Nitrogen Bridgehead Compounds. Part 30.[1] Vilsmeier–Haack Formylation of 6,7,8,9-Tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-ones †

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Depending on the substituents at C(3) and on the reaction conditions, Vilsmeier–Haack formylation (POCl$_3$–DMF) of 6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-ones (I) led to 9-(dimethylamino-methylene)- or 9-(ethoxymethylene)-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidines (II) and (IV), respectively, or 9-formyl-1,6,7,8-tetrahydro-4H-pyrido[1,2-a]pyrimidines (III). Compounds (II) may be converted into (III) or (IV). Owing to the enhanced activity of their 9-CH$_2$ group, the 3-carboxylic acid derivatives of (I) form compounds (II) even on the action of dimethylformamide diethyl acetal, and compounds (IV) on the action of triethyl orthoformate in Ac$_2$O. Compounds (III) may be converted back into (I) by hydrolysing the 9-formyl group. Their spectral data show that compounds (II) and (IV) exist exclusively in the E-configuration, and compounds (III) predominantly in the 1,6,7,8-tetrahydro-tautomeric form.

While investigating the reactivity of the reactive 9-CH$_2$ group of 6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidines towards electrophilic reagents,[2,3] we found [2] that ethyl 6,7,8,9-tetra-hydro-6-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxy-late (2) can be easily converted into the 9-dimethylamino-methylene derivative (31) on treatment with phosphoryl chloride (POCl$_3$)–dimethylformamide (DMF), and that compound (31) can, in turn, be transformed into the 9-formyl compound (60) upon acidic hydrolysis. The functional groups introduced in this way permit the synthesis of further derivatives of pyrido[1,2-a]pyrimidine which have valuable pharmacological properties.[4]

Following this single experiment with compound (2), we have investigated the applicability of this synthetic method to a number of 6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-ones (I) and have elucidated the structures of the products.

Results and Discussion.—Vilsmeier–Haack formylation (Scheme 1) was carried out by adding POCl$_3$ to a solution of a pyridopyrimidinone (I) in DMF at room temperature and then stirring the mixture at a temperature between 25—95 °C as specified in Table 1 [Route A(1)]. Sometimes the use of 1,2-dichloroethane as solvent was more advantageous [Route A(2)]. Reaction mixtures were then poured onto crushed ice. Work-up then gave the products summarized in Table 1.

If the compound (I) contained a strongly electron-with-drawing group at C(3), *i.e.* compounds (1)—(13), the cor-responding 9-dimethylaminomethylene derivative (II) (30)—(41) was obtained. From other 3-substituted substrates (19)—(29) the 9-formyl derivatives (III) (48)—(58) were formed as a result of hydrolysis upon work-up.

When C(3) was unsubstituted, Vilsmeier–Haack formyl-ation of compounds (14)—(17) at 60—95 °C yielded the 9-dimethylaminomethylene-3-formyl derivatives (42)—(45), *i.e.* the C(3) atom of the pyridopyrimidine ring was also attacked. Formylation of the 3-H compounds (17) and (18) under mild conditions, *i.e.* at 25 °C, resulted in the formation of the 9-formyl compounds unsubstituted at C(3) (46) and (47), indicating that formylation at C(9) preceded the reaction at

C(3). It is probably the amino-group of the 9-dimethyl-aminomethylene function of compounds (V) which activates the C(3) atom for further reaction (Scheme 2). This is sup-ported by the fact that the 9-(N-methyl-N-phenyl amino-methylene) derivative (78), prepared from the 9-formyl compound (46) with N-methylaniline, can be formylated at C(3) to afford the 3-formyl compound (79), whereas com-pound (80),[3b] containing an electron-withdrawing ethoxy-carbonyl group instead of the amino-function on the 9-methylene group, is recovered unchanged.

Of the tetrahydropyridopyrimidines (I) investigated, only the 9-methyl derivative (6) failed to react in the Vilsmeier–Haack formylation.

Formylation was sometimes accompanied by other re-actions. Thus, the 3-carboxyamides (9) and (10) gave the 3-nitriles (36) and (37). Under forcing conditions (95 °C) the amide nitrogen of the 3-(N-methylcarboxamide) (11) was also formylated and compound (39) was obtained. The 3-carbo-hydrazide (12) was transformed at 25 °C into the amidrazone (40) containing a dimethylaminomethylene moiety on the N(2) atom of the original hydrazido-group, whereas at 60 °C the hydrazide (12) gave the 3-carboxylic acid (41). It may be assumed that, under vigorous conditions, the N(1) atom of the hydrazido-group is attacked too and that the disubstituted hydrazido-group is cleaved by hydrolysis during the work-up. The 2-methoxy-derivative (16) was transformed into the 2-chloro-compound (44). Since heating compound (16) in neat POCl$_3$ does not effect the methoxy →chloro exchange, the methoxy-group is probably cleaved by the hydrogen chloride formed in the formylation reaction and the hydroxy-group is exchanged for chlorine by the excess of POCl$_3$. The 2-methyl derivative (14) decomposed with the formation of tar even at 60 °C and the 9-(dimethylaminomethylene)-3-formyl-2-methyl derivative (42) could only be isolated in low yield. Since the 2-methyl group of pyrido[1,2-a]pyrimidines is known to be reactive,[5] reaction at this position and formation of tar in the product may be assumed.

The 9-dimethylaminomethylene derivatives (30)—(45) can be hydrolysed to the corresponding 9-aldehydes with 0.5M hydrochloric acid (Route B).

When the formylation reaction mixture is treated with ethanol (Route C), irrespective of the nature of the substituent at C(3) the 9-ethoxymethylene derivatives (IV) are obtained.

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† Our initial paper on Vilsmeier–Haack formylations is reference 2.

Table 1. Products from Vilsmeier–Haack formylation of 6,7,8,9-tetrahydro-4-H-pyrido[1,2-a]pyrimidin-4-ones (I) and subsequent reactions (Scheme 1)

	Starting material					Reaction temp. (°C)	Product					Yield (%)	M.p. (°C)
Compound	R^1	R^2	R^3	R^4	Route		Compound	R^1	R^2	R^3	R^4		
(1)	H	H	H	CO_2Et	A-1	25	(30)	H	H	H	CO_2Et	65	151—152
(2)	6-Me	H	H	CO_2Et	A-1	25	(31)	6-Me	H	H	CO_2Et	76	136—137
(2)*	6-Me	H	H	CO_2Et	A-2	80	(31)*[a]	6-Me	H	H	CO_2Et	78	115—116
(3)	7-Me	H	H	CO_2Et	A-2	80	(32)	7-Me	H	H	CO_2Et	72	152—154
(4)	8-Me	H	H	CO_2Et	A-2	80	(33)	8-Me	H	H	CO_2Et	68	136—138
(5)	6-Me	8-Me	H	CO_2Et	A-2	80	(34)	6-Me	8-Me	H	CO_2Et	79	110
(6)	9-Me	H	H	CO_2Et	A-1	95					no reaction		
(7)	6-Me	H	H	CO_2Me	A-1	25	(35)	6-Me	H	H	CO_2Me	70	180
(8)	6-Me	H	H	CN	A-1	25	(36)	6-Me	H	H	CN	97	200—202
(9)	6-Me	H	H	$CONH_2$	A-1	25	(36)	6-Me	H	H	CN	98	200—202
(10)	6-Me	8-Me	H	$CONH_2$	A-1	25	(37)	6-Me	8-Me	H	CN	78	133—135
(11)	6-Me	H	H	CONHMe	A-1	15	(38)	6-Me	H	H	CONHMe	72	210—212
						95	(39)	6-Me	H	H	CON(CHO)Me	85	230—232
(12)	6-Me	H	H	$CONHNH_2$	A-1	25	(40)	6-Me	H	H	$CONHN=CHNMe_2$	68	177—178
						60	(41)	6-Me	H	H	CO_2H	45	206—208
(13)	6-Me	H	H	CO_2H	A-1	25	(41)	6-Me	H	H	CO_2H	59	206—208
(13)*	6-Me	H	H	CO_2H	A-1	25	(41)*[b]	6-Me	H	H	CO_2H	48	219
(14)	6-Me	H	Me	H	A-1	60	(42)	6-Me	H	Me	CHO	36	176—177
(15)	6-Me	H	Ph	H	A-1	60	(43)	6-Me	H	Ph	CHO	89	205
(16)	H	H	OMe	H	A-1	95	(44)	H	H	Cl	CHO	73	215—217
(17)	6-Me	H	H	H	A-1	95	(45)	6-Me	H	H	CHO	70	178—179
						25	(46)	6-Me	H	H	H	73	133
(17)*	6-Me	H	H	H	A-1	25	(46)*[c]	6-Me	H	H	H	40	102—104
(18)	6-Me	H	Pi	H	A-1	25	(47)	6-Me	H	Pi	H	43	206—207
(19)	6-Me	H	H	Me	A-1	60	(48)	6-Me	H	H	Me	81	130—131
(20)	H	H	H	CH_2CO_2Et	A-1	60	(49)	H	H	H	CH_2CO_2Et	72	162—164
(21)	6-Me	H	H	CH_2CO_2Et	A-1	60	(50)	6-Me	H	H	CH_2CO_2Et	88	109
(22)	7-Me	H	H	CH_2CO_2Et	A-1	60	(51)	7-Me	H	H	CH_2CO_2Et	85	144—145
(23)	8-Me	H	H	CH_2CO_2Et	A-1	60	(52)	8-Me	H	H	CH_2CO_2Et	71	102—103
(24)	6-Me	H	H	Ph	A-1	60	(53)	6-Me	H	H	Ph	86	106—107
(25)	H	H	H	$C_6H_3(NO_2)_2$-2,4	A-1	60	(54)	H	H	H	$C_6H_3(NO_2)_2$-2,4	84	264—266
(26)	6-Me	H	Me	Et	A-1	60	(55)	6-Me	H	Me	Et	73	114—116
(27)	7-CO_2Et	H	H	Ph	A-1	60	(56)	7-CO_2Et	H	H	Ph	61	146
(28)	6-Me	H	H	$[CH_2]_2CO_2Et$	A-1	60	(57)	6-Me	H	H	$[CH_2]_2CO_2Et$	79	112
(29)	6-Me	H	Me	CH_2Ph	A-1	95	(58)	6-Me	H	Me	CH_2Ph	70	oil
(30)	H	H	H	CO_2Et	B	25	(59)	H	H	H	CO_2Et	83	160—161
(31)	6-Me	H	H	CO_2Et	B	50	(60)	6-Me	H	H	CO_2Et	83	135—136
(31)*	6-Me	H	H	CO_2Et	B	50	(60)*[d]	6-Me	H	H	CO_2Et	65	93—94
(32)	7-Me	H	H	CO_2Et	B	50	(61)	7-Me	H	H	CO_2Et	85	122
(33)	8-Me	H	H	CO_2Et	B	50	(62)	8-Me	H	H	CO_2Et	86	133
(34)	6-Me	8-Me	H	CO_2Et	B	50	(63)	6-Me	8-Me	H	CO_2Et	92	135

No.	6	8	X	R	Route		No.	6	8	X	R	Yield (%)	M.p. (°C)
(35)	6-Me	H	H	CO$_2$Me	B	50	(64)	6-Me	H	H	CO$_2$Me	74	155
(36)	6-Me	H	H	CN	B	50	(65)	6-Me	H	H	CN	96	192—193
(37)	6-Me	8-Me	H	CN	B	50	(66)	6-Me	8-Me	H	CN	94	139—140
(38)	6-Me	H	H	CONHMe	B	50	(67)	6-Me	H	H	CONHMe	98	215—216
(41)*	6-Me	H	H	CO$_2$H	B	50	(68)	6-Me	H	H	CO$_2$H	94	185—186
(41)*	6-Me	H	H	CO$_2$H	B	50	(68)*^{e}	6-Me	H	H	CO$_2$H	71	168—170
(42)	6-Me	H	Me	CHO	B	50	(69)	6-Me	H	Me	CHO	85	134—135
(43)	6-Me	H	Ph	CHO	B	50	(70)	6-Me	H	Ph	CHO	98	161—163
(44)	H	H	Cl	CHO	B	50	(71)	H	H	Cl	CHO	92	231—233
(45)	6-Me	H	H	CHO	B	50	(72)	6-Me	H	H	CHO	97	183
(2)	6-Me	H	H	CO$_2$Et	C	50	(73)	6-Me	H	H	CO$_2$Et	55	114—116
(8)	6-Me	H	H	CN	C	50	(74)	6-Me	H	H	CN	74	166—167
(19)	6-Me	H	H	Me	C	60	(75)	6-Me	H	H	Me	64	100—102
(21)	6-Me	H	H	CH$_2$CO$_2$Et	C	60	(76)	6-Me	H	H	CH$_2$CO$_2$Et	72	oil
(24)	6-Me	H	H	Ph	C	60	(77)	6-Me	H	H	Ph	87	118
(31)	6-Me	H	H	CO$_2$Et	D	80	(73)	6-Me	H	H	CO$_2$Et	62	114—116
(36)	6-Me	H	H	CN	D	80	(74)	6-Me	H	H	CN	53	166—167
(73)	6-Me	H	H	CO$_2$Et	E	25	(60)	6-Me	H	H	CO$_2$Et	78	135—136
(74)	6-Me	H	H	CN	E	25†	(65)	6-Me	H	H	CN	85	192—193
(77)	6-Me	H	H	Ph	E	60	(53)	6-Me	H	H	Ph	72	106—107
(2)	6-Me	H	H	CO$_2$Et	F	80	(31)	6-Me	H	H	CO$_2$Et	58	136—137
(8)	6-Me	H	H	CN	F	80	(36)	6-Me	H	H	CN	68	200—202
(11)	6-Me	H	H	CONHMe	F	80	(38)	6-Me	H	H	CONHMe	65	210—212
(2)	6-Me	H	H	CO$_2$Et	G	140	(73)	6-Me	H	H	CO$_2$Et	58	114—116
(8)	6-Me	H	H	CN	G	140	(74)	6-Me	H	H	CN	74	166—167

* Optically active compound, having 6S absolute configuration (see reference 11). ^{a} $[\alpha]_D^{20}$ −345° (c, 2 in MeOH). ^{b} $[\alpha]_D^{20}$ −497° (c, 1 in MeOH). ^{c} $[\alpha]_D^{20}$ +25° (c, 2 in MeOH). ^{d} $[\alpha]_D^{20}$ +39 (c, 2 in MeOH). ^{e} $[\alpha]_D^{20}$ +5° (c, 1 in MeOH). † See, however, Experimental section, Route E. Pi = N-piperidyl.
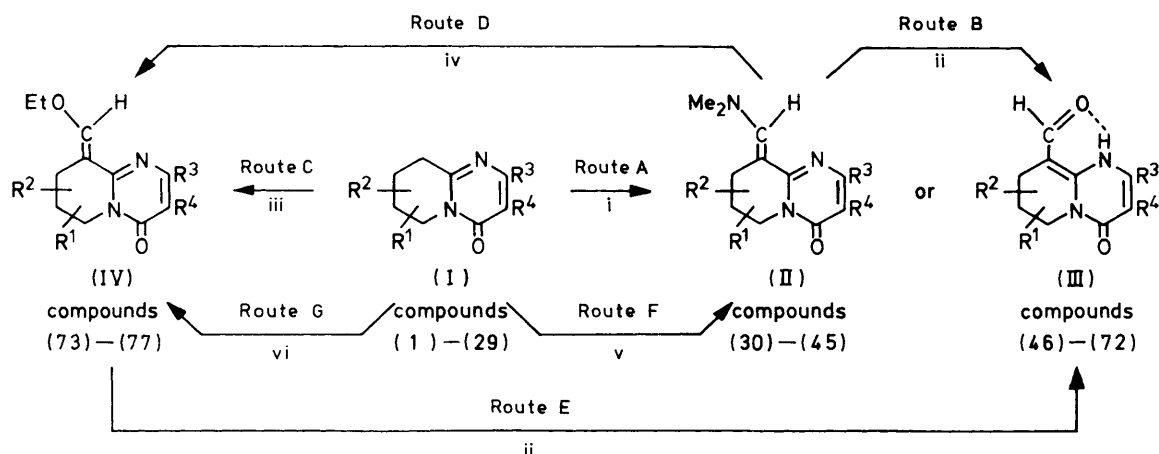
Scheme 1. *Reagents*: i, POCl₃-DMF, then H₂O; ii, H₃O⁺; iii, POCl₃-DMF, then EtOH; iv, EtOH-HCl; v, Me₂NCH(OEt)₂; vi, HC(OEt)₃-Ac₂O. Substituents R¹—R⁴ are given in Table 1
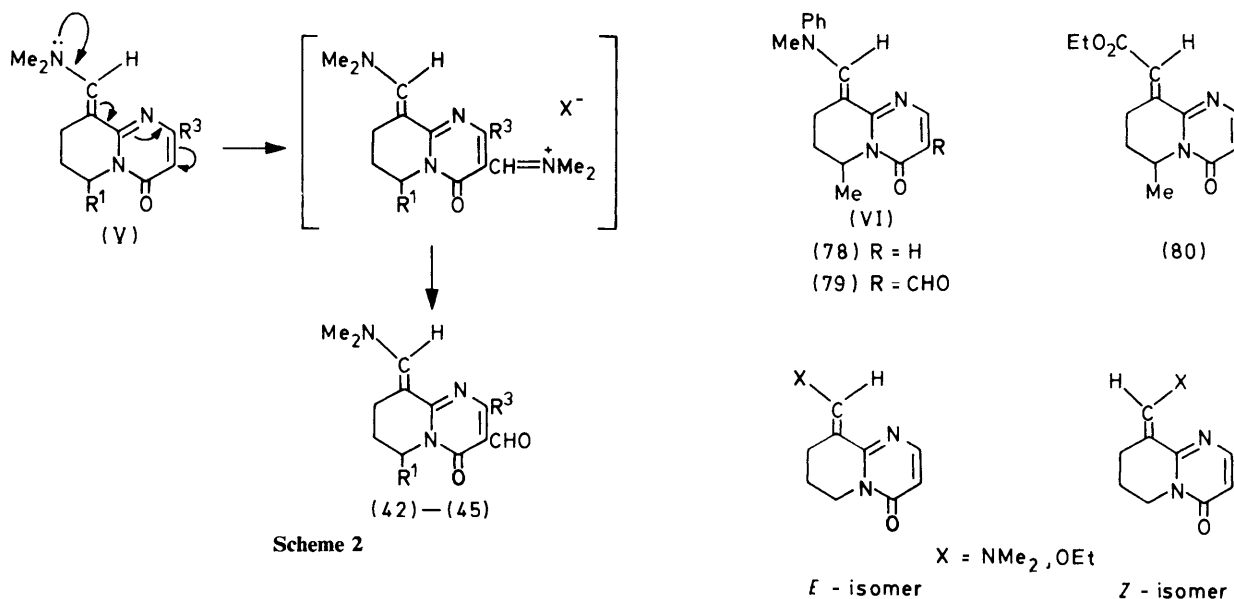
Scheme 2

Compounds (IV) can also be prepared by treating the 9-dimethylaminomethylene compounds (II) with ethanolic hydrogen chloride (Route D). The 9-ethoxymethylene derivatives (IV) can then be hydrolysed to the corresponding aldehydes (III) with 0.5M hydrochloric acid (Route E). Compounds (73) and (74) which contain an electron-withdrawing group at C(3) can be hydrolysed even at 25 °C. Hydrolysis of other compounds (IV), *e.g.* (77), requires more vigorous conditions.

Introduction of the 9-dimethylaminomethylene or 9-ethoxymethylene group into the 3-carboxylic acid derivatives of compounds (I) can also be effected with *NN*-dimethylformamide diethyl acetal in benzene (Route F) or ethyl orthoformate in acetic anhydride (Route G), respectively. Other substrates of type (I) remained unchanged under such conditions. By the addition of a Lewis acid, *e.g.* zinc chloride, to a reaction mixture of the 3-phenyl derivative (24) and ethyl orthoformate in acetic anhydride, traces of the 9-ethoxymethylene compound (77) could be detected by t.l.c.

As reported earlier, the 9-formyl group of the 3-carboxylic ester derivative (60) could be removed by stirring the compound in 5% aqueous hydrochloric acid or 5% aqueous sodium hydroxide at room temperature. Thus, the parent compound (2) or, under alkaline conditions the corresponding acid (13),

was recovered. Similarly, other compounds (III) containing an electron-withdrawing group at position 3 could also be deformylated to give the parent compounds (I) by acidic or alkaline hydrolysis. With other 9-formyl derivatives this was only feasible under alkaline conditions.

Structures of the Products.—Both the 9-dimethylaminomethylene (II) and the 9-ethoxymethylene derivatives (IV) may form *E*—*Z* pairs. In the *E*-isomers the dimethylamino- or the ethoxy-group is situated at a greater distance from the ring system, and these isomers are therefore favoured on energetic grounds. T.l.c. and ¹H n.m.r. spectroscopy in CDCl₃ and (CD₃)₂SO demonstrated that compounds (II) and (IV) consist of only one stereoisomer. Configurational assignment was possible on the basis of the signal of the 9-methylene proton. The methylene proton signal of the *E*-isomer is expected to appear at lower field, due to the anisotropic effect of the C(9a)=N(1) double bond. In the spectrum of the 9-(phenylaminomethylene)-6,7,8,9-tetrahydro-4*H*-pyrido-[1,2-*a*]pyrimidin-4-ones, which exist as *E*—*Z* isomeric mixtures, the methylene proton signal appears in the range δ 7.05—7.45 for the *Z*-isomers and δ 8.05—8.90 for the *E*-
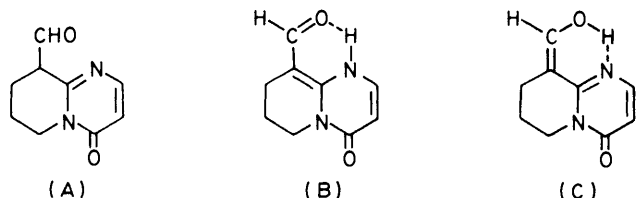
Figure 1. Tautomers of the 9-formyl compounds (III). (A) 9-formyl-6,7,8,9-tetrahydro-form; (B) 9-formyl-1,6,7,8-tetrahydro-form; (C) 9-hydroxymethylene-6,7,8,9-tetrahydro-form

isomers.[6] For the 9-dimethylaminomethylene derivatives (II) the methylene proton signal lies in the range δ 8.26—8.50 and, for the 9-ethoxymethylene derivatives (IV), at between δ 7.79—8.21, which indicates the presence of the E-isomers in both cases. In both compounds (II) and (IV) a long-range coupling was observed between the 9-methylene and the 8-H protons (^4J ca. 0.5—1.5 Hz).

For the formyl compounds (III) three tautomeric forms were considered: the 9-formyl-6,7,8,9-tetrahydro- (A), the 9-formyl-1,6,7,8-tetrahydro- (B), and the 9-hydroxymethylene-6,7,8,9-tetrahydro-tautomers (C) (Figure 1). Chelate formation is possible in the (B) form and in the Z-stereoisomer of the (C) form as shown. To decide which of the possible structures was present, u.v., i.r., and ^1H n.m.r. spectra were studied. If compounds (III) were present in the 9-formyl-6,7,8,9-tetrahydro form (A), their u.v. spectra should be very similar to those of the parent compounds (I), since the formyl group of these structures is not in conjugation. As the highest-wavelength maximum of the products displayed a bathochromic shift of more than 50 nm and also a hyperchromic effect when compared with the parent compounds (I), structure (A) could be ruled out as the predominant form. The u.v. spectral data on some 3-substituted 6,7,8,9-tetrahydro-6-methylpyrido[1,2-a]pyrimidines (I) and those of the corresponding formyl derivatives (III) are presented in Table 2. The i.r. spectra (KBr discs) of the derivatives (III) exhibited a strong or very strong band in the range 1 605—1 630 cm⁻¹. This was attributed to the stretching vibration of a conjugated and chelate-bonded carbonyl group, suggesting the presence of the 9-formyl-1,6,7,8-tetrahydro-tautomer (B) in the solid phase. As expected from literature data,[7] the stretching band of the 4-carbonyl group appeared in the range 1 640—1 700 cm⁻¹.

The presence of the (B) tautomer in compound (46) was confirmed by X-ray analysis. The molecular diagram, bond lengths, and selected bond angles are given in Figure 2. Final fractional co-ordinates are listed in Table 3 and torsion angles are listed in Table 4. The N(1)–H atom is involved in intramolecular bonding with the formyl oxygen: N(1) ... O 2.63 Å, H(1) ... O 1.76 Å, N(1)–H(1) ... O 140°. In compound (46) the formyl group and the 1,6,7,8-tetrahydro-4H-pyrido[1,2-a]pyrimidinone ring constitute a delocalized system, where bonds are less localized than in the 1,6,7,8,-tetrahydro-1,6-dimethyl-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxylic acid.[8] The pyrimidine ring is practically planar, while the piperidine ring assumes a ^7E envelope conformation.

According to ^1H n.m.r. spectroscopy the 9-formyl-1,6,7,8-tetrahydro-form (B) of compound (46) is predominant in solution too. The relatively low chemical shift of δ 8.61—9.18 for the 'formyl' proton, however, indicates that the 9-(hydroxymethylene)-6,7,8,9-tetrahydro-tautomer (C) must also be present as a minor component and that the signal observed is the time-averaged signal of a proton in fast prototropic equilibrium between forms (B) and (C). The formyl proton of compound (46) appears at δ 8.67 in a wide
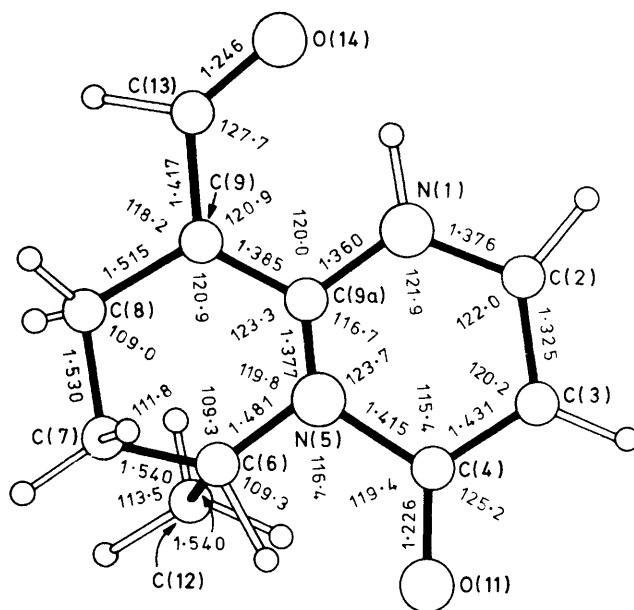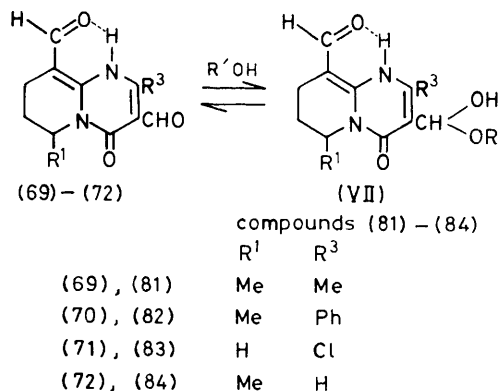

Figure 2. Molecular diagram for compound (46) with crystallographic atomic numbering, bond lengths (Å), and selected angles (°) for the non-hydrogen atoms. The C(3), N(5), and C(9a) atoms are in the plane of the drawing. E.s.d.s are in the range ≤0.008 Å and ≤0.5° for bond lengths and bond angles, respectively.

Scheme 3

variety of solvents [CD₃OD, (CD₃)₂CO, CDCl₃, (CD₃)₂SO], suggesting that the ratio of the tautomers (B) and (C) is not significantly dependent on the solvent. The chemical shift of the NH proton (δ >14.0) points to the presence of strong chelate bonding. There is long-range coupling (^5J ca. 0.5—1.6 Hz) between the protons of the NH and the CHO groups.

In alcoholic solution the 3,9-diformyl derivatives (69), (70), (71) and (72) form an equilibrium mixture with the 9-formyl 3-acetals (81)—(84) (Scheme 3). The transformation of the 3-formyl group of compound (72) in CD₃OD solution at 50 °C was followed by ^1H n.m.r. spectroscopy. The intensities of the signals of the 3-formyl proton at δ 9.81 and of the 2-H proton at δ 7.98 decreased, while two new signals appeared at δ 5.37 (acetal proton) and δ 7.53 [2-H proton of (84)] until the equilibrium ratio 12 : 88 was reached. The reaction rate was approximately 1×10^{-4} s⁻¹.

Experimental

M.p.s are uncorrected. Yields were not optimized. I.r. spectra were recorded in KBr pellets with a Zeiss US-20

Table 2. U.v. data on some pyrido[1,2-a]pyrimidin-4-ones (I) and (III) in EtOH

Compound	R⁴	6,7,8,9-Tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-ones (I) $\lambda_{max.}$ (log ε)		Compound	R⁴	9-Formyl-1,6,7,8-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-ones (III) $\lambda_{max.}$ (log ε)		
(17)	H		278 (3.70)	(46)	H	340 (4.31)	250i (3.44)	224 (4.02)
(19)	Me		278 (3.98)	(48)	Me	341 (4.31)		227 (3.98)
(21)	CH₂CO₂Et		280 (3.75)	(50)	CH₂CO₂Et	342 (4.36)	248i (3.41)	226 (3.97)
(13)	CO₂H		300 (3.90)	(68)	CO₂H	357 (4.20)	317i (3.89)	271 (3.36)	222 (4.09)
(2)	CO₂Et		301 (3.96)	(60)	CO₂Et	358 (4.34)	315i (3.86)	265 (3.49)	223 (4.20)
(24)	Ph	245 (3.73)	302 (4.00)	(53)	Ph	358 (4.42)	266i (3.85)	236 (4.07)
(8)	CN		307 (3.90)	(65)	CN	358 (4.38)	320i (3.96)	267 (3.51)	227 (4.09)
				(72)	CHO	373 (4.25)	321i (3.84)	245i (3.60)

The (I) $\lambda_{max.}$ values 227 (3.84), 231 (3.93), 229 (3.70), 230 (3.74), 230 (3.81), 223 (3.72), 231 (3.67) correspond to compounds (17), (19), (21), (13), (2), (24), (8) respectively.

i = inflection.

Table 3. Final fractional co-ordinates ($\times 10^4$) for atoms of compound (46) (estimated standard deviations in parentheses)

	x	y	z
N(1)	−2 662(8)	1 316(6)	1 092(3)
C(2)	−4 180(10)	2 721(7)	748(3)
C(3)	−5 750(10)	3 713(8)	1 290(3)
C(4)	−5 913(10)	3 340(7)	2 264(3)
N(5)	−4 330(7)	1 867(5)	2 576(2)
C(6)	−4 360(11)	1 536(8)	3 601(4)
C(7)	−3 899(12)	−747(9)	3 646(4)
C(8)	−1 362(12)	−1 280(9)	3 293(4)
C(9)	−1 295(11)	−685(8)	2 290(4)
C(9a)	−2 728(9)	830(7)	2 000(3)
O(11)	−7 258(7)	4 210(5)	2 831(2)
C(12)	−2 362(12)	3 190(9)	4 321(4)
C(13)	199(12)	−1 803(10)	1 642(4)
O(14)	568(8)	−1 506(7)	809(3)
H(1)	−1 437(8)	494(6)	701(3)
H(2)	−3 868(10)	2 733(7)	−3(3)
H(3)	−7 100(10)	4 568(8)	913(3)
H(6)	−6 383(11)	1 963(8)	3 742(4)
H(71)	−5 482(12)	−1 864(9)	3 219(4)
H(72)	−3 782(12)	−820(9)	4 421(4)
H(81)	215(12)	−530(9)	3 870(4)
H(82)	−1 320(11)	−2 961(9)	3 156(4)
H(121)	−397(12)	3 186(9)	4 173(4)
H(122)	−2 433(12)	2 959(9)	5 067(4)
H(123)	−3 022(12)	4 681(9)	4 241(4)
H(13)	794(12)	−3 080(10)	1 982(4)

Table 4 Selected torsion angles (°) for compound (46)

C(3)–C(4)–N(5)–C(6)	177		N(5)–C(6)–C(7)–C(8)	57
C(3)–C(4)–N(5)–C(9a)	0		C(12)–C(6)–C(7)–C(8)	−65
O(11)–C(4)–N(5)–C(6)	−2		C(6)–C(7)–C(8)–C(9)	−52
O(11)–C(4)–N(5)–C(9a)	−179		C(7)–C(8)–C(9)–C(9a)	24
C(4)–N(5)–C(6)–C(7)	149		C(7)–C(8)–C(9)–C(13)	−153
C(4)–N(5)–C(6)–C(12)	−86		C(8)–C(9)–C(9a)–N(1)	180
C(9a)–N(5)–C(6)–C(7)	−34		C(8)–C(9)–C(9a)–N(5)	−2
C(9a)–N(5)–C(6)–C(12)	91		C(13)–C(9)–C(9a)–N(1)	−2
C(4)–N(5)–C(9a)–N(1)	1		C(13)–C(9)–C(9a)–N(5)	176
C(4)–N(5)–C(9a)–C(9)	−176		C(8)–C(9)–C(13)–O(14)	−177
C(6)–N(5)–C(9a)–N(1)	−176		C(9a)–C(9)–C(13)–O(14)	5
C(6)–N(5)–C(9a)–C(9)	7			

Compound (7). The pyridopyrimidine-3-carboxylic acid (13) (0.05 mol) was dissolved in methanol (100 ml) and the solution was saturated with HCl gas at 0 °C. After 24 h the solution was evaporated to dryness. The residue was dissolved in water and the aqueous solution was neutralized with 10% aqueous Na_2CO_3 and extracted with $CHCl_3$ (3 × 10 ml). The combined extracts were dried (Na_2SO_4) and evaporated to dryness. The residue (8.3 g, 75%) was crystallized from ethyl acetate to give the *ester* (7), m.p. 117—119 °C.

Compound (10). The ethyl ester (5) (10 mmol) was dissolved in concentrated NH_4OH (10 ml). After 24 h the crystals that had formed were filtered off (1.8 g, 81%) and were recrystallized from ethanol to give the *amide* (10), m.p. 203 °C.

Compound (11). Methylamine hydrochloride (100 g), K_2CO_3 (40 g), and 20% aqueous Na_2CO_3 (50 ml) were added to a solution of the ester (2) (10 g) in water (200 ml). The mixture was kept at ambient temperature for a week and was then extracted with $CHCl_3$ (3 × 100 ml). The combined extracts were dried (Na_2SO_4) and evaporated, and the residue (6.35 g, 68%) was crystallized from ethyl acetate to give the N-*methylamide* (11), m.p. 117—119 °C.

Compound (12). A mixture of the ester (2) (10 mmol) and hydrazine hydrate (11 mmol) was refluxed in ethanol (5.0 ml) during 3 h. After the mixture had cooled the precipitated *hydrazide* (12) was filtered off (1.84 g, 83%) and was crystallized from ethanol, m.p. 145 °C.

Compound (25). To a cooled solution of 6,7,8,9-tetrahydro-

spectrophotometer; u.v. spectra in ethanolic solutions with a UNICAM SP-800 spectrophotometer; and ^{1}H n.m.r. spectra in $CDCl^3$ solutions (SiMe$_4$ as internal standard) with a JEOL FX-100 spectrometer. Analytical results on the new compounds agreed with calculated data; details given in the Supplementary Publication SUP No. 23465 (9 pp.).*

Starting Materials.—These were prepared by known methods,[3a,9—14] except for compounds (3)—(6), (14)—(16), (18), and (29), which were prepared from the appropriate unsaturated 4-oxo-4H-pyrido[1,2-a]pyrimidines[9,15—17] (10 mmol) by hydrogenation at 1 atm pressure over 10% Pd–C (0.3 g) in ethanol (20 ml). After absorption of hydrogen (2 mol equiv.) the reaction mixtures were worked up to give, respectively, the 6,7,8,9-*tetrahydro*-4H-*pyrido*[1,2-a]*pyrimidin-4-ones* (3), m.p. 88—90 °C, yield 78%; (4), m.p. 68—72 °C (70%); (5), oil (86%); (6), m.p. 38 °C (85%); (14), m.p. 40—42 °C (81%); (15), m.p. 105—106 °C (74%); (16), m.p. 94 °C (94%); (18), m.p. 123—124 °C (87%); and (29), m.p. 86—88 °C (86%).

3-phenyl-4H-pyrido[1,2-a]pyrimidin-4-one[3a] (10 mmol) in 98% H_2SO_4 (4 ml) was added, dropwise, aqueous HNO_2 (d 1.4; 3 ml) at 10—15 °C. The mixture was stirred at 25 °C during 1 h and at 40 °C during 1 h, and was then poured onto crushed ice (100 g) and the pH of the aqueous phase was adjusted to 3—4 with 20% aqueous Na_2CO_3. The precipitated *dinitro-compound* (25) was filtered off (3.0 g, 95%) and was recrystallized from ethanol, m.p. 205—208 °C.

Syntheses of the 9-*Substituted Pyrido*[1,2-a]*pyrimidin-4-ones* (II)—(IV).—*Route* A(1). To a cooled solution of the pyridopyrimidine (I) (10 mmol) in DMF (100 mmol) was added, dropwise, $POCl_3$ (20 mmol), at 15—20 °C and the mixture was then stirred during 2 h at the temperature indicated in Table 1. After the mixture had cooled it was poured onto crushed ice (30 g) and the pH of the aqueous phase was adjusted to 7 with 20% aqueous Na_2CO_3 at 0—5 °C. The mixture was kept at 25 °C for 2 h, after which time the precipitated product [(II) or (III)] was filtered off and recrystallized from ethanol (yields and m.p.s given in Table 1). For the preparations of compounds (36) from (9), (40) and (41) from (12), and (42)—(45) from (14)—(17), respectively, $POCl_3$ (30 mmol) was used; for the preparations of compound (46) and (47), $POCl_3$ (10 mmol) was used and the neutral, aqueous

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* For details of the Supplementary Publications scheme, see Notice to Authors No. 7, *J. Chem. Soc., Perkin Trans.* 1, 1981, Index issue.

mixture was kept at ambient temperature for 24 h before filtration. Compound (43) was recrystallized from ethyl acetate, (46) * from diethyl ether, and (54) from acetonitrile, and compound (58) was purified by column chromatography on silica gel with gradient elution using benzene–methanol. Thus prepared were, e.g. compound (45), $\lambda_{max.}$ 417 (log ε 4.69), 308 (3.54), and 262 nm (3.83); $\nu_{max.}$ 1 672 cm^{-1} (CHO and CO); δ 1.25 (3 H, d, 6-Me), 1.59—2.00 (2 H, m, 7-H$_2$), 2.61—3.10 (2 H, m, 8-H$_2$), 3.29 (6 H, s, NMe$_2$), 5.04—5.48 (1 H, m, 6-H$_{eq}$), 8.38 (1 H, s, 2-H), 8.50 [1 H, t, ^4J ca. 1.2 Hz, C(9)=CH], and 10.22 (1 H, s, CHO); compound (46), $\lambda_{max.}$— see Table 2; $\nu_{max.}$ 1 685 [C(4)O] and 1 615 cm^{-1} (CHO); δ 1.25 (3 H, d, 6-Me), 1.50—2.20 (2 H, m, 7-H$_2$), 2.44—2.78 (2 H, m, 8-H$_2$), 4.78—5.19 (1 H, m, 6-H$_{eq}$), 5.77 (1 H, dd, $^3J_{2,3}$ ca. 7.8, $^4J_{1,3}$ ca. 1.6 Hz, 3-H), 7.23 (1 H, dd, $^3J_{1,2}$ ca. 4.8, $^3J_{2,3}$ ca. 7.8 Hz, 2-H), 8.67 (1 H, d, $^5J_{1,CHO}$ ca. 1.6 Hz, CHO), and 14.22br (1 H, NH).

Route A(2). To a stirred solution of the pyridopyrimidine (I) (10 mmol) in 1,2-dichloroethane (20 ml) was added a mixture of DMF (20 mmol) and POCl$_3$ (20 mmol) at ambient temperature during 0.5 h and the mixture was then refluxed for 0.5 h. After the mixture had cooled it was poured onto crushed ice (20 g) and the pH of the aqueous phase was adjusted to 7 with 20% aqueous Na$_2$CO$_3$ at 0—5 °C. The aqueous phase was then extracted with 1,2-dichloroethane (2 × 10 ml). The combined extracts were dried (Na$_2$SO$_4$) and evaporated to dryness to obtain compounds (II) (yields and m.p.s given in Table 1). The products were crystallized from ethanol–diethyl ether [(31) * from ethyl acetate].

Route B. A solution of the 9-dimethylaminomethylene compound (II) (5 mmol) in 5% aqueous hydrochloric acid was stirred during 2 h at 25 °C and then during 1 h at 50 °C. After the mixture had cooled the precipitated 9-formyl derivative (III) (yields and m.p.s given in Table 1) was filtered off, washed with water, and crystallized from ethanol [(60) *, (63) from diethyl ether, (69)—(72) from ethyl acetate]. Thus prepared were, e.g. compound (72), $\lambda_{max.}$—see Table 2; $\nu_{max.}$ 1 740 and 1 710 (3-CHO, frequency coupling [7]), 1 645 [C(4)=O], and 1 610 cm^{-1} (9-CHO); δ 1.31 (3 H, d, 6-Me), 1.60—2.20 (2 H, m, 7-H$_2$), 2.55—2.75 (2 H, m, 8-H$_2$), 4.92—5.33 (1 H, m, 6-H$_{eq}$), 7.98 (1 H, d, $^3J_{1,2}$ ca. 5.5 Hz, 2-H), 8.89 [1 H, d, $^5J_{1,C(9)-CHO}$ ca. 0.9 Hz, 9-CHO)], 9.81 (1 H, s, 3-CHO), and 14.05br (1 H, NH).

Route C. To a cooled solution of the pyridopyrimidine (I) (10 mmol) in DMF (100 ml) was added POCl$_3$ (20 mmol) dropwise at 15—20 °C. The mixture was stirred during 2 h at the temperature indicated in Table 1 and was then treated with ethanol (20 ml) and refluxed during 1 h. After the mixture had been cooled to 5 °C it was poured onto crushed ice (50 g) and the pH of the aqueous phase was adjusted to 7 by the addition of 20% aqueous Na$_2$CO$_3$ solution to the mixture. The precipitated 9-ethoxymethylene derivative (IV) (yields and m.p.s given in Table 1) was filtered off and was recrystallized from ethanol [(73) from diethyl ether]. Compound (76) was purified as for compound (58) [see Route A(1)]. Thus, compound (73) had $\lambda_{max.}$ 350 (log ε 4.38) and 273 nm (4.02); $\nu_{max.}$ 1 700 cm^{-1} (2 × C=O); δ 1.12—1.61 (total 9 H, d, t, and t, 6-Me, CO$_2$CH$_2$Me, and CHOCH$_2$Me, respectively), 1.68—2.20 (2 H, m, 7-H$_2$), 2.37—2.78 (2 H, m, 8-H$_2$), 4.28 and 4.42 (total 4 H, 2 × q, 2 × COCH$_2$), 5.16—5.51 (1 H, m, 6-H$_{eq}$), 8.17 [1 H, t, ^4J ca. 1.5 Hz, C(9)=CH], and 8.65 (1 H, s, 2-H).

Route D. The 9-dimethylaminomethylene derivative (II) (5 mmol) was heated under reflux during 0.5 h in ethanol (15 ml) containing 10% HCl. After being cooled to 5 °C the mixture was worked up as described under Route C.

Route E. The 9-ethoxymethylene derivative (IV) (3 mmol) was stirred in 0.5M aqueous HCl (6 ml) at 25 °C during 1 h and the mixture was then neutralized with 20% aqueous Na$_2$CO$_3$. The precipitated 9-formyl derivative (III) (yields and m.p.s given in Table 1) was filtered off and was crystallized from ethanol. The hydrolysis of compound (74) was carried out at 60 °C during 5 h.

Route F. A mixture of the pyridopyrimidinone (I) (10 mmol) and NN-dimethylformamide diethyl acetal (11 mmol) was heated under reflux in benzene (20 ml) during 3 h, the solution was then evaporated to dryness, and the residue was crystallized from ethanol to afford the corresponding enamine (II) (data given in Table 1).

Route G. A mixture of the pyridopyrimidinone (I) (5 mmol) and triethyl orthoformate (30 mmol) was heated under reflux in acetic anhydride (20 ml) during 20 h. After removal of the solvent under reduced pressure (0.5 mmHg) the residue was treated with ethanol (5 ml) and the crystalline product was filtered off to afford the corresponding ether (IV). In the preparation of compound (73) the ethanolic solution was diluted with water (15 ml) before filtration.

6,7,8,9-*Tetrahydro-6-methyl-9-*(N-*methyl-*N-*phenylamino-methylene)-4H-pyrido*[1,2-a]*pyrimidin-4-one* (78).—A mixture of the 9-formylpyridopyrimidinone (46) (10 mmol) and N-methylaniline (10 mmol) was refluxed in ethanol (20 ml) during 3 h. After removal of the solvent the residue was crystallized from acetone to give the enamine (78) (1.9 g, 68%), m.p. 153—154 °C.

6,7,8,9-*Tetrahydro-6-methyl-9-*(N-*methyl-*N-*phenylamino-methylene)-4-oxo-4H-pyrido*[1,2-a]*pyrimidine-3-carbaldehyde* (79).—To a cooled solution of the pyridopyrimidinone (78) (5 mmol) in DMF (50 mmol) was added, dropwise, POCl$_3$ (10 mmol) at 15—20 °C. The mixture was stirred at ambient temperature during 1 h and at 100 °C during 1 h. After being cooled the mixture was poured onto crushed ice (15 g) and the pH of the aqueous phase was adjusted to 7 with 20% aqueous Na$_2$CO$_3$, the temperature being kept between 0—5 °C. The precipitated aldehyde (79) (0.9 g, 58%) was filtered off and was crystallized from ethanol, m.p. 260—261 °C.

Hydrolysis of the 9-Formyl Compounds (III).—(a) *In 5% aqueous hydrochloric acid.* The 9-formyl compound (III) (5 mmol) was stirred in 5% aqueous HCl (15 ml) during 24 h. The mixture was then decolourized with charcoal and the pH of the clear filtrate was adjusted to 7 with 20% aqueous Na$_2$CO$_3$. The neutralized solution was extracted with CHCl$_3$ (3 × 20 ml). The combined extracts were dried (Na$_2$SO$_4$) and evaporated to dryness to give the corresponding 6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one (I) in 65—85% yield.

(b) *In 5% aqueous sodium hydroxide.* The 9-formyl compound (III) (5 mmol) was stirred in 5% aqueous NaOH (20 ml) at ambient temperature during 24 h. The pH of the mixture was then adjusted to 7 with 1 : 1 aqueous HCl. The neutralized solution was extracted with CHCl$_3$ (3 × 20 ml). The combined extracts were dried (Na$_2$SO$_4$) and evaporated to dryness to give the corresponding 6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one (I) in 70—90% yield. However, from the esters (49)—(52) and (57)—(64), the corresponding carboxylic acids (I; R^4 = CO$_2$H) were also obtained.

X-*Ray Crystal Structure of Compound* (46).—Crystal data for (46): C$_{10}$H$_{12}$N$_2$O$_2$, M = 192.20. Monoclinic, a = 5.256(1), b = 6.513(2), c = 13.895(3) Å; α = 100.60(2), β = 97.87(2), γ = 95.31(2)°; U = 459.7 Å^3; D$_c$ = 1.39 g cm^{-3}; F(000) =

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* Asterisk indicates optically active (6S) compound.

204. Cu-K_α radiation, $\lambda = 1.5418$ Å, $\mu = 7.17$ cm^{-1}; space group $P\bar{1}$, $Z = 2$.

Data were collected on a SYNTEX P2$_1$ diffractometer with monochromated Cu-K_α radiation up to $\theta = 58°$. 723 of the observed 1 232 reflections were considered to be suitable, having $F > 2.5\sigma(F)$.

Data were corrected for Lorentz and polarization effects. Elucidation of the structure with MULTAN-74 [18] involved difficulties. Since an E-map calculated with 180 E-values revealed the molecule to be in an incorrect position (for space group $P\bar{1}$), we switched to space group $P1$ and determined the positions of the two molecules in the crystal lattice by subsequent structural factor and Fourier calculation. After returning to the centrosymmetric $P\bar{1}$ space group, full matrix refinement for the non-hydrogen atoms resulted in $R = 0.098$. The difference Fourier map gave the positions of all of the hydrogen atoms at this stage and they were kept riding throughout the refinement. The weighting scheme used was $w = 1.0/[\sigma^2(F) + 0.0001(F)^2]$; the final R-value was 0.058 with $R_w = 0.064$ for 704 observed reflections, and $R = 0.093$ with $R_w = 0.094$ for 1 215 reflections. 17 low-order reflections suffering from extinction were left out in the final stage of refinement.

Refinement was carried out by the SHELX program; [19] atomic scattering factors were those given in the program as default values. Observed and calculated structure factors and anisotropic thermal parameters are listed in the Supplementary Publication [No. SUP 23465 (9 pp.)].

References

1 Part 29, G. Tóth, Á. Szöllösy, B. Podányi, I. Hermecz, Z. Mészáros, and I. Bitter, J. Chem. Soc., Perkin Trans. 2, in the press.

2 I. Hermecz, I. Bitter, Á. Horváth, G. Tóth, and Z. Mészáros, Tetrahedron Lett., 1979, 2557.

3 (a) G. Náray-Szabó, I. Hermecz, and Z. Mészáros, J. Chem. Soc., Perkin Trans. 1, 1974, 1753; (b) I. Hermecz, Z. Mészáros, L. Vasvári-Debreczy, Á. Horváth, S. Virág, and J. Sipos, Arzneim.-Forsch., 1979, 29, 1833; (c) I. Bitter, I. Hermecz, G. Tóth, P. Dvortsák, Z. Bende, and Z. Mészáros, Tetrahedron Lett., 1979, 5039; (d) I. Hermecz, T. Breining, Z. Mészáros, G. Tòth, and I. Bitter, Heterocycles, 1980, 14, 1953.

4 Z. Mészáros, Kem. Közl., 1978, 5 , 173.

5 H. L. Yale and E. R. Spitzmiller, J. Heterocycl. Chem., 1976, 6, 869.

6 G. Tóth, A. Szöllösy, B. Podányi, I. Hermecz, Á. Horváth, Z. Mészáros, and I. Bitter, J. Chem. Soc., Perkin Trans. 2, in the press.

7 G. Horváth, M. Pongor-Csákvári, J. Á. Kiss, G. Fogarassi, and P. Pulay, Tetrahedron, 1977, 33, 2293.

8 K. Simon, Z. Mészáros, and K. Sasvári, Acta Crystallogr., Sect. B, 1975, 31, 1702.

9 Z. Mészáros, J. Knoll, P. Szentmiklósi, Á. Dávid, G. Horváth, and I. Hermecz, Arzneim.-Forsch., 1972, 22, 815.

10 I. Hermecz, T. Breining, Z. Mészáros, A. Horváth, L. Vasvári-Debreczy, F. Dessy, Chr. DeVos, and L. Rodriquez, J. Med. Chem., 1982, 25, 1140.

11 F. Fülöp, I. Hermecz, Z. Mészáros, G. Dombi, and G. Bernáth, J. Heterocycl. Chem., 1979, 16, 457.

12 I. Hermecz, M. Kajtár, P. Surján, T. Breining, K. Simon, G. Horváth, G. Tóth, and Z. Mészáros, J. Chem. Soc., Perkin Trans. 2, in the press.

13 I. Hermecz, Á. Horváth, J. Knoll, Z. Mészáros, and L. Vasvári-Debreczy, U.S.P. 4 209 622 (Chem. Abstr., 1981, 94, 30783).

14 CHINOIN Ltd., Belg. P. 873 195 (Chem. Abstr., 1979, 91, 57053).

15 G. R. Lappin, J. Am. Chem. Soc., 1948, 70, 3348.

16 I. Hermecz, Z. Mészáros, L. Vasvári-Debreczy, Á. Horváth, and M. Pongor-Csákvári, J. Chem. Soc., Perkin Trans. 1, 1977, 789.

17 S. Carboni, A. DaSettimo, P. L. Ferrarini, and O. Livi, Farmaco, Ed. Sci., 1978, 33, 315.

18 P. Main, M. M. Woolfson, and G. Germain, ' MULTAN a Computer Program for the Automatic Solution of Crystal Structure,' University of York, England, 1974.

19 G. M. Sheldrick, ' The Crystal Structure Calculation Program,' University of Cambridge, England, 1976.