2750 cm^{-1} (ν NH$^+$) [8] and no OH stretching band (no band in the region above 3200 cm^{-1}).

No derivative of the pyrido[1',2':1,2]pyrimido[4,5-b]quinoline heterocyclic system is reported in the literature. Only two 7H-pyrido[1',2':1,2]pyrimido[5,4-c]quinoline derivatives are described [11].
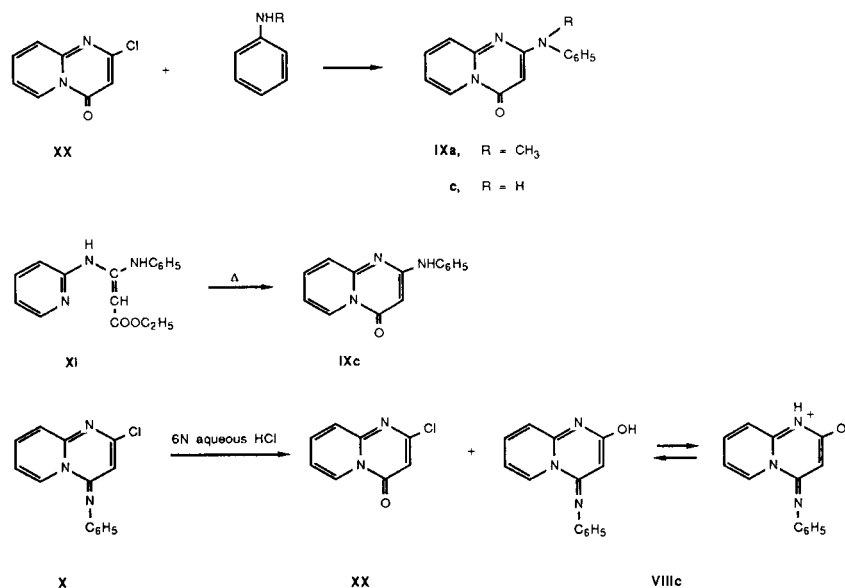
On the basis of these and previously [4,5] described results, we are now studying the reaction of **XII** with various N-phenylsubstituted ß-enaminocarbonylic compounds and with other suitable (phenylamino)substituted nucleophilic substrates, as an easy route to quinoline or 2,3-fused quinoline derivatives.

EXPERIMENTAL

4-[(N-Methyl,N-phenyl)amino]-2H-pyrido[1,2-a]pyrimidin-2-one (**VIIIa**) and 2-[(N-methyl,N-phenyl)amino]-4H-pyrido[1,2-a]pyrimidin-4-one (**IXa**).

Chart III

XX

IXa,   R = CH$_3$

c,   R = H

XI

IXc

X

6N aqueous HCl

XX

VIIIc

Phosphorus oxychloride (11.50 g, 75.0 mmoles) was added dropwise with stirring to 12.17 g (55.0 mmoles) of (N-methyl,N-phenyl)ethoxycarbonylacetamide (**VIa**) [4] which was contained in a flask cooled in an ice bath and protected from moisture with a calcium chloride tube. The resulting solution was then removed from the ice bath and stirred at room temperature for 30 minutes. A solution of 4.71 g (50.0 mmoles) of 2-aminopyridine in 30 ml of 1,2-dichloroethane was finally added and the reaction mixture was refluxed for 5 hours. After cooling, a solution of 68 g of trihydrate sodium acetate in 150 ml of water was added and the mixture was refluxed for 90 minutes while stirring. The mixture was then cooled, made alkaline by the addition of concentrated aqueous ammonia and shaken in a separatory funnel; afterwards the organic layer was recovered and the aqueous phase exhaustively extracted with chloroform. The combined organic layers were evaporated under reduced pressure to give a dark oil which was partitioned between 400 ml of water and 200 ml of ethyl ether, by shaking at room temperature for 30 minutes. After the phases were separated, the aqueous one was twice more extracted with the same solvent.

Compounds **VIIIa** and **IXa** were then obtained from the aqueous solution and from the combined ethyl ether portions, respectively, by the below described procedures.

Compound VIIIa.

The aqueous solution was saturated with sodium chloride and exhaustively extracted with chloroform. The combined extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure. The oily residue was then dissolved in a little absolute ethanol and treated with a saturated solution of hydrogen chloride in anhydrous ethyl ether. The yellow hydrochloride of **VIIIa** which precipitated was collected by filtration and dissolved in a little water. The aqueous solution was made alkaline with sodium carbonate, then exhaustively extracted with chloroform. The combined chloroform extracts were dried (anhydrous sodium sulfate), then evaporated under reduced pressure to afford a yellowish oil. By adding some ethyl acetate to this residue, 3.13 g (25%) of pure compound **VIIIa** separated out, pale yellow crystalline solid that melted at 162-163° after recrystallization from ethyl acetate; ir (chloroform): 1642 (CO), 1607 (broad), 1550, 1492 cm⁻¹; ¹H-nmr (deuteriochloroform): δ 3.44 (s, 3H, CH₃), 6.41 (s, 1H, H-3), 6.60-7.80 (m, 8H, H-7,8,9 + phenyl H's), 8.05 (mc, 1H, H-6).

Anal. Calcd. for C₁₅H₁₃N₃O: C, 71.69; H, 5.21; N, 16.72. Found: C, 71.78; H, 5.24; N, 16.89.

Compound IXa.

The ethyl ether solution was dried over anhydrous sodium sulfate, then the solvent removed to yield a dark oily residue which was purified by column chromatography (silica gel; 7:3 benzene/ethyl acetate) to give a thick oil. By adding a little ethyl ether to this oil and allowing the mixture to stand at room temperature, the crystallization of 2.53 g (20%) of pure **IXa** was obtained; white crystals melting at 121-122°, after recrystallization from ligroin; ir (chloroform): 1672 (CO), 1634, 1557, 1536, 1494 cm⁻¹; ¹H-nmr (deuteriochloroform): δ 3.55 (s, 3H, CH₃), 5.42 (s, 1H, H-3), 6.89 (mc, 1H, H-7), 7.12-7.70 (m, 7H, H-8,9 + phenyl H's), 8.93 (mc, 1H, H-6) (in deuteriotrifluoroacetic acid the H-6 signal is at δ = 9.41).

Anal. Calcd. for C₁₅H₁₃N₃O: C, 71.69; H, 5.21; N, 16.72. Found: C, 71.86; H, 5.29; N, 16.88.

4-[(N-Ethyl,N-phenyl)amino]-2H-pyrido[1,2-a]pyrimidin-2-one (VIIIb) and 2-[(N-ethyl,N-phenyl)amino]-4H-pyrido[1,2-a]pyrimidin-4-one (IXb).

Starting from 12.94 g (55.0 mmoles) of (N-ethyl,N-phenyl)ethoxycarbonylacetamide (**VIb**) [4], 11.50 g (75.0 mmoles) of phosphorus oxychloride and 4.71 g (50.0 mmoles) of 2-aminopyridine, and following the same procedure above described for the preparation of compounds **VIIIa** and **IXa**, 4.70 g (35%) of whitish crystalline **VIIIb** and 1.38 g (10.4%) of white crystalline **IXb** were obtained.

Compound VIIIb.

This compound had mp 140-141° after recrystallization from ethyl acetate; ir (chloroform): 1643 (CO), 1608 (broad), 1550, 1493 cm⁻¹;

¹H-nmr (deuteriochloroform): δ 1.35 (t, 3H, CH₃), 3.86 (q, 2H, CH₂), 6.50 (s, 1H, H-3), 6.60-7.82 (m, 8H, H-7,8,9 + phenyl H's), 8.04 (mc, 1H, H-6).

Anal. Calcd. for C₁₆H₁₅N₃O: C, 72.43; H, 5.70; N, 15.84. Found: C, 72.63; H, 5.85; N, 16.00.

Compound IXb.

This compound had mp 137-138°, after recrystallization from ligroin; ir (chloroform): 1670 (CO), 1633, 1557, 1536, 1495 cm⁻¹; ¹H-nmr (deuteriochloroform): δ 1.22 (t, 3H, CH₃), 4.08 (q, 2H, CH₂), 5.27 (s, 1H, H-3), 6.87 (mc, 1H, H-7), 7.10-7.69 (m, 7H, H-8,9 + phenyl H's), 8.91 (mc, 1H, H-6).

Anal. Calcd. for C₁₆H₁₅N₃O: C, 72.43; H, 5.70; N, 15.84. Found: C, 72.61; H, 5.87; N, 15.86.

2-(Phenylamino)-4H-pyrido[1,2-a]pyrimidin-4-one (IXc), 2-Chloro-N-phenyl-4H-pyrido[1,2-a]pyrimidin-4-imine (X) and Ethyl 3-(Phenylamino)-3-[(2-pyridyl)amino]propenoate (XI).

Phosphorus oxychloride (11.50 g, 75.0 mmoles) was added dropwise with stirring to an ice bath cooled solution of solid N-phenylethoxycarbonylacetamide (**VIc**) [5] (11.40 g, 55.0 mmoles) in 10 ml of 1,2-dichloroethane and the mixture was stirred at room temperature for 90 minutes. Following the same procedure above depicted for the preparation of compounds **VIIIa** and **IXa**, the reaction of this mixture with 2-aminopyridine (4.71 g, 50.0 mmoles) was then performed, treatment of the final reaction mixture with aqueous solution of trihydrate sodium acetate (68 g) and later with concentrated aqueous ammonia was carried out, the dichloroethane layer was recovered and the alkaline aqueous phase was exhaustively extracted with chloroform. The combined organic layers were dried (anhydrous sodium sulfate), the solvents removed and the thick oil residue was subjected to column chromatography (silica gel; 2:1:1 chloroform/ethyl ether/petroleum ether).

Compound XI.

A dark oil was the first eluted material from which whitish needles of pure compound **XI** (0.97 g, 6.8%) were obtained by adding a little ethyl ether and standing, mp 115-116°, after recrystallization from petroleum ether; ir (chloroform): 3340-2840 (NH), 1644 (CO), 1574 cm⁻¹; ¹H-nmr (deuteriochloroform): δ 1.22 (t, 3H, CH₃), 4.12 (q, 2H, CH₂), 4.44 (s, 1H, 2-CH), 6.68-7.06 (m, 2H, pyridyl H-3,5), 7.14-7.80 (m, 6H, pyridyl H-4 + phenyl H's), 8.14 (mc, 1H, pyridyl H-6), 11.66 and 11.77 (broad singlets, 2H, NH, partially disappeared with deuterium oxide).

Anal. Calcd. for C₁₆H₁₇N₃O₂: C, 67.82; H, 6.05; N, 14.83. Found: C, 68.04; H, 5.95; N, 14.97.

Compound X.

Going on with the elution, a yellowish solid material was then recovered which was purified by further column chromatography (neutral aluminum oxide; toluene) to give 1.22 g (9.5%) of pure compound **X**, deep yellow solid that melted at 161-162°, after crystallization from methanol; ir (chloroform): 1651, 1634, 1596 cm⁻¹; ¹H-nmr (deuteriochloroform): δ 6.23 (s, 1H, H-3), 6.75-7.90 (m, 8H, H-7,8,9 + phenyl H's), 9.31 (mc, 1H, H-6).

Anal. Calcd. for C₁₄H₁₀ClN₃: C, 65.76; H, 3.94; Cl, 13.87; N, 16.43. Found: C, 65.95; H, 3.94; Cl, 14.01; N, 16.34.

Compound IXc.

Finally, compound **IXc** was removed from the silica gel column by elution with 1:1 chloroform/ethyl acetate, then the eluate was evaporated. By adding a little ethyl acetate to the residue, whitish crystalline **IXc** (1.98 g, 17%) was obtained, mp 192-193°, after recrystallization from ethyl acetate with charcoal; ir (chloroform): 3400 (NH), 1672 (CO), 1634, 1600, 1570, 1536, 1512 cm⁻¹; ¹H-nmr (hexadeuteriodimethylsulfoxide): δ 5.75 (s, 1H, H-3), 6.91-8.08 (m, 8H, H-7,8,9 + phenyl H's), 8.92 (mc, 1H, H-6), 9.42 (s, 1H, NH, disappeared with deuterium oxide).

Anal. Calcd. for C₁₄H₁₁N₃O: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.91; H, 4.80; N, 17.81.

2-(Dialkylamino)-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carbaldehydes XIVa-c.

Phosphorus oxychloride (0.92 g, 6.0 mmoles) was added dropwise to a stirred 2 ml quantity of N,N'-dimethylformamide which was contained in a flask cooled with an ice bath and protected from moisture with a calcium chloride tube. The resulting solution was stirred at room temperature for 30 minutes, then a suspension of proper compound **III** [2] (4.0 mmoles) in 8 ml of N,N-dimethylformamide was added and the stirred mixture was heated at 95° for 90 minutes. After cooling, the mixture was poured onto crushed ice and the resulting solution was made alkaline by the addition of sodium carbonate, stirred at room temperature for 30 minutes, then exhaustively extracted with chloroform. The combined extracts were dried (anhydrous sodium sulfate) and solvents removed *in vacuo* to give a solid or oily residue from which compound **XIV** was obtained according to the following procedures.

1) 2-(Dimethylamino)-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carbaldehyde (XIVa).

When compound **IIIa** (0.76 g) was used in the reaction, the yellowish solid residue finally obtained was treated with a little ethyl ether and the resulting suspension was filtered, recovering 0.80 g (92%) of compound **XIVa**, pale yellow crystals melting at 163-164°, after crystallization from ethyl acetate with charcoal; ir (chloroform): 1688 (CO), 1645 (CO), 1640 (shoulder), 1553, 1533 (shoulder) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 3.19 (s, 6H, CH$_3$), 6.88 (mc, 1H, H-7), 7.20 (mc, 1H, H-9), 7.68 (mc, 1H, H-8), 8.79 (mc, 1H, H-6), 10.17 (s, 1H, CHO).

Anal. Calcd. for C$_{11}$H$_{11}$N$_3$O$_2$: C, 60.82; H, 5.10; N, 19.35. Found: C, 60.94; H, 5.08; N, 19.54.

2) 2-(Diethylamino)-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carbaldehyde (XIVb).

Starting from compound **IIIb** (0.87 g) a thick yellowish oil was finally obtained which was purified by column chromatography (silica gel; 1:1 chloroform/ethyl acetate). The eluate was evaporated and petroleum ether was added to the oil residue. After standing, whitish crystalline compound **XIVb** (0.85 g, 87%) separated out, mp 78-79° after recrystallization from the same solvent (lit [12], no melting point is reported); ir (chloroform): 1683 (CO), 1644 (CO), 1640 (shoulder), 1553, 1535 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.27 (t, 6H, CH$_3$), 3.69 (q, 4H, CH$_2$), 6.87 (mc, 1H, H-7), 7.20 (mc, 1H, H-9), 7.67 (mc, 1H, H-8), 8.80 (mc, 1H, H-6), 10.08 (s, 1H, CHO).

Anal. Calcd. for C$_{13}$H$_{15}$N$_3$O$_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.86; H, 6.26; N, 17.32.

3) 2-(1-Pyrrolidinyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carbaldehyde (XIVc).

Starting from compound **IIIc** (0.86 g) and proceeding as above described, a yellowish solid residue was finally obtained which was treated with some ethyl ether. By filtering the resulting suspension, compound **XIVc** (0.81 g, 83%) was recovered; pale yellow needles melting at 144-145°, after crystallization from ethyl acetate with charcoal; ir (chloroform): 1686 (CO), 1643 (CO), 1638 (shoulder), 1553, 1531 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.94 (mc, 4H, ß-CH$_2$), 3.60 (mc, 4H, α-CH$_2$), 6.85 (mc, 1H, H-7), 7.19 (mc, 1H, H-9), 7.66 (mc, 1H, H-8), 8.78 (mc, 1H, H-6), 10.30 (s, 1H, CHO).

Anal. Calcd. for C$_{13}$H$_{13}$N$_3$O$_2$: C, 64.18; H, 5.39; N, 17.28. Found: C, 64.26; H, 5.40; N, 17.29.

5,13-Dihydro-5-methyl-12H-pyrido[1',2':1,2]pyrimido[4,5-b]quinolin-12-one (XVIa) and 5-Methyl-12H-pyrido[1',2':1,2]pyrimido[4,5-b]quinoline-12,13(5H)-dione (XVIIa).

Following the procedure above described for the preparation of compounds **XIVa-c**, a suspension of 1.01 g (4.0 mmoles) of compound **IXa** in 8 ml of N,N-dimethylformamide was added to a mixture of 0.92 g (6.0 mmoles) of phosphorus oxychloride and 2 ml of N,N-dimethylformamide, heating then for 90 minutes at 95°, while stirring. After cooling and

pouring onto crushed ice, the resulting solution was treated with excess saturated aqueous solution of sodium acetate and stirred for 2 hours at room temperature. The suspension of amorphous solid ultimately obtained was extracted with chloroform. The combined extracts were washed with water, dried over anhydrous sodium sulfate and evaporated *in vacuo* to give a solid which was a mixture of compounds **XVIa** and **XVIIa**. The separation of these compounds was performed by the below described procedure.

Compound XVIIa.

The crude solid was crystallized from chloroform with charcoal to give 0.45 g (41%) of pure **XVIIa**, whitish needles which decomposed starting from 340°, after recrystallization from the same solvent; ir (potassium bromide): 1712 (CO), 1638 (CO), 1613, 1600, 1533, 1490 cm^{-1}; ^{1}H-nmr (deuteriotrifluoroacetic acid): δ 4.55 (s, 3H, CH$_3$), 7.35-8.48 (m, 6H, H-2,3,4,7,8,9), 8.78 (mc, 1H, H-1), 9.14 (mc, 1H, H-10); ms: m/e 277 (M$^+$).

Anal. Calcd. for C$_{16}$H$_{11}$N$_3$O$_2$: C, 69.30; H, 4.00; N, 15.16. Found: C, 69.50; H, 3.99; N, 15.08.

Compound XVIa.

Column chromatography of the chloroform filtrate (silica gel; 1:1 chloroform/ethyl acetate) afforded 0.39 g (37%) of compound **XVIa**, pale yellow solid that melted at 214-216°, after crystallization from ethanol; ir (potassium bromide): 1664 (CO), 1632, 1602, 1568, 1538, 1507 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 3.53 (s, 3H, CH$_3$), 4.10 (s, 2H, CH$_2$), 6.70-7.62 (m, 7H, H-1,2,3,4,7,8,9), 8.92 (mc, 1H, H-10); ms: m/e 263 (M$^+$).

Anal. Calcd. for C$_{16}$H$_{13}$N$_3$O: C, 72.98; H, 4.98; N, 15.96. Found: C, 72.87; H, 4.97; N, 15.74.

5-Ethyl-5,13-dihydro-12H-pyrido[1',2':1,2]pyrimido[4,5-b]quinolin-12-one (XVIb) and 5-Ethyl-12H-pyrido[1',2':1,2]pyrimido[4,5-b]quinoline-12,13(5H)-dione (XVIIb).

The same procedure above described for the preparation of compounds **XVIa** and **XVIIa** was followed, but using in the reaction the ethyl derivative **IXb** (1.06 g, 4.0 mmoles). The brownish solid ultimately obtained from the combined chloroform extracts was a mixture of compounds **XVIb** and **XVIIb** which were separated according to the following method.

Compound XVIb.

The crude solid was dissolved in a little chloroform and subjected to column chromatography (silica gel). By eluting with a mixture chloroform/ethyl acetate 1:1 compound **XVIb** was recovered (0.25 g, 23%), pale yellow needles melting at 211-213°, after crystallization from acetone; ir (potassium bromide): 1664 (CO), 1631, 1603, 1566, 1536, 1506 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.31 (t, 3H, CH$_3$), 4.13 (s, 2H, 13-CH$_2$), 4.26 (q, 2H, ethyl CH$_2$), 6.74-7.65 (m, 7H, H-1,2,3,4,7,8,9), 8.93 (mc, 1H, H-10); ms: m/e 277 (M$^+$).

Anal. Calcd. for C$_{17}$H$_{15}$N$_3$O: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.71; H, 5.43; N, 15.07.

Compound XVIIb.

By further elution of the column with a mixture chloroform/methanol 1:1 compound **XVIIb** (0.26 g, 22%) was then obtained; whitish crystals melting at 289-290° after crystallization from 2-propanol with charcoal; ir (potassium bromide): 1717 (CO), 1639 (CO), 1616, 1600, 1536, 1493 cm^{-1}; ^{1}H-nmr (deuteriotrifluoroacetic acid): δ 1.68 (t, 3H, CH$_3$), 5.26 (q, 2H, CH$_2$), 7.35-8.63 (m, 6H, H-2,3,4,7,8,9), 8.78 (mc, 1H, H-1), 9.14 (mc, 1H, H-10); ms: m/e 291 (M$^+$).

Anal. Calcd. for C$_{17}$H$_{13}$N$_3$O$_2$: C, 70.09; H, 4.50; N, 14.43. Found: C, 70.10; H, 4.50; N, 14.62.

2-(Phenylamino)-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carbaldehyde (XVIII) and 12H-Pyrido[1',2':1,2]pyrimido[4,5-b]quinolin-12-one (XIX).

A) Phosphorus oxychloride (0.92 g, 6.0 mmoles) was added dropwise with stirring to 2 ml of N,N-dimethylformamide which was contained in a flask cooled with an ice bath and protected from atmospheric moisture

with a calcium chloride tube. The solution obtained was stirred for 30 minutes at room temperature; a suspension of 0.95 g (4.0 mmoles) of **IXc** in 8 ml of N,N-dimethylformamide was then added and the mixture was heated with stirring for 90 minutes at 95°, then cooled and poured onto crushed ice. Sodium carbonate was then added to the solution until it was definitely alkaline and the mixture was further kept at room temperature for 30 minutes, while stirring. The orange yellow solid that separated was collected by filtration, washed with water, dried and crystallized from methyl ethyl ketone to give 0.54 g of compound **XIX**, orange needles melting at 272-273° dec, after recrystallization from the same solvent; ir (potassium bromide): 1690 (CO), 1640, 1618, 1587, 1535 (broad) cm^{-1}; ^{1}H-nmr (deuteriotrifluoroacetic acid): δ 7.56-8.79 (m, 7H, H-1,2,3,4,7,8,9), 9.37 (mc, 1H, H-10), 10.08 (s, 1H, H-13); ms: m/e 247 (M$^+$).

Anal. Calcd. for C$_{15}$H$_9$N$_3$O: C, 72.86; H, 3.67; N, 17.00. Found: C, 72.66; H, 3.72; N, 16.90.

The methyl ethyl ketone mother liquor was evaporated to dryness under reduced pressure, then the solid residue was dissolved in a little chloroform and subjected to column chromatography (neutral aluminum oxide). By eluting with 1:1 ethyl acetate/toluene and then removing the solvents from the eluate, compound **XVIII** (0.12 g, 11%) was obtained, yellow crystalline solid that melted at 199-200°, after recrystallization from ethyl acetate; ir (chloroform): 3115 (broad, NH), 1694 (4-CO), 1627 (broad, formyl CO), 1606, 1580, 1552, 1516, 1490 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 6.80-7.97 (m, 8H, H-7,8,9 + phenyl H's), 8.91 (mc, 1H, H-6), 10.27 (s, 1H, CHO), 11.64 (broad singlet, 1H, NH, partially disappeared with deuterium oxide).

Anal. Calcd. for C$_{15}$H$_{11}$N$_3$O$_2$: C, 67.91; H, 4.18; N, 15.84. Found: C, 68.13; H, 4.24; N, 15.78.

Further elution of the column with 1:1 chloroform/methanol afforded an additional crop (0.02 g) of compound **XIX** (total yield 57%).

B) The same procedure as in Method A was followed but the reaction was carried out at 45°. After cooling, the reaction mixture was poured onto crushed ice, the resulting solution was made alkaline by the addition of sodium carbonate, the mixture was stirred for 30 minutes at room temperature, then filtered. The yellow amorphous solid collected by filtration was washed with water, dried, then dissolved in a little chloroform and submitted to column chromatography (neutral aluminum oxide). Elution of the column with 1:1 ethyl acetate/toluene afforded 0.82 g (77%) of compound **XVIII**; further elution with 1:1 chloroform/methanol yielded 0.08 g (8.1%) of compound **XIX**.

Preparation of Compound IXc from 2-Chloro-4H-pyrido[1,2-a]pyrimidin-4-one (XX).

The mixture of 0.90 g (5.0 mmoles) of compound **XX** [7], 4.66 g (50.0 mmoles) of aniline and 10 ml of ethylene glycol was heated at 160° for 4 hours. The resulting solution was then cooled and poured onto crushed ice and water (200 ml), so that a dark thick oil precipitated. Ethyl ether (50 ml) was added and the mixture was vigorously stirred at room temperature for 30 minutes; the whitish crystalline solid that separated was then collected by filtration, washed with water and a little ethyl ether, and dried.

It was identical with compound **IXc** (mp, ir) and weighed 0.94 g (79%).

Compound IXc from XI.

A mixture of 0.57 g of compound **XI** and 5 ml of Dowtherm A was heated at 230° for 30 minutes. After cooling, the brownish solution obtained was submitted to column chromatography (neutral aluminum oxide). The column was first eluted with ethyl acetate until Dowtherm A was completely removed, then with 1:1 chloroform/methanol. After removing the solvents from this eluate, a little ethyl ether was added to the residue, obtaining the crystallization of compound **IXc** (0.38 g, 80%), which was identified by melting point and ir spectrum.

Hydrolysis of Compound X.

The suspension of 1.0 g of compound **X** in 40 ml of 6 N aqueous hydrochloric acid was heated at reflux for 30 minutes, while stirring. After cooling, the resulting solution was poured onto crushed ice, then made mildly alkaline by the careful addition of sodium bicarbonate. The suspension obtained was exhaustively extracted with chloroform, the combined extracts were dried over anhydrous sodium sulfate, then the solvent was evaporated in vacuo to give a yellowish solid residue which was treated with a little ethyl acetate and allowed to stand. By filtering the resulting suspension, 0.22 g (24%) of 4-(phenylimino)-4H-pyrido[1,2-a]pyrimidin-2-ol (**VIIIc**) was recovered, white crystals melting at 228-230° dec, after crystallization from methanol; ir (potassium bromide): 2750 (broad, ṄH), 1633, 1600, 1555 (broad), 1500, 1482 cm^{-1}; ^{1}H-nmr (deuteriotrifluoroacetic acid): δ 6.22 (s, 1H, H-3), 7.20-8.18 (m, 7H, H-7,9 + phenyl H's), 8.61 (mc, 1H, H-8), 9.19 (mc, 1H, H-6); ms: m/e 237 (M$^+$).

Anal. Calcd. for C$_{14}$H$_{11}$N$_3$O: C, 70.87; H, 4.67; N, 17.71. Found: C, 71.04; H, 4.86; N, 17.77.

The ethyl acetate filtrate was then evaporated to dryness and the yellow solid residue was dissolved in toluene and chromatographed on a neutral aluminum oxide column. Elution with the same solvent afforded 0.15 g of the starting compound **X**. Further elution with ethyl acetate yielded 0.07 g (9.9%) of 2-chloro-4H-pyrido[1,2-a]pyrimidin-4-one (**XX**), identified by comparison (mp, ir), with an authentic sample [7].

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