Chemistry of the Heterocyclic Pseudobasic Amino Alcohols, XXXVIII[1])

Ring-Chain Tautomerism of Pyrimido[6,1-a]isoquinolines

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In basic media, 4-substituted pyrimido[6,1-a]isoquinolin-2-imine hydrochlorides (**4**) constitute an equilibrium system involving the tautomeric forms characteristic of pseudobases **5**, **6**, **7** and the anhydro base **9**. In aqueous solution in the pH range 7−13 the ammonium hydroxide form **5** is present. Between pH 13 and 14 the pseudobase **6** probably arises from this by covalent binding of the hydroxy group. **6** is then converted to the more stable imino type anhydrobase **9**. Ring cleavage of **4** by excess alkali or of **9** by a small amount of water gives 1-(acylamidinomethylen)isoquinolines **7**. Compounds **7** and **9** are stable in the solid state or in aprotic solutions but revert to cation **5** in dilute protic solutions.

Our studies on cotarnine and its derivatives (**1−3**, R = CH$_3$) obtained from *Papaver* alkaloids were initiated more than thirty years ago[1,2]. Depending on conditions and the N-substituent these 3,4-dihydroisoquinolines exist in three tautomeric forms, i.e. as the cation **1**, the amino carbinol **2** (named pseudobase after Hantzsch[3]), or the open-chain carbonylamino form **3** (Scheme 1). Three major reviews have been published about pseudobases[4,5,6].
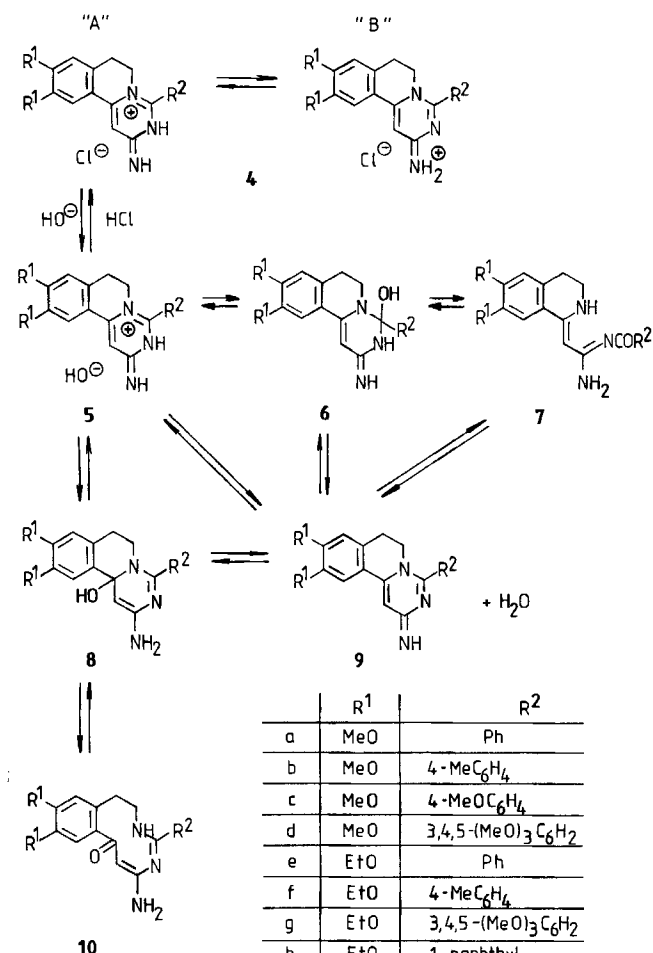
Scheme 1
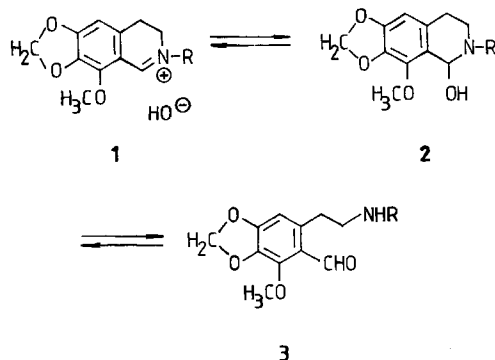
A recent publication[7] and the present paper on the synthesis and properties of pyrimido[6,1-a]isoquinolinium chlorides (**4**) are a continuation of this work. We found that in basic media the salts **4** give rise to an interesting novel pseudobase, which, depending on conditions, may exist in three different tautomeric forms (**5**, **6**, **7**) as well as form the corresponding anhydrobase (**9**) derived from them by loss of a proton or water (Scheme 2).

For the salt **4a**, X-ray diffraction showed constitution "B" in the solid state (Figure 1), while in dimethyl sulfoxide solution constitution "A" was deduced by ^{1}H-NMR spectroscopy.

Scheme 2

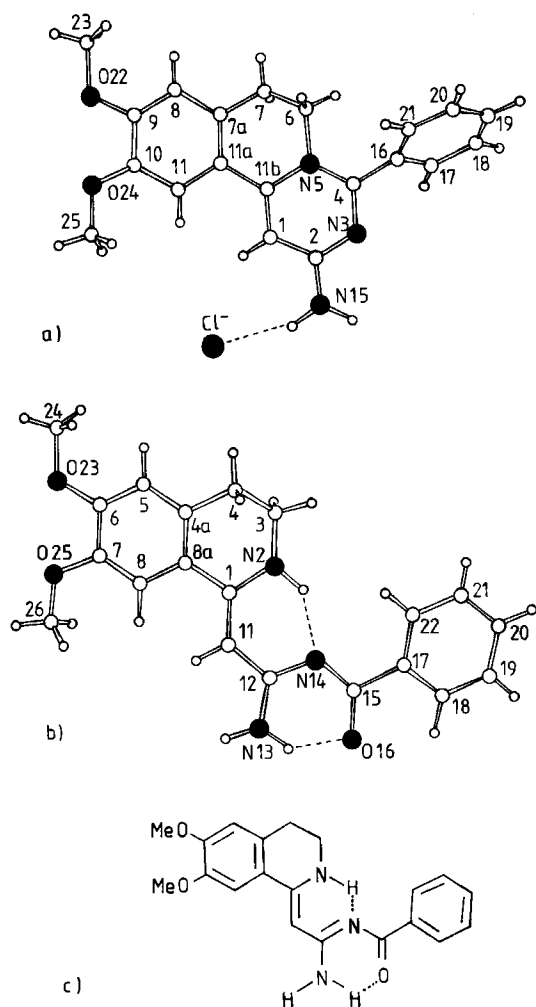|	R^1	R^2
a	MeO	Ph
b	MeO	4-MeC$_6$H$_4$
c	MeO	4-MeOC$_6$H$_4$
d	MeO	3,4,5-(MeO)$_3$C$_6$H$_2$
e	EtO	Ph
f	EtO	4-MeC$_6$H$_4$
g	EtO	3,4,5-(MeO)$_3$C$_6$H$_2$
h	EtO	1-naphthyl
i	EtO	2-pyridyl
j	EtO	3-pyridyl

Figure 1. a) Crystal structure of **4a**. — b) Crystal structure of **7a** indicating hydrogen bonds. — c) Schematic representation of the intramolecular chelate rings in **7a**

On adding alkali to a dilute aqueous solution of the chlorides **4** no apparent changes take place up to about pH 13. In the case of very strong alkalization (pH ≫ 14) a product precipitates, for which analytical and spectroscopic data (for **4a** and **4e** also X-ray diffraction) suggested that, by cleavage of the pyrimidine ring, the acylamidines **7a**—**j** were formed. On acidification with hydrochloric acid, the strongly basic amidines reverted to the original salts. The relative stability of acylamidines **7** may be attributed to their extended π-electron system and (as shown by X-ray diffraction) to the formation of two six-membered chelate rings (Figure 1). We had encountered similar chelate structures with related acyl-amidines earlier[8].

Detailed study of this interesting ring-opening-ring-closure process has been much facilitated by the use of electron spectroscopy, elaborated for such problems by Bunting, Metzger and others[6,9,10].

The UV spectra of the phenyl derivative **4a** [curve 1 in Figure 2 (a)] in chloroform and water were almost identical. On addition of alkali no change is seen up to pH 13, indicating analogous electronic structures for the salt and the

corresponding quaternary ammonium hydroxide (**5a**). On adding more alkali, reversible spectral changes with three isosbestic points take place [curves 2—5 in Figure 2 (a)]. For cation **5a** a pK_R of 13.4 can be calculated. It has to be noted that spectral changes of **4a** beyond pH 13 are time dependent. This is apparent from Figure 2 (b), which shows the spectrum of an aqueous solution of **4a** after the addition of sodium hydroxide in H_2O/dioxane (9:1) (pH 14) as a function of time over a period of 1—20 min. Curve 5 of
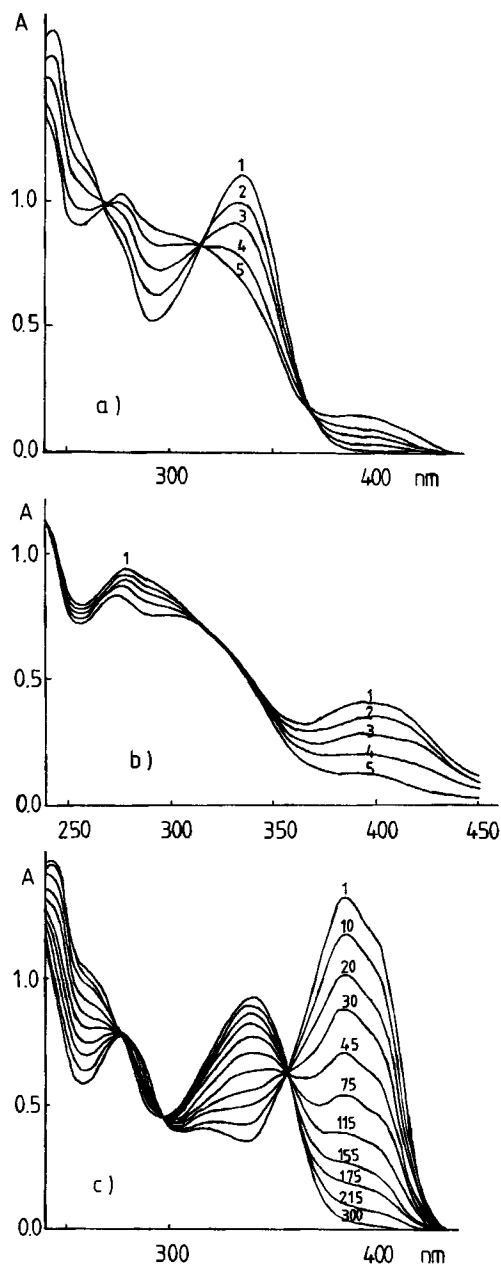

Figure 2. a) pH dependence of the UV spectrum of **4a** in aqueous solution ($c = 5.9 \times 10^{-5}$ mol/l; $d = 1$ cm). 1: pH 0—13; 2: pH 13.2; 3: pH 13.5; 4: pH 13.8; 5: pH 14.0. — b) UV spectrum of **4a** in H_2O/dioxane (9:1) at pH 14 as a function of time ($c = 4.4 \times 10^{-5}$ mol/l; $d = 1$ cm). 1: 1 min; 2: 6 min; 3: 11 min; 4: 16 min; 5: 21 min. — c) Spectrum of **7a** as a function of time in methanol/dioxane (1:1) (transformation **7a** → **5a**, $c = 6.6 \times 10^{-5}$ mol/l, $d = 1$ cm). Figures on curves denote time in min after dissolution

Figure 2 (a) corresponds to curve 5 in Figure 2 (b). For freshly prepared solutions the spectral changes are also reversible.

Time-dependent changes indicate a fast change of cation 5a followed by a slower one. Based on the literature and on our own earlier experience[2—6], the fast change was attributed to the formation of a pseudobase by covalent binding of the hydroxide ion, which in the case of 5a can involve both C-11b and C-4, giving 6 and 8, respectively (Scheme 2). For the slow, thermodynamically controlled change either the interconversion of 6 and 8 can be envisaged or the formation of the macrocyclic tautomer 10. The acylamidine structure 7a is excluded since it has a different UV spectrum [curve 1 in Figure 2 (c)].

Since we had previously succeeded in characterising pseudobases as their crystalline pseudobasic ethers[2a,2d], we attempted to prepare the ethyl ether of 6a by evaporating an ethanolic solution of the open-chain tautomer 7a. We were surprised to obtain the crystalline anhydrobase 9a in good yield, instead of the ethyl ether. The UV spectrum of the product was identical to curve 5 in Figure 2 (b). 9a can arise in basic media either by deprotonation of the cation 5a or by dehydration of the pseudobase 6a. Examples of fast pseudobase formation followed by slow conversion to an anhydrobase have already been reported[6,10]. Formation of the isomeric pseudobase 8a and its bicyclic tautomer 10a cannot be totally excluded, but since the acylamidine 7a can only be formed by ring opening of 6a, the UV spectrum of a freshly prepared solution of 4a at pH 14 has probably to be associated with 6a.

Further support for the complex equilibrium system presented in Scheme 2 is provided by changes in the UV spectra of the acylamidine 7a and the anhydrobase 9a in protic solvents. While in the solid state and in aprotic solvents (chloroform, benzene, dioxane) both are stable, in protic solvents they undergo changes which depend both on concentration and on the nature of the solvent. Thus the UV spectrum of a dilute solution of 7a in methanol after 2 h corresponds to that of 5a, i.e. the cation. This is notable since 7a can be recrystallized from relatively concentrated solutions in methanol or ethanol. This indicates that the equilibrium of 5a and 7a is concentration dependant. When water is added to a dilute solution of 7a in dioxane, ring closure to 5a proceeds at an easily measurable rate, which can be influenced by the dioxane/water ratio (Table 1).

A similar transformation also takes place in dioxane/methanol mixtures, though at a lower rate. Half-lives for 1:1

mixtures are 9 min for aqueous dioxane and 47 min for dioxane/methanol [Figure 2 (c)]. Note that the spectrum of the pseudobase 6a or of its ether is absent from Figure 2 (c), indicating that under such conditions the pseudobase has a very short lifetime.

On dilution of a dioxane solution of the anhydrobase 9a with water, similar but faster, spectral changes occur, indicating the formation of cation 5a. Half-life of the reaction 9a → 5a in 50% aqueous dioxane is only 2 min. In contrast, when adding an equimolar amount or only slightly more water to a dioxane solution of the anhydrobase 9a, the UV spectrum characteristic of the open-chain acylamidine appears. That means that competition between 5a and 7a is also dependent on the amount of water present. This remarkable feature can be exploited for preparative purposes. Thus, when the anhydrobase 9a is dissolved in a small amount of 96% ethanol the acylamidine 7a crystallizes spontaneously. The intermediate in this reversible transformation is apparently the pseudobase 6a.

Equilibrium systems similar to that presented in Scheme 2, involving a cation, cyclic and open-chain pseudobases as well as an anhydrobase, have been reported for situations when an alkyl chain containing a mobile proton was attached to a heterocyclic ring. Deprotonation occurred at a carbon atom, resulting in an anhydrobase containing an exocyclic C=C bond[6,9—12]. Anhydrobase formation by elimination of an amino proton, resulting an exocyclic C=N bond, has been reported too[13], but a system involving three forms of a pseudobase and an imino type anhydrobase, and further, their reversible interconversion, often at a measurable rate, seems to be unprecedented.

The central role of the pseudobase 6a is also supported by hydrogenation of the open-chain tautomer 7a in ethanol
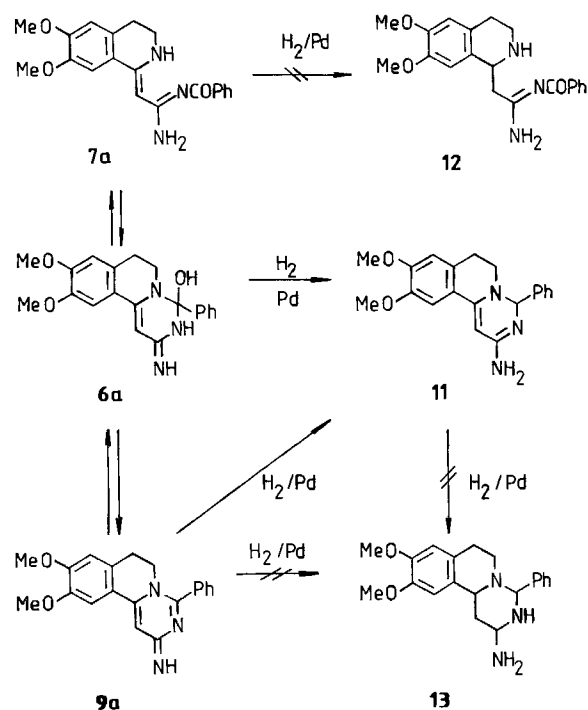
Table 1. Dependence of the half-life of cyclization 7a → 5a on solvent composition ($c = 1.3 \times 10^{-4}$ mol/l, $d = 1$ cm)

Dioxane/water (%)	Half-life $t_{1/2}$ [min]	K [s^{-1}]
70:30	52	0.0133
60:40	25	0.0277
50:50	9	0.0770
40:60	3	0.2310
30:70	1	0.6930

Scheme 3

over palladium/charcoal. This did not involve **12** as an intermediate, but rather **6a** and proceeded by cleavage of the C−O bond to give the stable crystalline pyrimido[6,1-a]isoquinoline **11** (Scheme 3).

Cotarnine-type pseudobases also undergo hydrogenolysis by C−O bond cleavage[2a,2d].

Catalytic hydrogenation of **9a** also leads to **11**. This is at variance with the hydrogenation of the analogue unsubstituted at C-2, which under similar conditions leads to complete saturation of the pyrimidine ring[14]. **11** lacks the tendency of the anhydrobase **9a** to add water, and in aqueous ethanol **11** is much less basic than **7a** or **9a**.

Thanks are due to Dr. *L. Pusztai*, Dr. *K. Horváth* and Dr. *T. Erős* for recording the IR and mass spectra and to Dr. *I. Remport* for elemental analyses.

Experimental

IR: Zeiss Specord M 80. − UV: Unicam SP 8200. − ^{1}H- and ^{13}C-NMR: Jeol FX-100 (100 and 25 MHz). − Mass spectra: Jeol D-300.

1-[(Benzoylamidino)methylene]-1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinoline (7a)

a) To a 50 °C solution of **4a**[7] (3.88 g, 10 mmol) in water (150 ml) a 50% aq. solution of potassium hydroxide (16.8 g, 300 mmol) was added in one portion. The oily precipitate, which rapidly solidified, was pulverized, filtered, and washed with water (2 × 20 ml). The dried product was recrystallized from benzene and dried over paraffin turnings (2.27 g, 65%), yellow crystals, m.p. 152 °C.

b) A solution of **9a** (0.33 g, 1.0 mmol) in 95% ethanol (1 ml) when set aside for 24 h in a refrigerator yielded **7a** (0.27 g, 77%). − IR (KBr): $\tilde{v}$ = 3400 cm^{-1}, 3260, 1630, 1610. − UV (CHCl$_3$): λ_{max} (lg ε) = 386 nm (4.480), 318 (3.936), 278 (4.221). − ^{1}H-NMR (CDCl$_3$): δ = 2.83 (t, J = 6 Hz, 2H, 4-H), 3.53 (m, 2H, 3-H), 3.85 (s, 3H, OCH$_3$), 3.89 (s, 3H, OCH$_3$), 4.97 (s, 1H, =CH), 6.66 (s, 1H, 5-H), 7.11 (s, 1H, 8-H), 7.3−7.5 (m, 3H, 3',4',5'-H) 7.8 (vb, 2H, NH$_2$), 8.0−8.2 (m, 2',6'-H), 11.64 (b, 1H, NH-2). − ^{13}C-NMR (CDCl$_3$): δ = 28.40 (C-4), 38.99 (C-3), 55.96 (OCH$_3$), 56.16 (OCH$_3$), 81.99 (=CH−), 108.41 (C-8), 110.83 (C-5), 121.86 (C-8a), 128.03 (C-2',6'), 128.56 (C-3',5'), 130.43 (C-4a), 130.81 (C-4'), 139.47 (C-1'), 147.87 (C-6), 151.20 (C-7), 155.88 (C-1), 168.78 [C=N(NH$_2$)], 177.47 (C=O).

C$_{20}$H$_{21}$N$_3$O$_3$ (351.4)   Calcd. C 68.36 H 6.02 N 11.96
                             Found C 68.34 H 6.16 N 12.05

1,2,3,4-Tetrahydro-6,7-dialkoxy-1-[(acylamidino)methylene]iso-quinolines (7b−j) (General Method): 4-Substituted 6,7-dihydro-9,10-dialkoxy-2H-pyrimidino[6,1-a]isoquinolin-2-imine hydrochlorides **4b−j**[7] (10 mmol) were treated as described for **7a** (method a). Yields, m.p's, IR spectral data and elementary analyses are compiled in Table 2, ^{1}H-NMR data in Table 3.
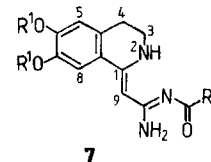
Crystal Data of **4a**, **7a**, **7e**[15]: All computations for the three structures were performed with the Enraf-Nonius SDP package with local modifications on the PDP 11/34 computer.

Crystal Data for **4a**: C$_{20}$H$_{20}$ClN$_3$O$_2$ · 3 H$_2$O (recrystallized from water), M = 423.9. Triclinic, a = 8.404(1), b = 12.414(2), c = 10.924(6) Å, α = 76.78(4), β = 110.07(3), γ = 90.37(2)°; space group $P\bar{1}$, Z = 2, V = 1039 Å^3, D_c = 1.355 g cm^{-3}. Data were collected on an Enraf Nonius CAD4 diffractometer with monochromated Mo-K_α radiation (λ = 0.7107). 2740 out of the 4534 reflections were considered observed [$I > 3\sigma(I)$]. The structure was solved by

Table 2. Yields, melting points, IR spectral and analytical data of compounds **7b−j**

No.	Yield %	M.p. °C	$\tilde{v}$max cm^{-1}	Formula Mol. wt.	Calcd. (Found) C	H	N
7b	77	178	3400 3255 1630 1610	C$_{21}$H$_{23}$N$_3$O$_3$ 365.4	69.02 (69.00)	6.34 (6.17)	11.50 (11.42)
7c	61	173	3420 3300 1632 1618	C$_{21}$H$_{23}$N$_3$O$_4$ 385.4	66.13 (66.25)	6.08 (6.02)	11.02 (10.94)
7d	70	156	3400 3260 1640 1620	C$_{23}$H$_{27}$N$_3$O$_6$ 441.5	62.57 (62.60)	6.16 (6.08)	9.52 (9.46)
7e	80	156	3380 3220 1620 1600	C$_{22}$H$_{25}$N$_3$O$_3$ 379.4	69.63 (69.48)	6.64 (6.50)	11.07 (10.94)
7f	72	183	3490 3380 1638 1618	C$_{23}$H$_{27}$N$_3$O$_3$ 393.5	70.20 (70.41)	6.92 (6.83)	10.68 (1o.41)
7g	69	160	3450 3390 1640 1620	C$_{25}$H$_{31}$N$_3$O$_6$ 469.5	63.94 (64.10)	6.66 (6.65)	8.95 (8.88)
7h	64	188	3300 3200 1620 1600	C$_{26}$H$_{27}$N$_3$O$_3$ 429.5	72.70 (72.62)	6.34 (6.28)	9.78 (9.57)
7i	62	135	3350 3200 1615 1595	C$_{21}$H$_{24}$N$_4$O$_3$ 380.4	66.30 (66.15)	6.36 (6.26)	14.73 (14.63)
7j	60	168	3350 3250 1620 1600	C$_{21}$H$_{24}$N$_4$O$_3$ 380.4	66.30 (66.21)	6.36 (6.21)	14.73 (14.67)

Table 3. ^{1}H-NMR data of **7b−j** (δ values, CDCl$_3$; J in Hz)

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2-H = 11.52−11.68, 3-H = 3.51−3.61, 4-H = 2.83−2.88, 5-H = 7.11−7.16, 8-H = 6.66−6.69, 9-H = 4.89−4.97, NH$_2$ = 7.6−7.8 (vb). − **a** (R^1 = CH$_3$): 3.85−3.91. − **b** (R^1 = CH$_3$CH$_2$): 1.43−1.48, (CH$_3$CH$_2$): 4.08−4.12

R^2

7b: 2.42 (s, 3H, CH$_3$), 7.44 (d, J = 8, 2H, 3',5'-H), 8.03 (d, J = 8, 2H, 2',6'-H)

7c: 3.86 (s, 3H, 4'-OCH$_3$), 6.93 (d, J = 9, 2H, 3',5'-H), 8.05 (d, J = 9, 2H, 2',6'-H)

7d: 3.92 (s, 3H, 4'-OCH$_3$), 3.94 [s, 6H, 3',5'-(OCH$_3$)$_2$], 7.42 (s, 2H, 2',6-H)

7e: 7.3−7.5 (m, 3H, 3',4',5'-H), 8.0−8.2 (m, 2H, 2',6'-H)

7f: 2.42 (s, 3H, CH$_3$), 7.44 (d, J = 8, 2H, 3',5'-H), 8.03 (d, J = 8, 2H, 2',6'-H)

7g: 3.91 (s, 3H, 4'-OCH$_3$), 3.92 [s, 6H, 3',5'-(OCH$_3$)$_2$], 7.42 (s, 2H, 2',6'-H)

7h: 7.4−8.3 (m, 9H, NH$_2$ and aromatic H)

7i: 7.78 (m, 2H, Py-4',5'-H), 8.20 (d, J = 8, 1H, Py-3'-H), 8.69 (d, 1H, Py-6'-H)

7j: 7.67 (m, 1H, Py-5'-H), 8.50 (m, 1H, Py-6'-H), 8.86 (m, 1H, Py-4'-H), 9.31 (m, 1H, Py-2'-H)

MULTAN 80[16]. 19 non-hydrogen atoms were found from an E map with best Figure of Merit (set number 82) supposing the centrosymmetric $P\bar{1}$ space group. The rest of the structure, including three water oxygen atoms, was found from subsequent structure factor-Fourier series calculation. A reasonable hydrogen bond pattern could be seen between the nitrogen, oxygen, and chlorine atoms, nevertheless one of the water oxygen atoms was found in a position too close to the 1/2, 1/2, 1/2 centre of symmetry. In order to resolve this problem we switched to the non-centrosymmetric $P1$ space group. After anisotropic refinement for the non-hydrogen atoms, all but those hydrogen atoms belonging to O5 and O6 could be determined from the difference Fourier map. Full matrix least-squares refinement was terminated at $R = 0.058$ for the 2740 reflections. Atomic coordinates for the non-hydrogen atoms are given in Table 4, with e.s.d.'s in parentheses. The corresponding atoms

(C1, C1*,... C126, C126*) are in a quasicentrosymmetric position $(1 - x, -y, -z)$. Two water oxygens (O5 and O6) are significantly out from this symmetry-related position.

Crystal Data of **7a**: $C_{20}H_{21}N_3O_3 \cdot 1/2\ C_6H_6$ (recrystallized from benzene), $M = 390.5$, monoclinic, $\alpha = 15.062(1)$, $b = 8.968(1)$, $c = 15.365(1)$ Å, $\beta = 92.82(2)°$, $V = 2073$ Å³, space group $P2_1/c$, $D_c = 1.251$ g cm⁻³. Data were collected on an Enraf Nonius CAD4 diffractometer with monochromated Cu-K_α radiation ($\lambda = 1.5418$ Å). Out of the 4268 reflections 3175 $[I > 3\sigma(I)]$ were considered observed and were used in the refinement. The structure was solved by direct methods using the MULTAN program with RANTAN options. All non-hydrogen atoms were found from the E map with best Figure of Merit. Subsequent structure factor-electron density calculation revealed that the benzene molecule is positioned at one of the centre of symmetry. After anisotropic refinement for the non-hydrogen atoms the hydrogen atom positions were found from the difference Fourier map, and were included isotropically in the final refinement. Final R value is 0.046. Atomic coordinates are given in Table 5.

Table 4. Atomic coordinates with e.s.d.'s in parentheses for **4a**. Because of the non-centrosymmetric space group (P_1) applied at the end of the refinement, there are two crystallographically independent ion pairs (the atoms of the latter are denoted by asterisks) and six water molecules (Ow1 ... Ow6)

	x	y	z
C1	0.1762(8)	0.0228(5)	0.1497(6)
C2	0.2993(8)	0.0151(5)	0.0882(6)
N3	0.3776(6)	-0.0839(4)	0.1039(4)
C4	0.3373(7)	-0.1725(5)	0.1749(5)
N5	0.2214(5)	-0.1692(4)	0.2371(4)
C6	0.1819(8)	-0.2718(6)	0.3165(6)
C7	0.1522(8)	-0.2478(6)	0.4409(6)
C7a	0.0212(7)	-0.1548(6)	0.3968(6)
C8	-0.0991(7)	-0.1536(6)	0.4617(6)
C9	-0.2151(7)	-0.0644(6)	0.4231(5)
C10	-0.2127(8)	0.0301(6)	0.3192(6)
C11	-0.1005(8)	0.0257(6)	0.2555(6)
C11a	0.0164(7)	-0.0671(5)	0.2922(6)
C11b	0.1402(8)	-0.0687(5)	0.2240(5)
N15	0.3377(6)	0.1026(4)	0.0154(5)
C16	0.4223(7)	-0.2802(5)	0.1843(5)
C17	0.3319(9)	-0.3649(6)	0.1366(7)
C18	0.419(1)	-0.4585(6)	0.1361(7)
C19	0.593(1)	-0.4684(6)	0.1854(7)
C20	0.6844(9)	-0.3859(6)	0.2344(7)
C21	0.5970(8)	-0.2905(6)	0.2320(6)
O22	-0.3366(5)	-0.0548(4)	0.4762(4)
C23	-0.3549(9)	-0.1480(8)	0.5706(7)
O24	-0.3313(6)	0.1136(4)	0.2933(4)
C25	-0.3250(11)	0.2129(7)	0.1982(8)
C126	0.1276(2)	0.3099(1)	0.0329(2)
C1 *	0.8222(7)	-0.0248(5)	-0.1475(6)
C2 *	0.7029(7)	-0.0174(5)	-0.0861(5)
N3 *	0.6233(6)	0.0833(4)	-0.1033(4)
C4 *	0.6645(7)	0.1730(5)	-0.1753(6)
N5 *	0.7754(6)	0.1695(4)	-0.2401(4)
C6 *	0.8193(8)	0.2721(5)	-0.3184(6)
C7 *	0.8490(9)	0.2498(6)	-0.4378(6)
C7a *	0.9802(7)	0.1562(6)	-0.3978(6)
C8 *	1.0962(8)	0.1533(6)	-0.4620(5)
C9 *	1.2139(8)	0.0634(6)	-0.4235(6)
C10 *	1.2155(7)	-0.0270(6)	-0.3204(6)
C11 *	1.1003(8)	-0.0254(6)	-0.2533(6)
C11a *	0.9847(7)	0.0669(5)	-0.2915(5)
C11b *	0.8623(7)	0.0675(5)	-0.2217(5)
N15 *	0.6634(7)	-0.1046(4)	-0.0120(5)
C16 *	0.5758(7)	0.2795(5)	-0.1851(5)
C17 *	0.6669(8)	0.3629(6)	-0.1336(7)
C18 *	0.5788(10)	0.4580(6)	-0.1363(8)
C19 *	0.4049(9)	0.4685(6)	-0.1852(7)
C20 *	0.3168(8)	0.3851(6)	-0.2347(7)
C21 *	0.4014(8)	0.2901(6)	-0.2333(6)
O22 *	1.3344(5)	0.0559(4)	-0.4779(4)
C23 *	1.3518(9)	0.1498(8)	-0.5744(6)
O24 *	1.3319(6)	-0.1125(4)	-0.2909(4)
C25 *	1.3243(9)	-0.2135(7)	-0.2004(8)
C126 *	0.8723(2)	-0.3102(1)	-0.0336(2)
Ow1	-0.0241(9)	0.4487(6)	0.1824(6)
Ow2	0.9044(13)	0.5357(7)	0.5614(7)
Ow3	0.0321(7)	0.5470(4)	0.1726(5)
Ow4	1.1165(14)	-0.5359(7)	0.4354(8)
Ow5	0.3945(13)	0.4162(9)	0.4372(10)
Ow6	0.5144(23)	0.5315(12)	0.5226(14)

Table 5. Atomic coordinates with e.s.d.'s in parentheses for **7a**. Cb1, Cb2, Cb3 denote the three independent atoms of the benzene molecule which is positioned at one of the centre of symmetry

	X	Y	Z
C1	0.70121(9)	-0.0227(1)	0.14965(9)
N2	0.77583(8)	0.0451(1)	0.12475(8)
C3	0.8151(1)	0.1730(2)	0.1695(1)
C4	0.8079(1)	0.1560(2)	0.2665(1)
C4a	0.7136(1)	0.1224(1)	0.2872(1)
C5	0.6773(1)	0.1765(1)	0.3631(1)
C6	0.5907(1)	0.1460(1)	0.38112(9)
C7	0.5376(1)	0.0602(1)	0.32173(9)
C8	0.5731(1)	0.0065(1)	0.2476(1)
C8a	0.6621(1)	0.0354(1)	0.22966(9)
C11	0.6629(1)	-0.1397(1)	0.1041(1)
C12	0.6072(1)	-0.1935(1)	0.0218(1)
N13	0.6422(1)	-0.3121(1)	-0.01049(9)
N14	0.75265(8)	-0.1253(1)	-0.02130(8)
C15	0.7689(1)	-0.1660(1)	-0.1043(1)
O16	0.72899(9)	-0.2628(1)	-0.14849(8)
C17	0.8433(1)	-0.0867(1)	-0.1451(1)
C18	0.8563(1)	-0.1109(2)	-0.2330(1)
C19	0.9253(1)	-0.0426(2)	-0.2730(1)
C20	0.9831(1)	0.0499(2)	-0.2271(1)
C21	0.9721(1)	0.0742(2)	-0.1399(1)
C22	0.9024(1)	0.0072(2)	-0.0987(1)
O23	0.54851(7)	0.1931(1)	0.45219(7)
O24	0.5963(1)	0.2875(3)	0.5118(1)
O25	0.45196(7)	0.0397(1)	0.34504(7)
C26	0.3915(1)	-0.0265(2)	0.2823(1)
Cb1	0.0712(1)	0.5957(2)	0.0043(1)
Cb2	0.0801(1)	0.4522(2)	0.0360(1)
Cb3	0.0085(1)	0.3580(2)	0.0316(1)

Crystal Data of **7e**: $C_{22}H_{25}N_3O_3$, $M = 379.5$ monoclinic, $a = 19.908(1)$, $b = 7.527(1)$, $c = 13.678(19)$ Å, $\beta = 108.94°$, $V = 1939$ Å³, $D_c = 1.30$ g cm⁻³, $Z = 4$, space group $P2_1/n$. Data were collected on an Enraf Nonius CAD4 diffractometer with monochromated Cu-K_α radiation. 3490 out of the total 4328 reflections were considered observed $[I > 3\sigma(I)]$. The structure was solved by the MULTAN program using the RANTAN option. All non-hydrogen atoms could be located from the E map with best Figure of Merit. Anisotropic refinement concluded with $R = 0.046$. Atomic coordinates are given in Table 6, with e.s.d.'s in parentheses.

6,7-Dihydro-9,10-dimethoxy-4-phenyl-2H-pyrimido[6,1-a]isoquinolin-2-imine (**9a**): A solution of **7a** (3.51 g, 10 mmol) in anhydrous ethanol (30 ml) was evaporated at atmospheric pressure and the residue heated on the steam bath in vacuo for another 30 min. The residue, a yellow oil, solidified on standing and was recrystallized from benzene to give **9a** (2.77 g, 83%), m.p. 194°C. − IR

(KBr): ṽ = 3400 cm⁻¹, 3260, 1642, 1612. — UV (CHCl₃): λ_max (lgε) = 303 nm (4.216), 280 (4.219). — ¹H-NMR (CDCl₃): δ = 2.84 (t, J = 6 Hz, 2H, 7-H), 3.76 (t, J = 6 Hz, 2H, 6-H), 3.92 (s, 6H, 2 OCH₃), 6.53 (s, 1H, 1-H), 6.66 (s, 1-H, 11-H), 7.20 (s, 1H, 8-H), 7.50 (m, 5H, aromatic). — ¹³C-NMR (CDCl₃): δ = 28.46 (C-7), 46.51 (C-6), 56.07 (2 OCH₃), 103.46 (C-1), 107.47 (C-11), 110.28 (C-8), 120.34 (C-11a), 127.62 (C-7a), 127.80 (C-2',6'), 128.91 (C-3',5'), 130.11 (C-4'), 134.73 (C-1'), 142.60 (C-11b), 148.71 (C-9), 151.05 (C-10), 157.75 (C-4), 162.72 (C-2).

C₂₀H₁₉N₃O₂ (333.4) Calcd. C 72.05 H 5.74 N 12.60
Found C 72.00 H 5.68 N 12.69

Table 6. Atomic coordinates with e.s.d.'s in parentheses for 7e

	X	Y	Z
C1	0.6787(1)	0.4151(3)	0.9625(1)
N2	0.72735(9)	0.4415(2)	1.0559(1)
C3	0.7108(1)	0.4386(3)	1.1522(1)
C4	0.6593(1)	0.2888(3)	1.1495(1)
C4a	0.5970(1)	0.2967(3)	1.0513(1)
C5	0.5295(1)	0.2414(3)	1.0488(1)
C6	0.4723(1)	0.2489(3)	0.9588(1)
C7	0.4821(1)	0.3144(3)	0.8675(1)
C8	0.5489(1)	0.3660(3)	0.8698(1)
C8a	0.6072(1)	0.3569(3)	0.9609(1)
C11	0.6933(1)	0.4409(3)	0.8717(1)
C12	0.7552(1)	0.5229(3)	0.8615(1)
N13	0.7557(1)	0.5465(3)	0.7643(1)
N14	0.81001(9)	0.5669(2)	0.9454(1)
C15	0.8619(1)	0.6773(3)	0.9382(1)
O16	0.85742(9)	0.7820(2)	0.8660(1)
C17	0.9296(1)	0.6715(3)	1.0270(1)
C18	0.9863(1)	0.7725(4)	1.0219(1)
C19	1.0513(1)	0.7654(5)	1.0995(2)
C20	1.0602(1)	0.6586(4)	1.1837(2)
C21	1.0038(1)	0.5591(4)	1.1912(2)
C22	0.9388(1)	0.5659(3)	1.1133(1)
O23	0.40472(7)	0.1994(2)	0.9498(1)
C24	0.3928(1)	0.1433(3)	1.0433(1)
C25	0.3151(1)	0.1000(3)	1.0167(1)
O26	0.42265(7)	0.3230(2)	0.7826(1)
C27	0.4297(1)	0.4106(3)	0.6932(1)
C28	0.3569(1)	0.4174(4)	0.6133(2)

3,4,6,7-Tetrahydro-9,10-dimethoxy-4-phenyl-2H-pyrimido[6,1-a]-isoquinolin-2-imine (11)

a) A solution of 7a (3.51 g, 10 mmol) in ethanol (100 ml) was hydrogenated over 8% palladium/charcoal (0.2 g). The usual workup and crystallization from benzene gave 11 (3.1 g, 92%), m.p. 201°C.

b) Hydrogenation of 9a (3.33 g, 10 mmol) in dioxane (100 ml) as described under a) gave 11 (3.15 g, 94%). — IR (KBr): ṽ = 3385 cm⁻¹, 3270, 1658. — ¹H-NMR (CDCl₃): δ = 2.87 (m, 2H, 7-

H), 3.10 (m, 2H, 6-H), 3.88 (s, 6H, 2 OCH₃), 5.19 (s, 1H, 1-H), 5.78 (s, 1H, 4-H), 6.61 (s, 1H, 11-H), 7.07 (s, 1H, 8-H), 7.2—7.6 (m, 7H, NH₂ aromatic, phenyl). — ¹³C-NMR (CDCl₃): δ = 28.72 (C-7), 44.67 (C-6), 55.93 (OCH₃), 56.05 (OCH₃), 79.24 (C-4), 81.41 (C-1), 107.50 (C-11), 110.42 (C-8), 121.31 (C-11a), 126.83 (C-2',6'), 127.77 (C-4'), 128.41 (C-3',5'), 128.50 (C-7a), 142.48 (C-1), 147.84 (C-9), 149.36 (C-10), 150.59 (C-11b), 157.84 (C-2).

C₂₀H₂₁N₃O₂ (335.4) Calcd. C 71.62 H 6.31 N 12.53
Found C 71.50 H 6.24 N 12.70

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