NOVEL SYNTHESES OF TRICYCLIC, N-ARYL, PYRIDINE- AND PYRAZINE-FUSED PYRIMIDONES

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Dedicated to Dr Miroslav Protiva.

2-Methylthio-2-imidazoline and 2-methylthio-1,4,5,6-tetrahydro-2-pyrimidine amidated 2-chloro-3-pyridine- and 2-chloro-3-pyrazinecarbonyl chlorides. The products reacted with aromatic amines forming a series of tricyclic, linearly fused N-aryl pyrimidones. Included among these pyrimidones were 10-aryl-2,3-dihydroimidazo[1,2-*a*]pyrido[2,3-*d*]pyrimidin-5(10*H*)-ones, 11-aryl-2,3,4,11-tetrahydropyrido[2,3-*d*]pyrimido[1,2-*a*]pyrimidin-6(6*H*)-ones, 10-aryl-2,3-dihydroimidazo[1,2-*a*]pyrazino[2,3-*d*]pyrimidin-5(10*H*)-ones, and 11-aryl-2,3,4,11-tetrahydropyrimido[1,2-*a*]pyrazino[2,3-*d*]pyrimidin-6(6*H*)-ones. 4,5,6,7-Tetrahydro-2-(methylthio)-1*H*-1,3-diazepine amidated the ethyl hydrogen carbonate of 2-(phenylamino)-3-pyridinecarboxylic acid, forming 12-phenyl-2,3,4,5-tetrahydropyrido[2',3':4,5]pyrimido[1,2-*a*][1,3]diazepine-7(12*H*)-one. A single-crystal X-ray analysis and an unambiguous synthesis established the structure of the linearly fused isomer 10-phenyl-2,3-dihydroimidazo[1,2-*a*]pyrido[2,3-*d*]pyrimidin-5(10*H*)-one.

Tricyclic, linearly fused 4-pyridones like *A* (ref.[1a]) and *B* (ref.[1b]) have anti-allergy activities expressed both in vivo and in vitro. In addition, pyridones *A* and *B* have neutrophil-dependent antiinflammatory activities[1]. Consequently, we modified the common central rings of *A* and *B* to learn whether or not these rings determined any of the observed pharmacological properties. We sought to make compounds *IV*, thinking that the structural changes they represent might augment or abolish the activities.

Here we report a novel, credible synthesis[2] of the linearly fused pyrimidones *IV* (Scheme 1). Also, we record for the first time certain crystallographic, spectral, and physical properties of pyrimidone *IVa*. A single-crystal X-ray analysis unequivocally established the nature of our sample of *IVa*, as did an unambiguous synthesis (Scheme 2).

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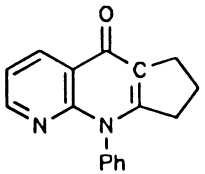
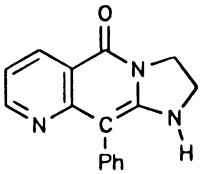
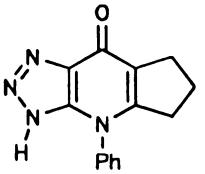
Procedures disclosed in Experimental and elsewhere[2] allow one to make authentic samples of pyridone *IVa*, m.p. 309 – 311 °C. Patents attribute antihypertensive activity to *IVa* and purportedly teach how to make it[3].



A



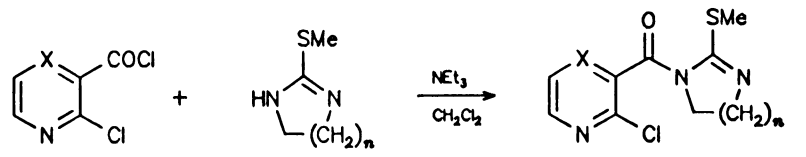
B



C

We judged that any attempt to confirm the reported[3] antihypertensive activity of pyrimidone *IVa*, would fail. Compound *IVa* was administered intravenously, a method that usually requires a water soluble substance. In our hands, however, *IVa* was only slightly soluble in water (< 0.1 mg/ml).

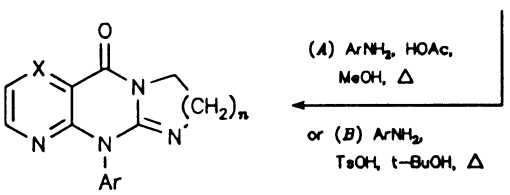
Compounds *IV* did possess anti-allergy and neutrophil-dependent antiinflammatory activities like those of pyridone *A* (ref.[1c]). The central 4-pyridone and -pyrimidone rings of *A* and *IV* were thus unimportant in determining the observed activities, as were the cyclopentene and dihydroimidazole rings. Elsewhere[1c] we argued that the common pyridine rings play a crucial but unknown role in determining the antiinflammatory



Ia, X = CH
Ib, X = N

IIa, n = 1
IIb, n = 2

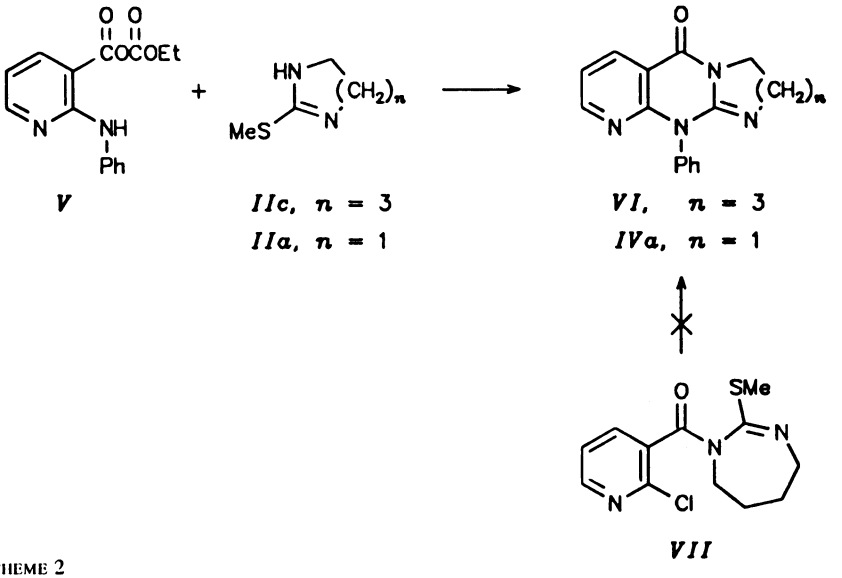
IIIa, X = CH; n = 1
IIIb, X = CH; n = 1
IIIc, X = N; n = 1
IIId, X = N; n = 2



IVa – IVs

SCHEME 1

activities of compounds *A*, *B*, and *IV*. By contrast, triazole-fused pyridones like *C* lacked both the pyridine rings and the antiinflammatory activity[1c].



V *IIc*, *n* = 3 *VI*, *n* = 3
IIa, *n* = 1 *IVa*, *n* = 1
VII

SCHEME 2

EXPERIMENTAL

IR spectra were determined as dichloromethane solutions unless otherwise stated, and ν-values are in cm^{-1}. These spectra were recorded with Sargent–Welch 3-200, Nicolet Model MX-1 FT-IR, or Perkin–Elmer 727B instruments. UV spectra were recorded with ethanol solutions; λ-values are in nm, and parenthetical ε-values are logarithmic. UV spectra were determined with a Beckman Model 25 or a Cary Model 118 spectrophotometer. Unless otherwise noted, ^1H and ^{13}C NMR spectra were determined with deuteriochloroform solutions. NMR spectra are reported as δ-values in ppm downfield from tetramethylsilane, and ^1H NMR spectra were determined at 90 MHz unless otherwise specified; *J* values are in Hz. ^1H and ^{13}C NMR spectra were recorded on Varian instruments (FT-80A, EM-390, VXR-200, XL-200, -300, or -400, as appropriate). Electron-impact mass spectra are reported unless specified otherwise; parenthetical numbers immediately following *m/z* values are relative ion intensities (%). Medium-resolution mass spectra were determined with AEI MS-9 or Varian CH5 instruments; high-resolution spectra were recorded with a Varian double-focusing MAT-312 spectrometer operated at 70 eV.

Merck (Darmstadt) supplied F-254 silica gel plates for TLC; developed plates were visualized in UV light or in iodine vapor. Baker or Merck provided silica gel for column chromatography, which was done with 60 – 200 mesh (gravity flow) or 40-μm particles (nitrogen pressure).

Uncorrected melting points were recorded by means of a Thomas-HOOVER uni-melt apparatus with open capillaries or a Thomas hot-stage apparatus (Model 40). Organic solutions were routinely dried over sodium or magnesium sulfate.

2-Chloro-3-pyridinecarbonyl chloride (*Ia*) and 2-chloro-3-pyrazinylcarbonyl chloride (*Ib*), 2-methylthio-2-imidazoline hydroiodide *IIa*, and 3,4,5,6-tetrahydro-2-pyrimidinethiol, from which *IIb* was made according to a published procedure[4], were commercially available. The ethyl hydrogen carbonate anhydride (*V*) of 2-(phenyl)amino-3-pyridinecarboxylic acid was prepared from this acid[4].

X-Ray Crystallographic Analyses

Crystal data: Compound *IVa*, $C_{15}H_{12}N_4O$, M = 264.29, monoclinic, a = 7.110 (1) Å, b = 19.999 (4) Å, c = 11.145 (1) Å, β = 128.29 (1)°, V = 1243.8 Å^3, Z = 4, D_{calc} = 1.411 g cm^{-3}, μ (CuK_α radiation) = 7.2 cm^{-1}. Space group $P2_1/c(C^5_{2h})$ uniquely from the systematic absences: $0k0$ when $k \neq 2n$, $h0l$ when $l \neq 2n$. Sample dimensions: 0.10 × 0.16 × 0.40 mm.

Crystallographic measurements: Preliminary unit cell parameters and space group information were obtained from oscillation and Weissenberg photographs. Intensity data were recorded on an Enraf–Nonius CAD-4 diffractometer ($Cu\text{-}K_\alpha$ radiation, incident-beam graphite monochromator; ω – 2θ scans, $\theta_{max.}$ = 67°). From totals of 2 261 unique reflections, after averaging equivalent forms, those 1 621 with $I > 3.0\sigma(I)$ were retained for the structure analyses and corrected for the usual Lorentz and polarization effects. Refined unit-cell parameters in each case were derived by least-squares treatment of the diffractometer setting angles for 25 reflections (42° < θ < 66°) widely separated in reciprocal space.

Structure analyses: The crystal structure was solved with some difficulty by direct methods. Crystallographic calculations were performed on a PDP11/44 computer by use of the Enraf–Nonius SDP suite of programs. The direct methods program MULTAN 11/82 was employed. E-maps generated by use of phase angles which yielded several of the highest combined figures-of-merit revealed the correct molecular orientation but the models failed to refine owing to the fact that they were misplaced with respect to the crystallographic center of symmetry. These problems were circumvented by the following approach. The monoclinic data set ($hk \pm l$) was expanded to ($h \pm k \pm l$) and the space group was reassigned as $P1$. Structure factors were calculated for an E-map derived sixteen atom fragment, and a weighted F_0 Fourier synthesis yielded coordinates for the other three molecules in the unit cell. Subsequent readily recognized transformations then reduced these to satisfy the equivalent positions of space group $P2_1/c$ with each molecule occupying a general position. Hydrogen atoms were located in difference Fourier syntheses evaluated following several rounds of full-matrix least-squares adjustment of non-hydrogen atom positional and anisotropic temperature factor parameters. Continuation of the least-squares calculations, with hydrogen atoms included at their calculated positions, led to convergence at R = 0.049 (R_w = 0.071). Final atomic positional and thermal parameters are in Tables I – VI.

Neutral atom scattering factors used in the structure-factor calculations were taken from ref.[5]. In the least-squares iterations, $\Sigma w\Delta^2$ [$w = 1/\sigma^2(|F_o|)$, $\Delta = (|F_o| - |F_c|)$] was minimized.

4,5,6,7-Tetrahydro-2-(methylthio)-1*H*-1,3-diazepine hydriodide (*IIc*)

Methyl iodide (79.5 g, 0.553 mol) was added to a stirred suspension of the known[6] hexahydro-2*H*-1,3-diazepine-2-thione (m.p. 178 – 190 °C, prepared from 1,4-diaminobutane and carbon disulfide according to ref.[7] in 53% yield) (72.0 g, 0.553 mol) in ethanol (250 ml). The resulting solution was stirred 18 h at ambient temperature under nitrogen. The bulk of the ethanol was evaporated and the residue was treated with ether to precipitate crude *IIc*. The collected precipitate (136.6 g) was recrystallized from ethanol–carbon tetrachloride to give *IIc* (102.5 g, 68%), m.p. 122 – 124 °C, as a hygroscopic solid. IR spectrum: 3 100, 1 600, 1 540, 1 380, 1 220, 990. ^{1}H NMR spectrum (90 MHz, CD_3CN): 3.6 – 3.4 m, 4 H (2 CH_2); 2.7 s, 3 H (CH_3); 1.97 – 1.74 m, 4 H (2 CH_2). Mass spectrum: 144 (27, M^+ for ^{32}S), 142 (100, $[M - 2]^+$ for ^{32}S), 130 (73). For $C_6H_{13}IN_2S$ (272.1) calculated: 26.48% C, 4.81% H, 10.29% N, 46.63% I, 11.78% S; found: 26.70% C, 4.69% H, 10.37% N, 46.87% I, 12.07% S.

General Procedure for Preparation of Compounds *IIIa – IIId* and *VII*

A solution of the acid chloride (5.14 mmol) in dichloromethane (25 ml) was added dropwise to a stirred, cooled solution of the hydriodides of compounds *IIa – IIc* and *VII* (5.14 mmol) and diisopropylethylamine (120 mmol) in dichloromethane (75 ml) at 0 °C. When the addition was complete, the mixture was allowed

to stir overnight at ambient temperature. The organic solution was washed with water, 1 M sodium bicarbonate solution, water, 1 M sodium bisulfite solution, and water. The organic solution was dried, filtered, and concentrated. The residue was purified by crystallization.

4,5-Dihydro-1-[(2-chloro-3-pyridinyl)carbonyl]-2-methylthio-1*H*-imidazole (*IIIa*)

Crystallized from 2-propylacetate, this compound formed colorless prisms, m.p. 105 – 106.5 °C, in a yield of 65.2%. IR spectrum: 1 655, 1 575, 1 370, 1 200, 1 180. ^{1}H NMR spectrum: 8.53 dd, 1 H (H (6), J(6-4) = 3, J(6-5) = 6); 7.70 dd, 1 H (H (4), J(4-6) = 3, J(4-5) = 7.5); 7.27 dd, 1 H (H (5), J(5-6) = 6, J(5-4) = 7.5); 3.97 brs, 4 H (2 CH_2); 2.46 s, 3 H (CH_3). Mass spectrum: 257 (3, M^+ for ^{37}Cl), 256 (1), 255 (7, M^+ for ^{35}Cl), 220 (23, [M – $^{35}Cl^+$), 142 (45, $[C_6H_3{}^{37}ClNO]^+$), 140 (100, $[C_6H_3{}^{35}ClNO]^+$). For $C_{10}H_{10}ClN_3OS$ (255.7) calculated: 46.97% C, 3.94% H, 13.86% Cl, 16.43% N, 12.54% S; found: 46.89% C, 3.96% H, 13.61% Cl, 16.57% N, 13.35% S. No acceptable analysis for S was obtained.

1,4,5,6-Tetrahydro-1-[(2-chloro-3-pyridinyl)carbonyl]-2-methylthiopyrimidine (*IIIb*)

Crystallized from dichloromethane–ether, this compound formed colorless prisms, m.p. 133 – 134 °C, in a yield of 82%. IR spectrum: 1 670 – 1 650, 1 610, 1 590, 1 570, 1 400, 1 350, 1 180, 1 160, 1 030. ^{1}H NMR spectrum: 8.50 dd, 1 H (H (6), J(6-4) = 3, J(6-5) = 6); 7.75 dd , 1 H (H (4), J(4-6) = 3, J(4-5) = 7.5); 7.30 dd, 1 H (H (5), J(5-6) = 6, J(5-4) = 7.5); 4.85 – 3.57 m, 4 H (2 CH_2); 2.24 s, 3 H (CH_3); 2.14

TABLE I
Non-hydrogen atom fractional coordinates (. 10^4) for *IVa*, with estimated standard deviations in parentheses

Atom	*x*	*y*	*z*
N(1)	6550(3)	−95(1)	3803(2)
C(2)	7191(4)	618(1)	4025(2)
C(3)	5670(4)	947(1)	2408(2)
N(4)	4271(3)	367(1)	1427(2)
C(5)	2648(3)	378(1)	−117(2)
C(5a)	1497(3)	−269(1)	−792(2)
C(6)	−268(4)	−332(1)	−2363(2)
C(7)	−1249(4)	−939(1)	−2964(2)
C(8)	−443(4)	−1475(1)	−1998(2)
N(9)	1248(3)	−1444(1)	−464(2)
C(9a)	2176(3)	−842(1)	113(2)
N(10)	3897(3)	−796(1)	1691(2)
C(10a)	4962(3)	−189(1)	2373(2)
O(11)	2229(3)	892(1)	−849(2)
C(1′)	4694(3)	−1382(1)	2664(2)
C(2′)	3277(4)	−1630(1)	3011(2)
C(3′)	4089(5)	−2179(1)	3981(3)
C(4′)	6276(6)	−2462(1)	4575(3)
C(5′)	7675(5)	−2207(1)	4224(3)
C(6′)	6867(4)	−1659(1)	3241(2)

– 1.87 m, 2 H (CH_2). Mass spectrum: 271 (1, M^+ for ^{37}Cl), 269 (1, M^+ for ^{35}Cl), 241 (17, [M – 28$^+$), 234 (33, [M – $^{35}Cl^+$), 206 (89, [M – 63$^+$), 143 (100, $[C_5H_7N_2OS]^+$). For $C_{11}H_{12}ClN_3OS$ (269.8) calculated: 48.98% C, 4.48% H, 13.14% Cl, 15.58% N, 11.89% S; found: 49.24% C, 4.46% H, 13.02% Cl, 15.81% N, 12.18% S.

4,5-Dihydro-1-[(2-chloro-3-pyrazinyl)carbonyl]-2-methylthio-1*H*-imidazole (*IIIc*)

Crystallized from dichloromethane–carbon tetrachloride, this compound formed colorless prisms, m.p. 102 – 105 °C, in a yield of 81%. IR spectrum: 1 670, 1 600, 1 400, 1 340, 1 190, 1 090. ^1H NMR spectrum: 8.56 d, 1 H (H (6), J = 2); 8.54 d, 1 H (H (5), J = 2); 4.00 br s, 4 H (2 CH_2); 2.47 br s, 3 H (CH_3). Mass spectrum: 258 (3, M^+ for ^{37}Cl), 256 (8, M^+ for ^{35}Cl), 209 (35, [M – SMe]$^+$), 193 (81, [M – 63]$^+$), 141 (33, [M – 115]$^+$), 115 (100, $[C_4H_7N_2S]^+$). For $C_9H_9ClN_4OS$ (256.7) calculated: 42.11% C, 3.53% H, 13.81% Cl, 21.82% N, 12.49% S; found: 42.36% C, 3.65% H, 13.88% Cl, 21.72% N, 12.47% S.

1,4,5,6-Tetrahydro-1-[(2-chloro-3-pyrazinyl)-2-methylthio-pyrimidine (*IIId*)

Crystallized from chloroform–ether, this compound formed colorless crystals, m.p. 136 – 138 °C, in a yield of 71.5%. IR spectrum: 1 670, 1 600, 1 400, 1 340, 1 190, 1 040. ^1H NMR spectrum: 8.50 d, 1 H (H (6),

TABLE II
Anisotropic temperature factor parameters[a] (. 10^4) for *IVa*, with estimated standard deviations in parentheses

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N(1)	567(8)	426(10)	302(6)	11(8)	181(5)	3(7)
C(2)	628(10)	443(13)	400(8)	–26(9)	255(6)	–56(8)
C(3)	588(8)	350(11)	551(8)	–14(8)	366(5)	–13(8)
N(4)	459(6)	388(9)	333(6)	–1(7)	205(4)	22(6)
C(5)	484(7)	443(11)	425(6)	98(8)	303(4)	113(8)
C(5a)	362(6)	519(13)	281(6)	49(8)	190(4)	62(7)
C(6)	502(8)	595(13)	306(6)	53(9)	219(5)	68(8)
C(7)	541(9)	671(13)	306(7)	–23(10)	213(5)	13(9)
C(8)	549(9)	545(13)	334(7)	–96(9)	218(5)	–55(9)
N(9)	576(7)	470(10)	298(6)	–81(7)	216(4)	–13(7)
C(9a)	410(6)	462(11)	263(6)	–21(7)	197(4)	–1(7)
N(10)	464(6)	363(9)	235(5)	–17(6)	158(4)	29(6)
C(10a)	422(7)	357(10)	330(6)	23(7)	222(4)	17(7)
O(11)	779(7)	495(9)	489(6)	78(7)	354(4)	180(6)
C(1')	546(8)	328(10)	239(6)	6(8)	185(5)	–4(7)
C(2')	636(10)	481(13)	387(8)	–76(10)	252(6)	49(9)
C(3')	1001(13)	545(13)	477(9)	–256(11)	380(7)	11(10)
C(4')	1229(13)	328(11)	377(9)	38(13)	336(9)	41(9)
C(5')	937(13)	519(13)	392(9)	290(11)	283(8)	37(9)
C(6')	684(13)	507(13)	366(7)	137(9)	288(6)	20(8)

[a] In the form: $\exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{12}hka^*b^* + 2U_{13}hla^*c^* \ldots + 2U_{23}klb^*c^*)]$.

J = 2); 8.43 d, 1 H (H (5), J = 2); 3.84 t, 2 H ((CH_2), J = 6); 3.64 t, 2 H ((CH_2), J = 6); 2.19 s, 3 H (CH_3); 2.20 – 1.90 m, 2 H (CH_2). Mass spectrum: 271 (1, $[M + 1]^+$ for ^{35}Cl), 270 (0.2, M^+ for ^{35}Cl), 235 (5, $[M - {}^{35}Cl]^+$), 224 (67, $[M - SCH_2]^+$), 223 (46, $[M - SCH_3]^+$), 154 (100, $[C_5H_4{}^{35}ClN_3O]^+$), 143 (93, $[C_5H_7N_2OS]^+$), 113 (78, $[C_4H_2{}^{35}ClN_2]^+$). For $C_{10}H_{11}ClN_4OS$ (270.7) calculated: 44.36% C, 4.10% H, 13.10% Cl, 20.69% N, 11.84% S; found: 44.41% C, 4.12% H, 13.06% Cl, 20.70% N, 11.86% S.

The inter-related pyrimidones *IVa – IVs* were prepared according to either of two methods *A*) and *B*), as specified below. Yields appear in Table VI and microanalytical data in Table VII.

10-Phenyl-2,3-dihydroimidazol[1,2-*a*]pyrido[2,3-*d*]pyrimidin-5(10*H*)-one (*IVa*)

This compound was prepared by both methods, *A*) and *B*), and was also made from 2-(phenylamino)-3-pyridine carboxylic acid.

Method A): A solution of compound *IIIa* (2.55 g, 10 mmol) and aniline (0.93 g, 10 mmol) in a solution of acetic acid (1 ml) and methanol (25 ml) was refluxed 4.5 h. The reflux condenser was connected in series with two 500 ml sodium hypochlorite traps, through which effluent was passed. The reaction mixture began to deposit crystals after about 5 min heating. After 4.5 h, the methanol was evaporated, and the residue was partitioned between chloroform and 1M sodium bicarbonate solution. The organic solution was washed with water, dried, filtered, and concentrated. The residual yellow solid (2.48 g) was crystallized from methanol–chloroform to give white crystals (1.98 g, 75%), m.p. 307 – 310 °C.

Method B): A mixture of compound *IIIa* (10.23 g, 40 mmol), aniline (3.72 g, 40 mmol) and *p*-toluenesulfonic acid monohydrate (0.4 g, 2 mmol) in tert-butanol (180 ml) was refluxed 20 h under nitrogen. The solvent was evaporated, and the residue was partitioned between 1M aqueous sodium bicarbonate solution and chloroform. The organic layer was washed with water, dried, filtered, and concentrated. The solid residue was washed with carbon tetrachloride and with a little chloroform, and was dried to give pyridone *IVa* (9.5 g, 90%), m.p. 307 – 310 °C. IR spectrum (KBr pellet): 1 690 (CO), 1 650, 1 640, 1 600 (guanidine C=N), 1 580, 1 480, 1 450, 1 300, 780. UV spectrum: 245 (4.26), 338 (3.60). ^1H NMR spectrum (200

TABLE III
Hydrogen atom fractional coordinates[a] (. 10^3) and isotropic thermal parameters (. 10^3) for *IVa*

Atom	*x*	*y*	*z*	*U* (Å^2)
H(2a)	903	67	456	53
H(2b)	680	84	470	53
H(3a)	676	114	216	49
H(3b)	455	133	230	49
H(6)	−81	7	−304	49
H(7)	−253	−100	−409	54
H(8)	−116	−192	−246	51
H(2′)	170	−142	257	54
H(3′)	309	−237	425	73
H(4′)	685	−286	527	76
H(5′)	927	−241	467	70
H(6′)	786	−147	296	55

[a] Hydrogen atoms bear the same labels as the atoms to which they are bonded and were assigned the equivalent isotropic thermal parameters of these atoms.

MHz, CD_3SOCD_3): 8.35 dd (H (8), *J* (8-6) = 1.5, *J* (8-7) = 3); 8.26 dd (H (6), *J* (6-8) = 1.5, *J* (6-7) = 6); 7.55 – 7.35 m, 5 H (Ar); 7.17 dd (H (7), *J* (7-6) = 6, *J* (7-8) = 3); 4.04 t, 2 H ((CH_2), *J* = 7.5); 3.72 t, 2 H ((CH_2), *J* = 7.5). ^{13}C NMR spectrum (CD_3SOCD_3): 157 (C(5)), 153.1 (C(10a)), 152.8 (C(9a)), 150 (C(8)), 137 (C(1')), 136 (C(6)), 129.4 (C(3')*), 128.9 (C(2')*), 128 (C(4')), 116 (C(7)), 110 (C(5a)), 50 (C(2)^), 44 (C(3)^). Mass spectrum: 266 (2, $[M + 2]^+$), 265 (21, $[M + 1]^+$), 264 (100, M^+), 263 (94, $[M - 1]^+$), 196 (9, $[C_{12}H_8N_2O]^+$), 168 (53, $[C_{11}H_8N_2]^+$).

TABLE IV

Interatomic distances (Å) and angles (in °) for *IVa*, with estimated standard deviations in parentheses

Atoms	Distances	Atoms	Distances
N(1)–C(2)	1.471(3)	C(8)–N(9)	1.351(2)
N(1)–C(10a)	1.273(2)	N(9)–C(9a)	1.331(3)
C(2)–C(3)	1.560(3)	C(9a)–N(10)	1.390(2)
C(3)–N(4)	1.477(3)	N(10)–C(10a)	1.383(3)
N(4)–C(5)	1.354(2)	N(10)–C(1')	1.452(3)
N(4)–C(10a)	1.396(3)	C(1')–C(2')	1.376(4)
C(5)–C(5a)	1.465(3)	C(1')–C(6')	1.370(3)
C(5)–O(11)	1.229(3)	C(2')–C(3')	1.391(4)
C(5a)–C(6)	1.390(2)	C(3')–C(4')	1.379(5)
C(5a)–C(9a)	1.400(3)	C(4')–C(5')	1.373(6)
C(6)–C(7)	1.353(4)	C(5')–C(6')	1.397(3)
C(7)–C(8)	1.368(3)		
Atoms	**Angles**	**Atoms**	**Angles**
C(2)–N(1)–C(10a)	107.2(2)	C(5a)–C(9a)–N(10)	119.8(2)
N(1)–C(2)–C(3)	107.1(2)	N(9)–C(9a)–N(10)	117.1(2)
C(2)–C(3)–N(4)	101.0(2)	C(9a)–N(10)–C(10a)	120.4(2)
C(3)–N(4)–C(5)	125.5(2)	C(9a)–N(10)–C(1')	121.4(2)
C(3)–N(4)–C(10a)	107.8(1)	C(10a)–N(10)–C(1')	118.1(1)
C(5)–N(4)–C(10a)	126.7(2)	N(1)–C(10a)–N(4)	116.9(2)
N(4)–C(5)–C(5a)	113.8(2)	N(1)–C(10a)–N(10)	125.2(2)
N(4)–C(5)–O(11)	121.5(2)	N(4)–C(10a)–N(10)	117.9(1)
C(5a)–C(5)–O(11)	124.7(2)	N(10)–C(1')–C(2')	119.1(2)
C(5)–C(5a)–C(6)	120.5(2)	N(10)–C(1')–C(6')	118.8(2)
C(5)–C(5a)–C(9a)	121.3(1)	C(2')–C(1')–C(6')	122.1(2)
C(6)–C(5a)–C(9a)	118.2(2)	C(1')–C(2')–C(3')	118.7(3)
C(5a)–C(6)–C(7)	119.4(2)	C(2')–C(3')–C(4')	119.9(3)
C(6)–C(7)–C(8)	118.5(2)	C(3')–C(4')–C(5')	120.8(3)
C(7)–C(8)–N(9)	124.8(2)	C(4')–C(5')–C(6')	119.8(3)
C(8)–N(9)–C(9a)	116.0(2)	C(1')–C(6')–C(5')	118.8(3)
C(5a)–C(9a)–N(9)	123.1(1)		

Samples from methods *A*) and *B*) were identified by TLC, m.p., m.m.p., microanalytical values, and IR, ^{1}H NMR, and mass spectra.

From 2-(Phenylamino)-3-pyridine Carboxylic Acid via Anhydride *V*

A solution of ethyl chloroformate (2.7 g, 25 mmol) in dichloromethane (25 ml) was added to a cold (3 °C) solution of triethylamine (2.5 g, 25 mmol) and 2-phenylamino-3-pyridine carboxylic acid (5.35 g, 25 mmol) in dichloromethane (100 ml). The resulting mixture was kept under nitrogen at 3 °C for 2 h. Triethylamine (2.5 g, 25 mmol) followed by the hydroiodide (6.1 g, 25 mmol) of *IIa* was added. The reaction mixture was then stirred 2 h in an ice bath, and 20 h at room temperature. The solution was washed with 1M sodium bicarbonate solution, water, and with 1M sodium bisulfite solution. The organic solution was extracted with 1M hydrochloric acid solution, after which combined acidic extracts were

TABLE V
Torsion angles (in °) for *IVa*[a]

Atoms	Torsion angles	Atoms	Torsion angles
C(10a)–N(1)–C(2)–C(3)	−0.8	C(6)–C(7)–C(8)–N(9)	1.4
C(2)–N(1)–C(10a)–N(4)	0.3	C(7)–C(8)–N(9)–C(9a)	−0.6
C(2)–N(1)–C(10a)–N(10)	179.7	C(8)–N(9)–C(9a)–C(5a)	−0.9
N(1)–C(2)–C(3)–N(4)	0.9	C(8)–N(9)–C(9a)–N(10)	179.2
C(2)–C(3)–N(4)–C(5)	−179.5	C(5a)–C(9a)–N(10)–C(10a)	−0.7
C(2)–C(3)–N(4)–C(10a)	−0.7	C(5a)–C(9a)–N(10)–C(1′)	−178.3
C(3)–N(4)–C(5)–C(5a)	−179.0	N(9)–C(9a)–N(10)–C(10a)	179.3
C(3)–N(4)–C(5)–O(11)	1.2	N(9)–C(9a)–N(10)–C(1′)	1.6
C(10a)–N(4)–C(5)–C(5a)	2.4	C(9a)–N(10)–C(10a)–N(1)	180.0
C(10a)–N(4)–C(5)–O(11)	−177.4	C(9a)–N(10)–C(10a)–N(4)	−0.7
C(3)–N(4)–C(10a)–N(1)	0.3	C(1′)–N(10)–C10a)–N(1)	−2.2
C(3)–N(4)–C(10a)–N(10)	−179.1	C(1′)–N(10)–C(10a)–N(4)	177.1
C(5)–N(4)–C(10a)–N(1)	179.0	C(9a)–N(10)–C(1′)–C(2′)	−78.7
C(5)–N(4)–C(10a)–N(10)	−0.3	C(9a)–N(10)–C(1′)–C(6′)	103.0
N(4)–C(5)–C(5a)–C(6)	177.9	C(10a)–N(10)–C(1′)–C(2′)	103.5
N(4)–C(5)–C(5a)–C(9a)	−3.7	C(10a)–N(10)–C(1′)–C(6′)	−74.7
O(11)–C(5)–C(5a)–C(6)	−2.3	N(10)–C(1′)–C(2′)–C(3′)	−178.1
O(11)–C(5)–C(5a)–C(9a)	176.1	C(6′)–C(1′)–C(2′)–C(3′)	0.1
C(5)–C(5a)–C(6)–C(7)	177.9	N(10)–C(1′)–C(6′)–C(5′)	177.6
C(9a)–C(5a)–C(6)–C(7)	−0.6	C(2′)–C(1′)–C(6′)–C(5′)	−0.6
C(5)–C(5a)–C(9a)–N(9)	−177.0	C(1′)–C(2′)–C(3′)–C(4′)	0.1
C(5)–C(5a)–C(9a)–N(10)	3.0	C(2′)–C(3′)–C(4′)–C(5′)	0.2
C(6)–C(5a)–C(9a)–N(9)	1.5	C(3′)–C(4′)–C(5′)–C(6′)	−0.7
C(6)–C(5a)–C(9a)–N(10)	−178.6	C(4′)–C(5′)–C(6′)–C(1′)	0.9
C(5a)–C(6)–C(7)–C(8)	−0.7		

[a] The torsion angle A–B–C–D is defined as positive if, when viewed along the B–C bond, atom A must be rotated clockwise to eclipse atom D. [b] σ 0.2 – 0.5°. [c] σ 0.3 – 0.6°.

cooled and basified with 50% sodium hydroxide solution. The precipitated crystals were collected, washed with water, and dried to give *IVa* (2.64 g, 40%), m.p. 307 – 309 °C, recrystallization from acetone–dichloromethane raised the m.p. to 309 – 311 °C. This sample was identified with an authentic one (from method *A*) by TLC, microanalysis, ^{1}H NMR, IR, and mass spectra.

10-(3-Nitrophenyl)-2,3-dihydroimidazo[1,2-*a*]pyrido[2,3-*d*]pyrimidin-5(10*H*)-one (*IVb*)

Prepared by method *B*), m.p. 286 – 287 °C, crystallized from chloroform–ether. IR spectrum: 1 685 (CO), 1 650 (NO_2), 1 600, 1 480, 1 450, 1 410, 1 350. ^{1}H NMR spectrum: 8.50 – 8.33 m, 4 H (H (8), H (6), 2 H, Ar); 7.78 – 7.72 m, 2 H (Ar); 7.12 dd (H (7), *J*(7-8) = 5, *J*(7-6) = 8); 4.32 – 4.12 m, 2 H (CH_2); 4.00 – 3.80 m, 2 H (CH_2). Mass spectrum: 311 (2, $[M + 2]^+$), 310 (19, $[M + 1]^+$), 309 (100, M^+), 308 (49, $[M - 1]^+$), 262 (45, $[M - HNO_2]^+$), 213 (23, $[C_{11}H_{17}N_3O_2]^+$).

10-(3-Chlorophenyl)-2,3-dihydroimidazo[1,2-*a*]pyrido[2,3-*d*]pyrimidin-5(10*H*)-one (*IVc*)

Prepared by method *B*), m.p. 305 – 307 °C, crystallized from methanol. IR spectrum (KBr): 1 690, 1 630, 1 600, 1 580. ^{1}H NMR spectrum (200 MHz, CD_3SOCD_3): 8.37 dd (H (8), *J*(8-6) = 2, *J*(8-7) = 6); 8.26 dd

TABLE VI
Structures and yields of pyrimidones *IV*

No.	X	*n*	Ar	Yield, %[a]
IVa	CH	1	C_6H_5	75[b]
IVb	CH	1	C_6H_4-NO_2-3′	39[c]
IVc	CH	1	C_6H_4-Cl-3′	39[b]
IVd	CH	1	C_6H_3-Cl_2-3′,4′	50[b]
IVe	CH	1	C_6H_4-OMe-3′	78[b]
IVf	CH	1	C_5H_4N-3′	52[c]
IVg	CH	1	C_6H_4-OH-4′	84[c]
IVh	CH	2	C_6H_5	87[c]
IVi	CH	2	C_6H_4-NO_2-3′	53[c]
IVj	CH	2	C_6H_4-Cl-3′	64[c]
IVk	CH	2	C_6H_3-Cl_2-3′,4′	67[c]
IVl	CH	2	C_6H_4-OMe-3′	82[c]
IVm	N	1	C_6H_5	39[b]
IVn	N	1	C_6H_4-NO_2-3′	80[c]
IVo	N	1	C_6H_4-Cl-3′	42[b]
IVp	N	1	C_6H_3-Cl_2-3′,4′	58[b]
IVq	N	1	C_6H_4-OMe-3′	44[b]
IVr	N	2	C_6H_5	47[c]
IVs	N	2	C_6H_4-NO_2-3′	43[c]

[a] Except as noted, yields are unoptimized and referred to amides *III*. [b] Prepared by method *A*). [c] Prepared by method *B*).

(H (6), J(6-8) = 2, J(6-7) = 8); 7.57 – 7.50 m, 3 H (Ar); 7.45 – 7.35 m, 1 H (Ar); 7.20 dd (H (7), J(7-8) = 6, J(7-6) = 8); 4.14 – 3.94 m, 2 H (CH_2); 3.82 – 3.62 m, 2 H (CH_2). Mass spectrum: 300 (32, M^+ for ^{37}Cl), 299 (44, $[M - 1]^+$ for ^{37}Cl), 298 (100, M^+ for ^{35}Cl), 297 (96, $[M - 1]^+$ for ^{35}Cl), 204 (17, $[C_{11}H_7{}^{37}ClN_2]^+$), 202 (51, $[C_{11}H_7{}^{35}ClN_2]^+$).

10-(3,4-Dichlorophenyl)-2,3-dihydroimidazo[1,2-*a*]pyrido[2,3-*d*]pyrimidin-5(10*H*)-one (*IVd*)

Prepared by method *A*), m.p. 252 – 254 °C, crystallized from methanol. IR spectrum (KBr): 1 690, 1 640, 1 600, 1 580. ^1H NMR spectrum (200 MHz, CD_3SOCD_3): 8.37 dd (H (8), J(8-6) = 2, J(8-7) = 5); 8.25 dd (H (6), J(6-8) = 2, J(6-7) = 8); 7.85 d (H (5'), J(5'-6') = 9); 7.82 d (H (2'), J(2'-6') = 3; 7.46 q (H (6'), J(6'-5') = 9, J(6'-2') = 3); 7.21 dd (H (7), J(7-6) = 8, J(7-8) = 5); 4.16 – 3.96 m, 2 H (CH_2); 3.82 – 3.62 m, 2 H (CH_2). Mass spectrum: 336 (11, M^+ for ^{37}Cl), 334 (67, M^+ for ^{37}Cl, ^{35}Cl), 332 (100, M^+ for $2\,^{35}Cl$), 331 (77, $[M - 1]^+$ for $2\,^{35}Cl$), 240 (7, $[C_{11}H_6{}^{37}Cl_2N_2]^+$), 238 (38, $[C_{11}H_6{}^{37}Cl{}^{35}ClN_2]^+$), 236 (58, $[C_{11}H_6{}^{35}Cl_2N_2]^+$).

10-(3-Methoxyphenyl)-2,3-dihydroimidazo[1,2-*a*]pyrido[2,3-*d*]pyrimidin-5(10*H*)-one (*IVe*)

Prepared by method *A*), m.p. 308.0 – 308.5 °C (decomp.), crystallized from methanol. IR spectrum (KBr): 1 690, 1 640, 1 610 – 1 570. ^1H NMR spectrum (200 MHz, CD_3SOCD_3): 8.36 dd (H (8), J(8-6) = 1.5, J(8-7) = 5); 8.24 dd (H (6), J(6-8) = 1.5, J(6-7) = 8); 7.41 t, 1 H (Ar, J = 7.5); 7.15 dd (H (7), J(7-6) = 8, J(7-8) = 5); 7.04 – 6.90 m, 3 H (Ar); 4.02 t, 2 H ((CH_2), J = 8); 3.76 s, 3 H (CH_3); 3.70 t, 2 H ((CH_2), J = 8). Mass spectrum: 296 (2, $[M + 2]^+$), 295 (19, $[M + 1]^+$), 294 (96, M^+), 293 (100, $[M - 1]^+$), 198 (38, $[C_{12}H_{10}N_2O]^+$).

10-(3-Pyridyl)-2,3-dihydroimidazo[1,2-*a*]pyrido[2,3-*d*]pyrimidin-5(10*H*)-one (*IVf*)

Prepared by methods *A*) and *B*), m.p. 273.5 – 274.5 °C, was eluted from silica gel by $CHCl_3$–MeOH–conc. aq. NH_3 (97.5 : 2.25 : 0.25 by volume) and crystallized from methanol as colorless prisms. IR spectrum (KBr): 1 700 (br), 1 420 (br), 1 310 (br), 1 200 (br), 920 (br), 640 (br). ^1H NMR spectrum (CD_3SOCD_3): 8.65 d (H (2'), J = 2); 8.63 d (H (4'), J = 2); 8.37 dd (H (8), J(8-6) = 2, J(8-7) = 4.5); 8.29 dd (H (6), J(6-8) = 2, J(6-7) = 6); 7.90 dq (H (6'), J(6'-5') = 6, J(6'-4') = 2, J(6'-2') = 1); 7.59 dq (H (5'), J(5'-4') = 4.5, J(5'-6') = 6, J(6'-2') = 1); 7.22 dd (H (7), J(7-6) = 6, J(7-8) = 4.5); 4.05 t, 2 H ((CH_2), J = 6); 3.73 t, 2 H ((CH_2), J = 6). Mass spectrum: 267 (3, $[M + 2]^+$), 266 (30, $[M + 1]^+$), 265 (100, M^+), 264 (93, $[M - 1]^+$), 237 (22, $[M - 28]^+$), 236 (36, $[M - 29]^+$), 196 (40, $[M - C_3H_5N_2]^+$), 169 (90, $[C_{10}H_7N_3]^+$).

10-(4-Hydroxyphenyl)-2,3-dihydroimidazol[1,2-*a*]pyrido[2,3-*d*]pyrimidin-5(10*H*)-one (*IVg*)

Prepared by method *B*), m.p. 313 – 316 °C, crystallized from methanol–ether. IR spectrum (mineral oil): 3 525, 3 400, 3 225 (OH), 1 700, 1 660, 1 640, 1 600, 1 510, 1 420, 1 300, 1 240. ^1H NMR spectrum (CD_3SOCD_3): 10.44 s, 1 H ((OH), ex.); 8.70 dd (H (8), J(8-6) = 1.5, J(8-7) = 5); 8.60 dd (H (6), J(6-8) = 1.5, J(6-7) = 9); 7.57 dd (H (7), J(7-8) = 5, J(7-6) = 9); 7.32 d, 2 H (Ar, J = 9); 7.07 d, 2 H (Ar, J = 9); 4.46 – 4.26 m, 2 H (CH_2); 3.98 – 3.78 m, 2 H (CH_2). Mass spectrum: 282 (3, $[M + 2]^+$), 281 (26, $[M + 1]^+$), 280 (100, M^+), 279 (84, $[M - 1]^+$), 251 (27, $[M - 29]^+$), 184 (68, $[C_{11}H_8N_2O]^+$).

11-Phenyl-2,3,4,11-tetrahydropyrido[2,3-*d*]pyrimido[1,2-*a*]pyrimidin-6(6*H*)-one (*IVh*)

Prepared by methods *A*) and *B*), m.p. 252 – 254 °C, crystallized from dichloromethane–ether. IR spectrum: 1 680, 1 640, 1 600, 1 480, 1 450, 1 400, 1 350, 1 290, 1 270 – 1 250. ^1H NMR spectrum: 8.36 s (H (9)); 8.31 s (H (7)); 7.55 – 7.40 m, 3 H (Ar); 7.30 – 7.20 m, 2 H (Ar); 6.93 dd, (H (8), J(8-9) = 3, J(8-7) = 6); 4.03 t, 2 H ((CH_2), J = 6); 3.44 t, 2 H ((CH_2), J = 6); 2.00 – 1.73 m, 2 H (CH_2). ^{13}C NMR spectrum (200 MHz): 160 (C(6)), 154 (C(9)), 143 (C(11a)), 137.9 (C(10a)), 137.0 (C(7)), 130.0 (C(1')), 129.7 (2C((2')),

129.6 (2C(3')), 128 (C(4')), 117 (C(8)), 109 (C(6a)), 44.4 and 44.1 (C(1) and C(4)), 20 (C(3)). Mass spectrum: 279 (3, $[M + 1]^+$), 278 (21, M^+), 277 (100, $[M - 1]^+$), 168 (13, $[C_{11}H_8N_2]^+$), 130 (82).

11-(3-Nitrophenyl)-2,3,4,11-tetrahydropyrido[2,3-*d*]pyrimido[1,2-*a*]pyrimidin-6(6*H*)-one (*IVi*)

Prepared by method *B*), m.p. 243 – 245 °C, gave light yellow crystals from chloroform–ether. IR spectrum: 1 685, 1 650, 1 600, 1 530 (NO_2), 1 480, 1 450, 1 400, 1 350, 970. ^{1}H NMR spectrum: 8.35 – 8.10 two dd (H (9) and H (7), 2 H, Ar, overlapping with the m cited next); 7.72 – 7.51 m, 2 H (Ar); 6.97 dd (H (8), J(8-7) = 8, J(8-9) = 5); 4.00 t, 2 H ((CH_2), J = 6); 3.39 t, 2 H ((CH_2), J = 6); 2.00 – 1.73 t, 2 H ((CH_2), J = 6). Mass spectrum: 324 (4, $[M + 1]^+$, 323 (25, M^+), 322 (100, $[M - 1]^+$), 276 (48, $[M - HNO_2]^+$).

11-(3-Chlorophenyl)-2,3,4,11-tetrahydropyrido[2,3-*d*]pyrimido[1,2-*a*]pyrimidin-6(6*H*)-one (*IVj*)

Prepared by method *B*), m.p. 235 – 237 °C, gave colorless crystals from dichloromethane–ether. IR spectrum: 1 680, 1 640, 1 600, 1 580, 1 480, 1 450, 1 400, 1 350, 970. ^{1}H NMR spectrum: 8.30 s, 1 H (H (9)); 8.28 s, 1 H (H (7)); 7.43 – 7.33 m, 2 H (Ar); 7.23 – 7.07 m, 2 H (Ar); 6.94 t (H (8), J = 6); 4.00 t, 2 H ((CH_2), J = 6); 3.42 t, 2 H ((CH_2), J = 6); 2.00 – 1.72 m, 2 H (CH_2). Mass spectrum: 314 (8, M^+ for ^{37}Cl), 313 (34), 312 (22, M^+ for ^{35}Cl), 311 (100, $[M - 1]^+$ for ^{35}Cl), 283 (15, $[M - 29]^+$ for ^{35}Cl).

11-(3,4-Dichlorophenyl)-2,3,4,11-tetrahydropyrido[2,3-*d*]pyrimido[1,2-*a*]pyrimidin-6(6*H*)-one (*IVk*)

Prepared by method *B*), m.p. 234 – 236 °C, crystallized from chloroform–ether. IR spectrum: 1 690, 1 640, 1 600, 1 590, 1 485, 1 450, 1 400, 1 360, 980. ^{1}H NMR spectrum: 8.40 s, (H (9)); 8.33 s (H (7)); 7.60 d, 1 H (H (5'), J = 8); 7.40 d, 1 H (H (2'), J = 3); 7.15 q (H (6'), J(6'-5') = 8, J(6'-2') = 3); 6.98 d (H (8), J = 7); 4.05 t, 2 H ((CH_2), J = 6); 3.48 t, 2 H ((CH_2), J = 6); 2.00 – 1.76 m, 2 H (CH_2). Mass spectrum: 350 (5, M^+ for ^{37}Cl, ^{37}Cl), 348 (31, M^+ for ^{37}Cl, ^{35}Cl), 346 (49, M^+ for ^{35}Cl, ^{35}Cl), 345 (100, $[M - 1]^+$ for ^{35}Cl, ^{35}Cl).

11-(3-Methoxyphenyl)-2,3,4,11-tetrahydropyrido[2,3-*d*]pyrimido[1,2-*a*]pyrimidin-6(6*H*)-one (*IVl*)

Prepared by method *B*), m.p. 230 – 231 °C, crystallized from dichloromethane–ether. IR spectrum: 1 680, 1 640, 1 600, 1 490, 1 450, 1 400, 1 360, 1 140, 1 050, 970. ^{1}H NMR spectrum: 8.37 s, 1 H (H (9)); 8.29 s, 1 H (H (7)); 7.40 t, 1 H (H (5'), J = 8); 6.98 s, 1 H (H (2')); 6.95 – 6.82 m, 2 H (Ar); 6.77 d, 1 H (H (8), J = 2); 4.00 t, 2 H (CH_2, J = 6); 3.81 s, 3 H (OCH_3); 3.45 t, 2 H ((CH_2), J = 6); 2.00 – 1.76 m, 2 H (CH_2). Mass spectrum: 309 (3, $[M + 1]^+$), 308 (22, M^+), 307 (100, $[M - 1]^+$), 292 (19, $[M - 16]^+$).

10-Phenyl-2,3-dihydroimidazo[1,2-*a*]pyrazino[2,3-*d*]pyrimidin-5(10*H*)-one (*IVm*)

Prepared by method *A*), m.p. > 315 °C, crystallized from chloroform–petroleum ether. IR spectrum: 1 700, 1 650, 1 600, 1 540, 1 470, 1 440, 1 400, 1 190. UV spectrum: 258 (4.11), 355 (3.71). ^{1}H NMR spectrum: 8.38 d, 1 H (H (8), J = 2); 8.29 d, 1 H (H (7), J = 2); 7.60 – 7.42 m, 3 H (Ar); 7.42 – 7.23 m, 2 H (Ar); 4.33 – 4.10 m, 2 H (CH_2); 4.00 – 3.77 m, 2 H (CH_2). ^{13}C NMR spectrum (400 MHz, CD_3SOCD_3): 156 (C(5)), 151 (C(9a)†), 150 (C(10a)†), 146 (C(8)), 138 (C(7), 136 (C(1')), 129.3 (2C(2')), 129.2 (2C(3')), 128.4 (C(5a)), 128.3 (C(4')), 50 (C(2*)), 45 (C(3*)). Mass spectrum: 266 (7, $[M + 1]^+$), 265 (43, M^+), 264 (22, $[M - 1]^+$, 169 (8, $[C_{10}H_7N_3]^+$).

10-(3-Nitrophenyl)-2,3-dihydroimidazo[1,2-*a*]pyrazino[2,3-*d*]pyrimidin-5(10*H*)-one (*IVn*)

Prepared by methods *A*) and *B*), m.p. 285 – 286 °C, gave bright yellow crystals from chloroform–ether. IR spectrum: 1 710 (CON), 1 660, 1 540, 1 480, 1 440, 1 400, 1 360, 1 190, 1 140. ^{1}H NMR spectrum: 8.40d,

1 H (H (8), J(7-8) = 2); 8.23 d , 1 H (H (7), J(8-7) = 2); 8.30 – 8.20 overlapping m, 2 H (Ar); 7.80 – 7.65 m, 2 H (Ar); 4.32 – 4.10 m, 2 H (CH_2); 4.00 – 3.78 m, 2 H (CH_2). Mass spectrum: 312 (3, $[M + 2]^+$), 311 (22, $[M + 1]^+$), 310 (100, M^+), 309 (67, $[M - 1]^+$), 282 (33, $[M - 28]^+$), 263 (53 $[M - HNO_2]^+$), 214 (9, $[C_{10}H_6N_4O_2]^+$).

10-(3-Chlorophenyl)-2,3-dihydroimidazo[1,2-*a*]pyrazino[2,3-*d*]pyrimidin-5(10*H*)-one (*IVo*)

Prepared by method *A*), m.p. > 315 °C, crystallized from dichloromethane. IR spectrum (mineral oil): 1 690 (CON), 1 650, 1 530, 1 430, 1 400, 1 290, 1 180. ^{1}H NMR spectrum ($CDCl_3$–CD_3SOCD_3): 8.39 s, 2 H (H (8) and H (7)); 7.55 – 7.32 m, 4 H (Ar); 4.24 – 4.02 m, 2 H (CH_2); 3.90 – 3.68 m, 2 H (CH_2). Mass spectrum: 301 (56, M^+ for ^{37}Cl), 299 (100, M^+ for ^{35}Cl), 298 (96, $[M - 1]^+$), 270 (50, $[M - 29]^+$), 217 (60, $[M - 82]^+$), 203 (30, $[C_{10}H_6{}^{35}ClN_3]^+$).

10-(3,4-Dichlorophenyl)-2,3-dihydroimidazino[1,2-*a*]pyrazino[2,3-*d*]pyrimidin-5(10*H*)-one (*IVp*)

Prepared by method *A*), m.p. 267 – 268 °C, crystallized from chloroform–petroleum ether. IR spectrum: 1 700 (CON), 1 660, 1 540, 1 470, 1 440, 1 400, 1 190, 1 140, 1 040. ^{1}H NMR spectrum: 8.45 d, 1 H (H (8), J(8-7) = 2); 8.29 d, 1 H (H (7), J(7-8) = 2); 7.60 d, 1 H (H (5'), J(5'-6') = 9); 7.47 d, 1 H (H (2'), J(2'-6') = 3); 7.20 q, 1 H (H (6'), J(6'-5') = 9, J(6'-2') = 3); 4.37 – 4.17 m, 2 H (CH_2); 4.02 – 3.82 m, 2 H (CH_2). Mass spectrum: 337 (11, M^+ for ^{37}Cl, ^{37}Cl), 335 (61, M^+ for ^{37}Cl, ^{35}Cl), 333 (94, M^+ for ^{35}Cl, ^{35}Cl), 332 (48, $[M - 1]^+$ for ^{35}Cl, ^{35}Cl), 306 (23, $[M - 28]^+$), 251 (30, $[M - 82]^+$), 237 (15, $[C_{10}H_5N_3{}^{35}Cl]^+$).

10-(3-Methoxyphenyl)-2,3-dihydroimidazo[1,2-*a*]pyrazino[2,3-*d*]pyrimidin-5(10*H*)-one (*IVq*)

Prepared by method *A*), m.p. > 315 °C, crystallized from dichloromethane–petroleum ether. IR spectrum (mineral oil): 1 700 (CON), 1 650, 1 600 (guanidine C=N), 1 540, 1 480, 1 430, 1 400, 1 280, 1 250, 1 040. ^{1}H NMR spectrum ($CDCl_3$–CD_3SOCD_3): 8.36 s, 2 H (H (8) and H (7)); 7.50 – 7.30 m, 1 H (Ar); 7.10 – 6.90 m, 3 H (Ar); 4.22 – 4.00 m, 2 H (CH_2); 3.86 – 3.64 m, 2 H (CH_2); 3.80 s, 3 H (CH_3). Mass spectrum: 297 (4, $[M + 2]^+$), 296 (36, $[M + 1]^+$), 295 (100, M^+), 294 (99.7, $[M - 1]^+$), 266 (79, $[M - 29]^+$), 199 (38, $[C_{11}H_9N_3O]^+$).

11-Phenyl-2,3,4,11-tetrahydropyrimido[1,2-*a*]pyrazino[2,3-*d*]pyrimidin-6(6*H*)-one (*IVr*)

Prepared by method *B*), m.p. 271 – 273 °C, crystallized from chloroform–carbon tetrachloride. IR spectrum: 1 700 (CON), 1 640, 1 540, 1 480, 1 440, 1 400, 1 340, 1 300 – 1 260, 1 210, 1 160. ^{1}H NMR spectrum: 8.30 d (H (9), J(9-8) = 2); 8.27 d (H (8), J(8-9) = 2); 7.60 – 7.40 m, 3 H (Ar); 7.27 – 7.12 m, 2 H (Ar); 4.12 t, 2 H ((CH_2), J = 6); 3.47 t, 2 H ((CH_2), J = 6); 2.02 – 1.76 m, 2 H (CH_2). Mass spectrum: 280 (11, $[M + 1]^+$), 279 (88, M^+), 278 (100, $[M - 1]^+$), 250 (57, $[M - 28]^+$), 169 (19, $[C_{10}H_7N_3]^+$). Exact mass: calculated for $C_{15}H_{14}N_5O$ ($[M + 1]^+$): m/z 280.1198; found (FAB-MS): m/z 280.1213.

11-(3-Nitrophenyl)-2,3,4,11-tetrahydropyrimido[1,2-*a*]pyrazino[2,3-*d*]pyrimidin-6(6*H*)-one (*IVs*)

Prepared by method *B*), m.p. 228 – 229 °C, crystallized from chloroform–ether. IR spectrum: 1 700 (CON), 1 660, 1 540, 1 480, 1 440, 1 350, 1 190, 1 140. ^{1}H NMR spectrum: 8.40 d, 1 H (H (9), J(9-8) = 2); 8.23 d, 1 H (H (8), J(8-9) = 2); 8.20 – 8.10 m, 2 H (Ar); 7.80 – 7.50 m, 2 H (Ar); 4.12 t, 2 H ((CH_2), J = 6); 3.40 t, 2 H ((CH_2), J = 6); 2.05 – 1.80 m, 2 H (CH_2). Mass spectrum: 325 (3, $[M + 1]^+$), 324 (23, M^+), 323 (100, $[M - 1]^+$), 277 (45, $[M - HNO_2]^+$).

2-Phenylamino-3-pyridine Carboxylic Acid, Ethyl Hydrogen Carbonate Anhydride (*V*)

A solution of triethylamine (2.5 g, 25 mmol) was added to a cooled suspension of 2-phenylamino-3-pyridinecarboxylic acid (5.35 g, 25 mmol) in dichloromethane (100 ml). The solid dissolved and a solution of ethyl chloroformate (2.71 g, 25 mmol) in dichloromethane (25 ml) was added at 0 °C. The resulting yellow solution was stirred 2 h at 3 °C under N_2. The solution was then washed with 1M sodium bicarbonate solution and water. The dried, filtered solution was evaporated to give anhydride *V* (3.66 g, 51%), m.p. 137.5 – 139.5 °C, after crystallization from chloroform–petroleum ether. IR spectrum: 3 460 (NH), 1 720 – 1 710 (O=C–O–C=O), 1 500, 1 440, 1 370, 1 320, 1 100, 1 070. ^{1}H NMR spectrum: 9.90 s (ex. NH); 8.66 dd, 1 H (H (6), *J*(6-4) = 2, *J*(6-5) = 4); 8.40 dd, 1 H (H (4), *J*(4-6) = 2, *J*(4-5) = 7.5); 7.43 – 7.28 m, 5 H (Ar and H (5)); 4.13 q, 2 H (CH_2); 1.16 t, 3 H ((CH_3), *J* = 6). Mass spectrum: 287 (3, $[M + 1]^+$), 286 (15, M^+), 285 (6, $[M - 1]^+$), 196 (79, $[PhN=(C_5H_3N)=C=O]^+$), 168 (100). For $C_{15}H_{14}N_2O_4$ (286.3) calculated: 62.93% C, 4.92% H, 9.78% N; found: 62.67% C, 4.76% H, 9.80% N.

TABLE VII
Microanalytical data for pyridones *IV*

No.	Formula	Calculated				Found			
		%C	%H	%Cl	%N	%C	%H	%Cl	%N
IVa	$C_{15}H_{12}N_4O$	68.17	4.58	–	21.20	67.88	4.59	–	21.27
IVb	$C_{15}H_{11}N_5O_3$	58.25	3.58	–	22.65	58.09	3.34	–	22.82
IVc	$C_{15}H_{11}ClN_4O$	60.31	3.71	11.87	18.75	60.14	3.71	11.80	18.63
IVd	$C_{15}H_{10}Cl_2N_4O$	54.07	3.02	21.28	16.82	54.16	3.09	21.00	16.88
IVe	$C_{16}H_{14}N_4O_2$	65.30	4.79	–	19.04	65.08	4.77	–	19.05
IVf	$C_{14}H_{11}N_5O$	63.39	4.18	–	26.40	63.21	4.24	–	26.46
IVg	$C_{15}H_{15}ClN_4O_3$[a]	53.81	4.52	10.59	16.74	53.90	4.24	10.25	16.68
IVh	$C_{16}H_{14}N_4O$	69.05	5.07	–	20.13	69.06	4.85	–	20.16
IVi	$C_{16}H_{13}N_5O_3$	59.44	4.05	–	21.66	59.31	4.02	–	21.91
IVj	$C_{16}H_{13}ClN_4O$	61.44	4.19	11.34	17.92	61.25	4.27	11.39	17.94
IVk	$C_{16}H_{12}Cl_2N_4O$	55.34	3.48	20.42	16.14	55.14	3.28	20.20	16.04
IVl	$C_{17}H_{16}N_4O_2$	66.22	5.23	–	18.17	65.85	5.28	–	18.09
IVm	$C_{14}H_{11}N_5O$	63.38	4.18	–	26.40	62.98	4.08	–	26.22
IVn	$C_{14}H_{10}N_6O_3$	54.20	3.25	–	27.08	54.05	3.25	–	26.86
IVo	$C_{14}H_{10}ClN_5O$	56.10	3.36	11.83	23.37	55.96	3.34	12.04	23.28
IVp	$C_{14}H_9Cl_2N_5O$	50.32	2.71	21.22	20.96	50.23	2.72	21.22	20.62
IVq	$C_{15}H_{13}N_5O_2$	61.01	4.44	–	23.72	60.87	4.33	–	23.30
IVr	$C_{15}H_{13}N_5O$[b]	64.51	4.69	–	25.07	63.54	4.65	–	24.71
IVs	$C_{15}H_{12}N_6O_3$	55.55	3.73	–	25.92	55.41	4.00	–	26.00

[a] I.e., for the monohydrate hydrochloride. [b] No acceptable value for C was obtained.

12-Phenyl-2,3,4,5-tetrahydropyrido[2',3',4,5]pyrimido[1,2-*a*][1,3]diazepine-7(12*H*)-one (*VI*)

A solution of triethylamine (5 g, 50 mmol) and hydriodide *IIc* (6.8 g, 25 mmol) in dichloromethane (125 ml) was added to a solution of the ethyl hydrogen carbonate anhydride (*V*) (7.15 g, 25 mmol). The reaction mixture was stirred in an ice bath for 2 h and for 50 h at 20 °C. Triethylamine and dichloromethane were removed by distillation at atmospheric pressure, and were replaced by tert-butanol (100 ml) containing *p*-toluenesulfonic acid monohydrate (1 g). The reaction mixture was then refluxed 15 h. The cooled mixture was concentrated, and the residue was partitioned between 1M sodium bicarbonate solution and dichloromethane. The dichloromethane solution was extracted with 1M hydrochloric acid solution. Combined acidic extracts, basified with 50% sodium hydroxide solution, were extracted with dichloromethane. Combined organic layers were dried, filtered, and concentrated. Trituration of the residue with ethyl acetate caused crystallization, and compound *VI* (1.00 g) was obtained. Another portion (0.5 g) of *VI* was obtained by chromatography of the mother liquor over silica gel; dichloromethane eluted *VI*. Crystallization of combined samples from chloroform–petroleum ether gave a pure sample (0.72 g, 9.9%) of *VI*, m.p. 217 – 220 °C. IR spectrum: 1 680, 1 640, 1 600, 1 480, 1 450, 1 400, 1 350. ^{1}H NMR spectrum: 8.37 dd, 1 H (H (10), J(10-8) = 1, J(10-9) = 2); 8.30 dd, 1 H (H (8), J(8-9) = 6, J(8-10) = 1); 7.55 – 7.42 m, 3 H (Ar); 7.30 – 7.19 m, 2 H (Ar); 6.96 dd, 1 H (H (9), J(9-10) = 2, J(9-8) = 6); 4.27 t, 2 H (CH_2), J = 6); 3.73 t, 2 H (CH_2, J = 6); 2.15 – 1.75 m, 4 H (2 CH_2). Chemical ionization mass spectrum (CH_4): 295 (3, $[M + 3]^+$), 294 (21, $[M + 2]^+$), 293 (100, $[M + 1]^+$), 292 (8, M^+), 291 (13, $[M - 1]^+$). For $C_{17}H_{16}N_4O$ (292.3) calculated: 69.84% C, 5.52% H, 19.16% N; found: 69.58% C, 5.41% H, 19.10% N.

4,5,6,7-Tetrahydro-1-[(2-chloro-3-pyridinyl)carbonyl]-2-methylthio-1*H*-1,3-diazepine (*VII*)

Prepared according to the general procedure given for compounds *IIIa* – *IIId*, compound *VII* formed white crystals, m.p. 122 – 124 °C (ether–dichloromethane), in a yield of 79%. IR spectrum: 1 660, 1 610, 1 570, 1 400, 1 350, 1 140, 1 100, 1 060. ^{1}H NMR spectrum: 8.40 dd, 1 H (H (6), J(6-4) = 3, J(6-5) = 6); 7.50 dd, 1 H (H (4), J(4-6) = 3, J(4-5) = 6); 7.19 dd, 1 H (H (5), J(5-6) = 6, J(5-4) = 7.5); 3.80 – 3.55 m, 4 H (2 CH_2); 2.06 s, 3 H (CH_3); 1.88 – 1.60 m, 4 H (2 CH_2). Mass spectrum: 286 (0.2, $[M + 1]^+$ for ^{37}Cl), 284 (1, $[M + 1]^+$ for ^{35}Cl), 157 (100), 140 (94, $[C_6H_3{}^{35}ClNO]^+$), 112 (47, $[C_5H_4{}^{35}ClN]^+$). For $C_{12}H_{14}ClN_3OS$ (283.8) calculated: 50.79% C, 4.97% H, 12.49% Cl, 14.81% N, 11.30% S; found: 50.79% C, 4.90% H, 12.42% Cl, 14.71% N, 11.40% S.

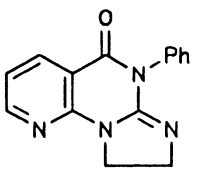
RESULTS AND DISCUSSION

Methylthioamidines *IIa* and *IIb* amidated acid chlorides *Ia* and *Ib*, respectively, yielding *IIIa* (65%), *IIIb* (100%), *IIIc* (81%), and *IIId* (69%) (Scheme 1). These amidations, which were carried out at ice bath temperature, were uneventful.

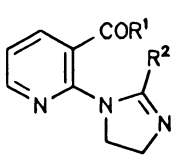
Aromatic amines in methanol containing acetic acid (method *A*) converted *IIIa* to *IVa* and to *IVc* – *IVe*, e.g. (Scheme 1, Table VI). In some cases, use of this method gave complex mixtures (TLC) and low yields of *IV*. Changing solvent and acid to the non-nucleophilic tert-butanol and *p*-toluenesulfonic acid (method *B*) avoided mixtures and raised yields. Thus, *IIIa* and 3-aminopyridine provided 52% of *IVf* by method *B*) but afforded only 8% by method *A*). Other yields were similarly affected. Method *B*) gave 80 and 87% of *IVn* and *IVh*, respectively; whereas method *A*) furnished 21% (*IVn*) and 22% (*IVh*) yields of the same products.

Making the homologous pyrimidone *VI* which incorporates a 7-membered ring, required a different synthesis (Scheme 2). The intended precursor (*VII*) of pyrimidone *VI* did not form it on treatment with aniline, according to TLC. Aniline and *VII* reacted to give a product of unknown structure. Compound *VI* would have been detected, as shown by TLC comparisons of the crude product to an authentic sample of *VI*. Methylthioamidine *IIc*, however, effectively amidated the mixed anhydride *V* which formed and reacted in situ (Scheme 2). Cyclization accompanied amidation, providing the desired *VI* albeit in a low yield (10%). Whether amidation preceded or followed elimination of methanethiol was not established.

The synthesis (Scheme 1) that exclusively gave the linear isomers *IV* was formally ambiguous. Condensation of aniline with any of the three hypothetical intermediates *IX* – *XI* might have formed the angular isomer *VIII* of pyrimidone *IVa*. The possibility for ambiguity in the preparation of pyrimidones *IV* seemed unlikely but consequential, so we sought an unambiguous synthesis of *IVa*. Such a synthesis (41%) resulted on treatment of *V* with methylthioamidine *IIa* (Scheme 2). Samples of *IVa* prepared by the two routes were identical (m.p., m.m.p., TLC, IR, ^{1}H and ^{13}C NMR, and mass spectra).

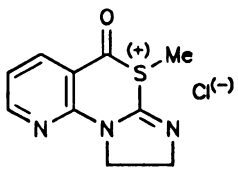


VIII



IX R^1 = SMe; R^2 = Cl

X R^1 = Cl; R^2 = SMe



XI

X-Ray crystallographic analysis established unequivocally the structure of *IVa*. The solid-state conformation of this molecule is shown in Fig. 1. The fused heterocyclic ring atoms N(1)–C(10a) are approximately coplanar (maximum atomic displacement is 0.035 Å and root-mean-square deviation is 0.019 Å). The carbonyl oxygen atom, O(11), and directly bonded phenyl ring carbon arom, C(1'), lie close to and on the same side of the least-squares plane through N(1)–C(10a) Δ = 0.096 Å for O(11), Δ = 0.045 Å for C(1'). The dihedral angle between the N(1)–C(10a) plane and that through the pendant phenyl ring carbon atoms is 76.12(6)°. In the main, bonded distances are not unusual[8] except for the C(2)–C(3) single bond length at 1.560(3) Å, where it is significantly elongated due to bond strain resulting from the eclipsed conformation of the C(2)/C(3) methylene hydrogen atoms in the planar dihydroimidazole ring.

A stereoview of the crystal packing arrangement of *IVa* is presented in Fig. 2. Molecules of *IVa* related by the crystallographic centers of symmetry have their fused heterocyclic rings stacked along the *a*-direction.

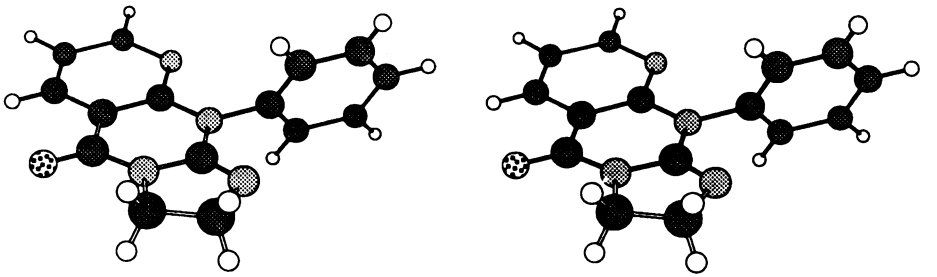


FIG. 1
Stereoview of *IVa*: structure and solid-state conformation

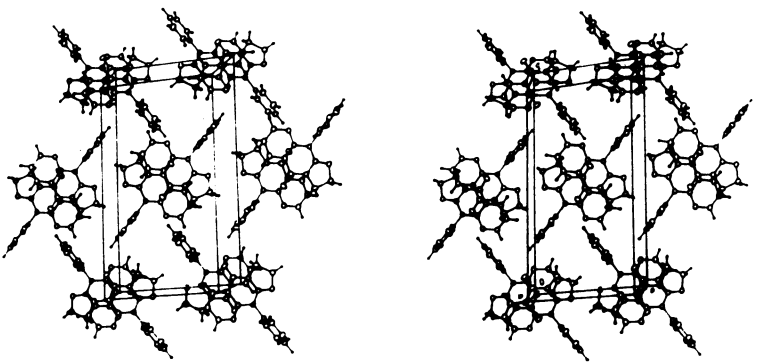


FIG. 2
Stereoview of the crystal packing arrangement of *IVa*

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