Nitrogen Bridgehead Compounds. Part 86 [1]. Synthesis and Reactivity of 7,12-Dihydropyrimido[1',2';1,2]pyrido[3,4-*b*]indol-4(6*H*)-ones. Debenzologues of Rutaecarpine Alkaloids

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Dedicated to the memory of Professor Nicholas Alexandrou

A series of 7,12-dihydropyrimido[1',2':1,2]pyrido[3,4-*b*]indole-4(6*H*)-ones was prepared by Fischer indolization of 9-arylhydrazono-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones. Quantum chemical calculations (ab initio and AM1) indicate that position 3 of 7,12-dihydropyrimido[1',2':1,2]pyrido-[3,4-*b*]indole-4(6*H*)-one can be involved in electrophilic substitutions, while position 2 is sensitive towards nucleophilic attack. Bromination of 6-methyl-7,12-tetrahydropyrimido[1',2':1,2]pyrido-[3,4-*b*]indol-4(6*H*)-one **16** with bromine afforded 3-bromo derivative **25**, which was reacted with cyclic amines to give 2-amino-7,12-dihydropyrimido[1',2':1,2]pyrido[3,4-*b*]indol-4(6*H*)-ones **26-30** in an addition-elimination reaction. Vielsmeier-Haack formylation of compound **16** gave 12-formyl **31** and 3,12-diformyl **32** derivatives (an *N*-formyl-1-deaza derivative of nauclefidine alkaloid **34**) at 60° and 100°, respectively. 3,12-Diformyl compound **32** was oxidized to 3-carboxyl derivative **33** with potassium permanganate. The quaternary salt **35**, obtained from compound **16** with dimethyl sulfate, suffered a ring opening on the action of aqueous sodium hydroxide. The new compounds have been characterized by elemental analyses uv, ^{1}H nmr and in some cases by ^{13}C ruler, CD spectra and X-ray investigations.

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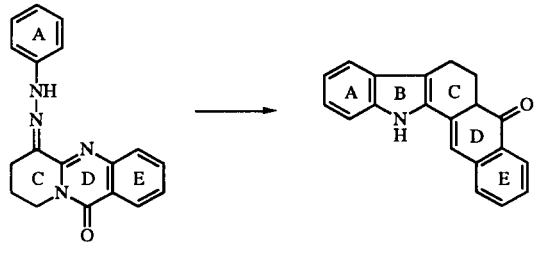
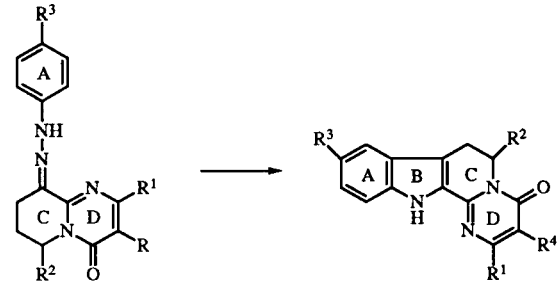
Introduction.

Recently we reported a facile total synthesis of rutaecarpine alkaloid **2** [2], and its substituted derivatives in rings A, C and E [3], furthermore its tetrahydro derivatives in ring E [4]. According to this new method pentacyclic ring systems were obtained from 6-arylhydrazono-11*H*-pyrido[2,1-*b*]quinazolin-11-ones **1** [2,4,5] by Fischer indolization [6] by heating in Dowtherm A at 220° [4], in polyphosphoric acid at 180° [2,3,4] or in melted zinc chloride at 200° [3]. Best yields were achieved in polyphosphoric acid [3]. In the earlier approaches the indolopyridoquinazoline skeleton was built up by the connection of the C and E, or the B and D rings [7-11] in the last step of the syntheses, while at Fischer indolization the ring connection between A and C rings was formed finally.



1 **2**

Rutaecarpine **2** was a constitution element of the traditional Chinese folk-medicines, Whu-Chu-Yu [12] and Shih-Hu [13], which had been administered for the treatment of headache, abdominal pain, dysentery, postpartum disturbances and worm infestations [12-14]. In modern literature rutaecarpine and its derivatives command interest as hypertensive, diuretic and uterotonic agents [15].



3-14 **15-24**

In this paper we investigate the extension of the applicability of the Fischer-indolization in the preparation of tetracyclic debenzo analogues **15-24** of rutaecarpine **2** starting from antiallergic 9-arylhydrazono-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **3-14** [16,17], and the reactivity of the pyrimido[1',2':1,2]-pyrido[3,4-*b*]indole sceleton in some reactions. Until now only a few derivatives of pyrimido[1',2':1,2]-pyrido[3,4-*b*]indole ring system have been prepared and investigated [18].

Synthesis

Alkyl derivatives of 9-phenylhydrazono-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **8-10**, **12** and **13** (R = R^2 = H, R^1 = Me, R^3 = Cl; R = R^3 = H; R^1 = Me, R^2 = H, Me; R^1 = R^2 = R^3 = H, R = Me; R = Et, R^1 = R^2 = Me, R^3 = H) were prepared from the appropriate 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones [19], similarly to the other 9-arylhydrazonotetrahydropyridopyrimidinones [16,17] reacting the active 9-methylene group of the 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones [20] with phenyldiazonium chloride[21].

When ethyl 9-phenylhydrazono-6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-3-carboxylate **5** was heated in polyphosphoric acid at 180° (Method B) only ester hydrolysis occured to yield 9-phenylhydrazonotetrahydropyrido[1,2-*a*]pyrimidine-3-carboxylic acid **4**. At higher temperature, above 200°, strong decomposition was observed. Finally the Fischer indolization of the ester **5** was succesful in 85% phosphoric acid at 180° for 60 minutes (Method A), but indolization was accompanied by ester hydrolysis and decarboxylation, too, and 6-methyl-7,12-dihydropyrimido[1',2':1,2]pyrido[3,4-*b*]indol-4(6*H*)-one **16** could be prepared in 71% yield. This product **16** was also obtained from the carboxylic acid **4** by heating in 85% phosphoric acid in 68% yield, and from 9-phenylhydrazono-6-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **6** in polyphosphoric acid at 180° in 33% yields (Scheme 1). The optically active 6-R derivative of **16** (**17**), and its 6-desmethyl analogue **15** was prepared in 74-78% yield by heating the

Scheme 1

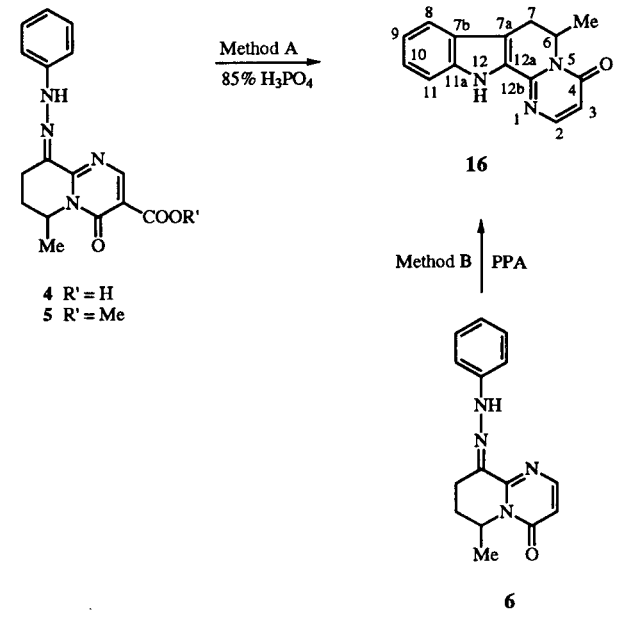


Table 1

Fisher Indolization of 9-Arylhydrazono-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **3-14**

Starting Compound	Product						Method	Reaction Period minutes	Yield %	Mp° (solvent)	Formula (Mol weight)	Analysis Calcd./Found		
	R	R^1	R^2	R^3	R^4	No.						C%	H%	N%
3	COOH	H	H	H	H	**15**	A	60	78	282-284 (EtOH)	$C_{14}H_{11}N_3O$ 237.263	70.87 70.95	4.67 4.63	17.71 17.62
4	COOH	H	Me	H	H	**16**	A	60	67.5	212-213 (EtOAc)	$C_{15}H_{13}N_3O$ 251.289	71.70 71.52	5.21 5.38	16.72 16.69
5	COOEt	H	Me	H	H	**16**	A	60	71	210-212 (EtOAc)				
6	H	H	Me	H	H	**16**	B	60	33	209-211 (EtOAc)				
7 [a]	COOH	H	Me	H	H	**17** [b]	A	60	74	198-200 (EtOH)	$C_{15}H_{13}N_3O$ 251.289	71.70 71.91	5.21 5.40	16.72 16.66
8	H	H	Me	Cl	H	**18**	B	45	79	227-229 (EtOH)	$C_{15}H_{12}ClN_3O$ 285.735	63.05 62.87	4.23 4.22	14.70 14.84
9	Me	H	H	H	Me	**19**	B	30	77	278-280 (EtOH)	$C_{15}H_{13}N_3O$ 251.289	71.70 71.92	5.21 5.28	16.72 16.64
10	H	Me	H	H	H	**20**	B	25	85	256-259 (EtOH)	$C_{15}H_{13}N_3O$ 251.289	71.70 71.75	5.21 5.40	16.72 16.57
11	Me	H	Me	H	Me	**21**	B	30	77	196-198 (EtOAc)	$C_{16}H_{15}N_3O$ 265.316	72.43 72.53	5.70 5.79	15.84 16.02
12	H	Me	Me	H	H	**22**	B	40	66	222-224 (EtOH)	$C_{16}H_{15}N_3O$ 265.316	72.43 72.38	5.70 5.83	15.84 15.85
13	Et	Me	Me	H	Et	**23**	B	30	81	203-205 (EtOAc)	$C_{18}H_{13}N_3O$ 287.323	75.24 75.44	4.56 4.60	14.62 14.71
14	Ph	H	Me	H	Ph	**24**	B	30	79	221-224 (EtOH)	$C_{21}H_{17}N_3O$ 327.388	77.04 76.86	5.23 5.31	12.83 12.99

[a] 6-*R* optically active derivative [15a]. [b] 6-*R* optically active derivative, $[\alpha]_D^{20}$ = -229° (c = 1, ethanol).

appropriate 9-arylhydrazono-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid **7** and **3**, respectively in 85% phosphoric acid at 180°.

The alkyl and phenyl derivatives of the tetracyclic ring system **18-24** were obtained from 9-phenylhydrazonotetrahydropyrido[1,2-*a*]pyrimidines **8-14** (R=H, Me, Et, Ph; R^1 = H, Me; R^2 = H, Me, R^3 = H, Cl) in polyphosphoric acid at 180° in good yields (see Table 1).

Quantum Chemical Calculations.

Possible electrophilic and nucleophilic substitution sites of compounds **16** and **25** were identified using Mulliken charges and superdelocalisability indices, both obtained from molecular orbital calculations. These were performed at the semiempirical AM1 and ab initio 3-21G levels of theory, using the MOPAC [22] and GAMESS [23] suite of programs, respectively. The geometries of compounds **16** and **25** were fully optimised at the AM1 level, whereas the optimised AM1 geometry was used in the single point ab initio calculations. Superdelocalisability [24] was defined as

$$S_E, S_N = 2\sum_j n_j \sum_{m=1} \frac{(C_{j,m})^2}{\varepsilon_j} \qquad (1)$$

where the summation over j is over the occupied orbitals in the electrophilic (S_E) and the unoccupied ones in the nucleophilic (S_N) case, n_j is the number of electrons on orbital j, $C_{j,m}$ is the MO coefficient and ε is the eigenvalue of the orbital. Due to their definition, superdelocalisabilities incorporate both charge and orbital energy related information and it has been shown that this quantity correlates well with reactivities in case steric effects are insignificant.

Table 2

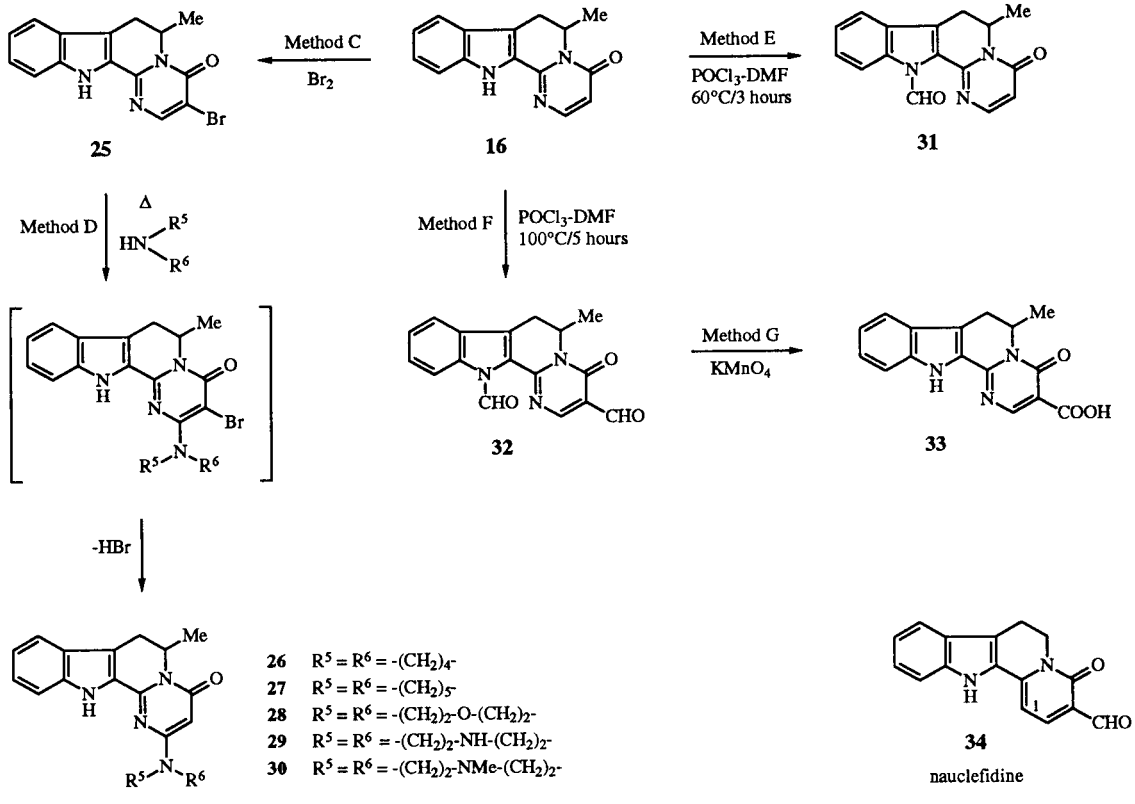
Ab initio 3-21G and AM1 Calculated Properties for positions 2 and 3 in compounds **16** and **25**

	Compound **16**		Compound **25**	
	at 2-C	at 3-C	at 2-C	at 3-C
Charge [a]	0.06 (-0.01)	-0.37 (-0.28)	0.12 (0.03)	-0.54 (-0.34)
S_E [b]	-3.63 (-0.24)	-4.97 (-0.27)	-3.75 (-0.23)	-5.65 (-0~27)
S_N [b]	200.09 (8.67)	231.01 (4.40)	248.17(-3.82)	211.66(-0.01)

[a] Charges were calculated by Mulliken analysis. [b] S_E and S_N are electrophilic and nucleophilic delocalisabilities (in units of eV^{-1}), as defined by equation (1). AM1 values are shown in brackets.

For judging the reactivities of in compounds **16** and **25** local Mulliken charges and superdelocabilities (electrophilic and nucleophilic) were calculated, as shown in Table 2. Although the AM1 and ab initio values are numerically at variance (*e.g.* the number and type of basis functions are different) the trends are the same with both methods. In compound **16** atom 3-C is

Scheme 2



more negative clearly indicating that it is more susceptible to electrophilic and centre 2-C for nucleophilic attack.

The value of superdelocalisability, shown in Table 2, is more negative on 3-C atom (both in AM1 and ab initio calculations) indicating that this will be the centre attacked by electrophiles. Nucleophilic attack would be expected at the centre with the more positive S_N value. Although AM1 results show 2-C atom to be favored at the AM1 level, this is not supported by the ab initio results. However, on introducing bromine at 3-C clearly changes the situation: 2-C will be by far more favorable for nucleophilic attack at the AM1 level; a result also shown by the ab initio values.

These predicted reactivities were observed in electrophilic (bromination, Vielsmeyer-Haack formylation) and nucleophilic (amination) reactions (see below).

Reactions.

The reactivity of the tetracyclic ring system was investigated using compound **16**. The 3-bromo derivative **25** was prepared almost in quantitative yield when chloroformic solution of compound **16** was treated with bromine at ambient temperature (Method C) (Scheme 2).

When bromo derivative **25** was gently heated in a cyclic amine at boiling temperature 2-amino-6-methyl-7,12-dihydropyrimido[1',,2':1,2]pyrido[3,4-*b*]indol-4(6*H*)-ones **26-30** were obtained in good yields (Table 3). In the first step the addition of cyclic amine on the C(2)-C(3) double bond occurs to give 2,3,7,12-tetrahydro derivative from which 2-amino-7,12-dihydropyrido[1',2':1,2]pyrido[3,4-*b*]indol-4(6*H*)-ones formed by hydrogen bromide elimination. Earlier it was demonstrated that pyrimidin-4(3*H*)-one moiety of nitrogen bridgehead ring systems is sensitive towards nucleophilic attack at position 6 (in our case, at position 2) [25].

Vielsmeier-Haack formylation of compound **16** with a mixture of phosphoryl chloride and dimethyl formamide at 60° for 3 hours afforded 12-formyl derivative **31** in 60% yield (Method E). When the reaction temperature was raised to 100° and reaction period was 5 hours diformylation occured to afford 3,12-diformyl derivative **32**, (Method F), which can be considered as *N*-formyl-1-aza derivative of nauclefidine alkaloid **34**, isolated from *Nauclea officinals*, which had been used as antiinflammatory and antibacterial agent in folk medicine in China [26].

The diformyl derivative **32** was oxidized by potassium permanganate and from the aqueous reaction mixture pyrimidopyridoindole-3-carboxylic acid **33**, (which could not be prepared directly from either 9-phenylhydrazonotetrahydropyridopyrimidine-3-carboxylate **5** or 3-carboxylic acid **4**) was prepared in 82% yield (Method G). When compound **16** was reacted with dimethyl sulfate in boiling toluene quaternary salt **35** was obtained in 91% yield in *cca* 85% purity (Method H) (Scheme 3). The treatment of quaternary salt **35**

Table 3
Some Reactions of 7,12-Dihydropyrimido[1',2':1,2]pyrido[3,4-*b*]indole-4(6*H*)-ones

Starting Compound	Product			Method	Yield	Mp°	Formula	Analysis Calcd./Found		
No.	R^4	R^5	No.		%	(solvent)	(Mol Weight)	C	H	N
16			**25**	C	98	232-235	$C_{15}H_{12}BrN_3O$	54.56	3.66	12.72
						(EtOH)	330.191	54.67	3.49	12.80
25	-$(CH_2)_4$-		**26**	D	96	255-257	$C_{19}H_{20}N_4O$	71.23	6.29	17.48
						(EtOH)	320.397	71.31	6.34	17.39
25	-$(CH_2)_5$-		**27**	D	90	170-172	$C_{20}H_{22}N_4O$	71.83	6.63	16.75
						(EtOH)	334.424	71.90	6.49	16.81
25	-$(CH_2)_2$-O-$(CH_2)_2$-		**28**	D	75	180-181	$C_{19}H_{20}N_4O_2$	67.84	5.99	16.65
						(EtOH)	336.397	67.75	6.03	16.72
25	-$(CH_2)_2$NH$(CH_2)_2$-		**29**	D	81	178-180	$C_{19}H_{21}N_5O$	68.04	6.31	20.88
						(EtOH)	335.411	68.14	6.50	20.83
25	-$(CH_2)_2$NMe$(CH_2)_2$-		**30**	D	83	168-170	$C_{20}H_{23}N_5O$	68.74	6.63	20.04
						(EtOH)	349.438	68.91	6.69	19.95
16			**31**	E	47	181-183	$C_{16}H_{13}N_3O_2$	68.82	4.69	15.05
						(EtOAc)	279.230	68.75	4.58	15.10
16			**32**	F	63	212-214	$C_{17}H_{13}N_3O_3$	66.44	4.26	13.67
						(EtOH)	307.330	66.65	4.12	13.70
32			**33**	G	82	289-291	$C_{16}H_{13}N_3O_3$	65.08	4.44	14.23
						(DMF)	295.299	64.93	4.51	14.33
16			**35** [a]	H	91	183-185	$C_{17}H_{19}N_3O_5S$	54.07	5.08	11.14
						(PhMe)	377.421	53.89	5.12	11.40
35			**38** [b]	I	43	97-102	$C_{16}H_{17}N_3O_2$	67.83	6.05	14.83
						(EtOAc)	283.33	67.99	6.00	14.92

[a] Purity *ca* 85%. [b] *ca* a 7:1 mixture of *Z* and *E* isomers.

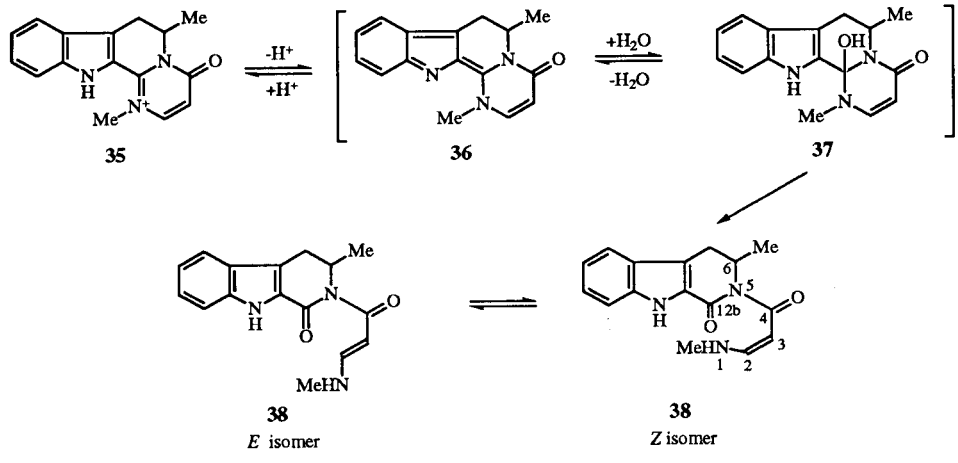
with 3% aqueous sodium hydroxide solution resulted in the formation of ring-opened product **37**. The suggested mechanism for ring opening is depicted on Scheme 3.

Spectroscopic Investigations

Some characteristic uv, ^{1}H nmr data are tabulated in Tables 4 and 5. ^{13}C nmr data on selected pyrimidopyridoindoles in deuteriochloroform, are collected in Table 6. that of the respective carbon of rutaecarpine **2** (113.3 ppm) [27]

The coupling constants between H-6 and the protons of 7-methylene group suggest that the 6-methyl group of pyrimidopyridoindoles **16** occupies the quasiaxial position to avoide 1,3-allylic strain between an quasi-equatorial methyl group and the adjacent 4-carboxyl group in an alternative conformation [28- 30].

Scheme 3



Whereas the 7a-C, 7b-C, 9-C, 10-C, 11-C, 11a-C and 12a-C chemical shifts of the indole moiety of compounds **16**, **22**, **26**, **27** and **28** in deuteriochloroform resemble those of the appropriate carbons of the indole moiety of rutaecarpine **2** in DMSO-d_6, the chemical shift of 8-C (between 120.0 and 120.2 ppm) differs significantly from

The *Z* geometry of the major isomer of the ring-opened product **38** was justified by NOE experiments in deuteriochloroform. The irradiation of the sign of 2-H atom resulted in a 12.4% intensity enhancement on the sign of 3-H proton while that of 3-H caused a 12.3% intensity inhancement on the sign of 2-H atom. When a 12.5: 87.5

Table 4

UV Data on 7,12-Dihydropyrido[1',2':1,2]pyrido[3,4-*b*]indol-4(6*H*)-ones **15**,**16**,**18-20**,**22**,**23**,**25-33** and **35** in Ethanol

Compound No.	Absorption maxima nm									(ε)
15	360 [i]	(19900)	348	(24600)	336 [i]	(21900)			252	(10100)
16	362 [i]	(18600)	349	(22900)	338 [i]	(20400)			252	(10040)
18	362 [i]	(18700)	347	(23600)	336 [i]	(20100)			254	(12600)
19	362 [i]	(17000)	347	(23400)	336 [i]	(21400)			254	(9800)
20	360 [i]	(7770)	346	(9770)	336 [i]	(8920)			251	(4680)
22	361 [i]	(19000)	347	(24600)	338 [i]	(22400)			251	(10140)
23	364 [i]	(17400)	349	(24000)	338 [i]	(21900)			254	(10000)
25 [a]	375 [i]	(-)	362	(-)	351 [i]	(-)	276	(-)	254	(-)
26					326	(19500)	276	(7200)	252	(37200)
27					326	(19100)	277	(7900)	253	(36300)
28					330	(17000)	278	(6400)	253	(32400)
29					330	(16200)	277	(6000)	252	(28200)
30					329	(17000)	278	(8100)	252	(24000)
31	357 [i]	(15200)	345	(22900)	332	(23400)			230	(17800)
32	358	(24000)					276	(9500)	228	(17000)
33	364	(28100)					283	(10500)	231	(18700)
35	360	(26900)							230	(13800)

[i] Inflexion. [a] In saturated solution.

Table 5

^{1}H NMR Data on 7,12-Dihydropyrido[1',2':1,2]pyrido[3,4-*b*]mdol-4(6*H*)-ones **15**,**16**,**19-23**,**25-33**,**35**,**38** in $CDCl_3$

Compound No	H-2	H-3	H-6 or H_2-6	H_2-7	H-8	H-9	H-10	H-11	H-12	Others
15	7.80 d	6.31 d	4.46 t	3.17 t		6.92-7.65 m			9.62 *s*	
16 [a]	7.89 d	6.41 d	5.63 m	3.13 dd [b] 3.38 dd [c]	7.62 dd	7.17 t	7.33 t	7.33 dd	10.69 *s*	1.40 d (6-Me)
19	7.80 *s*	-	4.53 t	3.20 t		7.00-7.75 m			9.50 *s*	2.13 *s* (3-Me)
20	-	6.26 d	4.48 t	3.18 t		7.00-7.80 m			9.80 *s*	2.28 d (2-Me)
21	7.88 *s*	-	5.61 m	3.05 dd [b] 3.28 dd [c]		7.00-7.80 m			9.62 *s*	1.78 d (6-Me), 1.90 *s* (3-Me)
22 [a]		6.21 d	5.56 m	3.10 dd [b] 3.33 dd [c]	7.61 dd	7.17 t	7.32 t	7.38 dd	9.47 *s*	1.36 d (6-Me), 2.30 *s* (2-Me)
23		-	5.58 m	3.03 dd [b] 3.38 dd [c]		7.00-7.70 m			9.68 *s*	1.15 t (3-CH_2-Me), 1.35 d (6-Me), 2.35 *s* (2-Me) 1.30 q (3-CH_2)
25	-	8.23 *s*	5.59 m	3.15 dd [b] 3.25 dd [c]		7.00-7.80 m			9.70 *s*	1.40 d (6-Me)
26 [a]	-	5.21 *s*	5.56 m	3.02 dd [b] 3.29 dd [c]	7.59 dd	7.15 t	7.30 t	7.41 dd	9.26 *s*	1.31 d (6-Me), 1.90-2.10 m $(CH_2)_2$ 3.50-3.65 m (2 x NCH_2)
27 [a]	-	5.46 *s*	5.53 m	3.02 dd [b] 3.29 dd [c]	7.58 dd	7.14 t	7.28 t	7.39 dt	9.47 *s*	1.31 d (6-Me), 1.60-1.80 m $(CH_2)_3$ 3.50-3.60 m (2 x NCH_2)
28 [a]	-	5.43 *s*	5.53 m	3.05 dd[b] 3.32 dd [c]	7.61 dd	7.18 t	7.33 t	7.43 dd	8.94 *s*	1.33 d (6-Me), 3.78 (2 x OCH_2), 3.57 ($2NCH_2$)
29	-	5.52 *s*	5.58 m	3.05 dd [b] 3.30 dd [c]		7.00-7.80 m			9.25 *s*	1.35 d (6-Me), 2.80-3.10 m (2 x CH_2) 3.50-3.70 m (2 x CH_2)
30	-	5.60 *s*	5.52 m	3.05 dd [b] 3.28 dd [c]		7.00-7.80 m			9.30 *s*	1.35 d (6-Me), 2.35 *s* (NMe), 2.60-3.00 m (2 x CH_2) 3.60-3.90 m (2 x CH_2)
31	7.95 d	6.45 d	5.60 m	3.18 dd [b] 3.25 dd [c]		7.20-7.80 m			-	1.40 d (6-Me), 10.62 *s* (NCHO)
32	8.55 *s*	-	5.55 m	3.20 dd [b] 3.27 dd [c]		7.00-7.80 m			-	1.43 d (6-Me), 8.78 *s* (3-CHO_3), 10.62 *s* (NCHO)
33	8.32 *s*	-	5.67 m	3.15 dd [b] 3.38 dd [c]		7.00-7.80 m			10.83 *s*	1.48 d (6-Me), 13.70 *s* (COOH)
35 [a,d]	7.84 d	6.48 d	5.63 m	3.24 d [b] 4.13 dd [c]	7.90 d	7.23 t	7.50 t	7.62 d	12.06 *s*	1.28 d (6-Me), 3.74 *s* N(l)Me, 4.47 *s* ($MeSO_4$)
38 [a,e]	6.80 dd	6.00 d 6.19 d [f]	5.29 m	2.90 dd [b] 3.30 dd [c]	7.61 d	7.14 t	7.33 t	7.45 d	9.21 *s*	1.35 d (6-Me), 3.04 d [N(1)-Me] 8.80 m [N(1)H]

Compound No.	Coupling Constant (Hz)
15	$J_{2,3}$ ~ 6.4
16 [a]	$J_{2,3}$ ~ 6.6, $J_{6,Me}$ ~ 6.7, $J_{6e,7a}$ ~ 6.9, $J_{6e,7e}$ ~ 0.8, $J_{7e,7a}$ ~ -16.8, $J_{8,9}$ ~ 8.1, $J_{8,11}$ ~ 0.6, $J_{9,10}$ ~ 8.1, $J_{10,11}$ ~ 8.4, $J_{9,11}$ ~ 1.0, $J_{11,NH}$ ~ 1.0
20	$J_{3,Me}$ ~ 0.8
21	$J_{6e,7e}$ ~ 1.8, $J_{6e,7a}$ ~ 6.4, $J_{7e,7a}$ ~ -16.6
22[a]	$J_{3,Me}$ ~ 0.8, $J_{6,Me}$ ~ 6.7, $J_{6e,7a}$ ~ 6.9, $J_{6e,7e}$ ~ 0.8, $J_{7e,7a}$ ~ -16.8, $J_{8,9}$ ~ 8.1, $J_{9,10}$ ~ 7.8, $J_{10,11}$ ~ 8.2
23	$J_{6e,7e}$ ~ 1.7, $J_{6e,7a}$ ~ 6.3, $J_{7e,7a}$ ~ -16.6
25	$J_{6,Me}$ ~ 7.0, $J_{6e,7e}$ ~ 1.9, $J_{6e,7a}$ ~ 6.1, $J_{7e,7a}$ ~ -16.9
26 [a]	$J_{6,Me}$ ~ 6.6, $J_{6e,7a}$ ~ 6.8, $J_{6e,7e}$ ~ 2.0, $J_{7e,7a}$ ~ -16.6, $J_{8,9}$ ~ 7.9, $J_{9,10}$ ~ 6.9, $J_{10,11}$ ~ 8.3
27 [a]	$J_{6,Me}$ ~ 6.6, $J_{6e,7a}$ ~ 6 9, $J_{6e,7e}$ ~ 1.0; $J_{7e,7a}$ ~ -16.6, $J_{8,9}$ ~ 8.0, $J_{8,10}$ ~ 1.0, $J_{9,10}$ ~ 6.9, $J_{9,11}$ ~ 1.0, $J_{10,11}$ ~ 8.2
28 [a]	$J_{6,Me}$ ~ 6.7, $J_{6e,7a}$ ~ 6.9, $J_{6e,7e}$ ~ 0.8, $J_{7e,7a}$ ~ -16.7; $J_{8,9}$ ~ 7.7, $J_{9,10}$ ~ 8.2, $J_{10,11}$ ~ 8.3
29	$J_{6,Me}$ ~ 7.0, $J_{6e,7e}$ ~ 2.0, $J_{6e,7a}$ ~ 7.0, $J_{7e,7a}$ ~ -17.0
30	$J_{6,Me}$ ~ 7.0, $J_{6e,7e}$ ~ 2.0, $J_{6e,7a}$ ~ 7.0, $J_{7e,7a}$ ~ 17.0
31	$J_{6,Me}$ ~ 6.8, $J_{2,3}$ ~ 6.2, $J_{6,Me}$ ~ 7.0, $J_{6e,7e}$ ~ 2.0, $J_{6e,7a}$ ~ 6.0, $J_{7e,7a}$ ~ -18.0, $J_{10,11}$ ~ 8.0
32	$J_{6,Me}$ ~ 7.0, $J_{6e,7e}$ ~ 1.8, $J_{6e,7a}$ ~ 6.4, $J_{7e,7a}$ ~ -17.0
33	$J_{6,Me}$ ~ 7.0, $J_{6e,7e}$ ~ 2.0, $J_{6e,7a}$ ~ 7.0, $J_{7e,7a}$ ~ 17.0
35 [a]	$J_{6,Me}$ ~ 6.8, $J_{2,3}$ ~ 7.8, $J_{6e,7a}$ ~ 6.6, $J_{7e,7a}$ ~ -17.2, $J_{8,9}$ ~ 8.6, $J_{9,10}$ ~ 7.5, $J_{10,11}$ ~ 8.2
38 [a][g]	$J_{2,3}$ ~ 7.9, $J_{6e,Me}$ ~ 6.6, $J_{6e,7e}$ ~ 6.7, $J_{6e,7a}$ ~ 6.2, $J_{7e,7a}$ ~ -16.6, $J_{8,9}$ ~ 7.9, $J_{9,10}$ 7.5, $J_{10,11}$ ~ 7.9, $J_{NH,Me}$ ~ 5.0, $J_{NH,2}$ ~ 13.0

[a] On a Bruker AC 400 spectrometer. [b] Equatorial proton. [c] Axial proton. [d] Purity: *ca* 85%. [e] *ca* a 7:1 mixture of *E* and *Z* isomers. [f] *Z* isomer. [g] $J_{2,3}$ 12.7 Hz in *E* isomer.

Table 6

^{13}C NMR Data on Compounds **16,22,26-28** in $CDCl_3$ (ppm) [a]

Compound No.	2-C	3-C	4-C	6-C	7-C	7a-C	7b-C	8-C	9-C	10-C	11-C	11a-C	12a-C	12b-C	Others
2 [b]						117.3	124.1	113.1	119.3	124.1	112.1	138.1	126.5		
16	151.7	113.2	160.9	47.1	25.5	116.8	126.1	120.2	120.6	125.8	112.2	139.0	125.7	149.2	18.7 (Me)
22	162.2	110.6	161.3	46.8	25.6	116.4	126.3	120.1	120.6	125.7	112.1	138.5	125.7	149.2	19.0 (6-Me), 23.4 (2-Me)
26	162.1	84.0	158.9	46.2	25.6	116.2	126.4	120.1	120.4	125.2	112.0	138.2	126.3	147.1	19.3 (Me), 46.6 (NCH_2), 25.3 (CH_2)
27	160.6	84.7	162.8	46.3	25.6	116.3	126.3	120.0	120.3	125.3	112.0	138.3	126.1	147.1	19.2 (Me), 45.6 (NCH_2), 25.4 (2'-CH_2), 24.5 (3-CH_2)
28	160.9	85.5	162.5	46.4	25.6	116.7	126.4	120.2	120.6	125.6	112.0	138.2	126.0	147.1	19.2 (Me), 44.7 (NCH_2), 66.5 (OCH_2)

[a] On a Bruker AC 400 spectrometer. [b] From ref [25].

ratio of *E-Z* mixture of compound **38** was left to stand in DMSO-d_6 at ambient temperature an *E-Z* isomerization was obserwed which is characteristic for push-pull ethylenes [31, 32]. The *E-Z* ratio was *cca* 40:60 after 1 week, *ca* 71:29 after 2 weeks, and 81:19 after 1 month.

The uv and cd spectra of the optically active enantiomer **17** 6-*R* absolute configuration are shown in ethanol on Figure 1.

The molecular structure of **22** is shown on Figure 2 as determined by X-ray crystallography. Table 7 shows the crystal and refinement data, Table 8 the atomic coordinates, Table 9 the bond lengths and angles while Table 10 the torsion angles. The molecule looks mostly planar (Figure 2) apart from the 6-C atom of the half-chair ring C as well as its axial methyl substituent. However, a more careful investigation shows that the plane formed

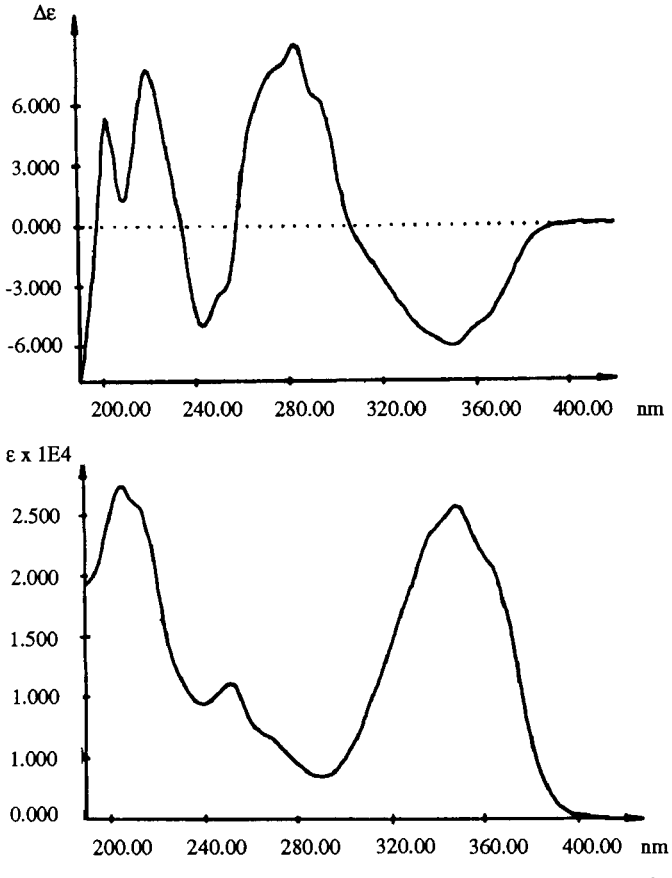


Figure 1. Circular dichromism (above) and ultraviolet (below) spectra of compound **17** with *6R* absolute configuration in ethanol.

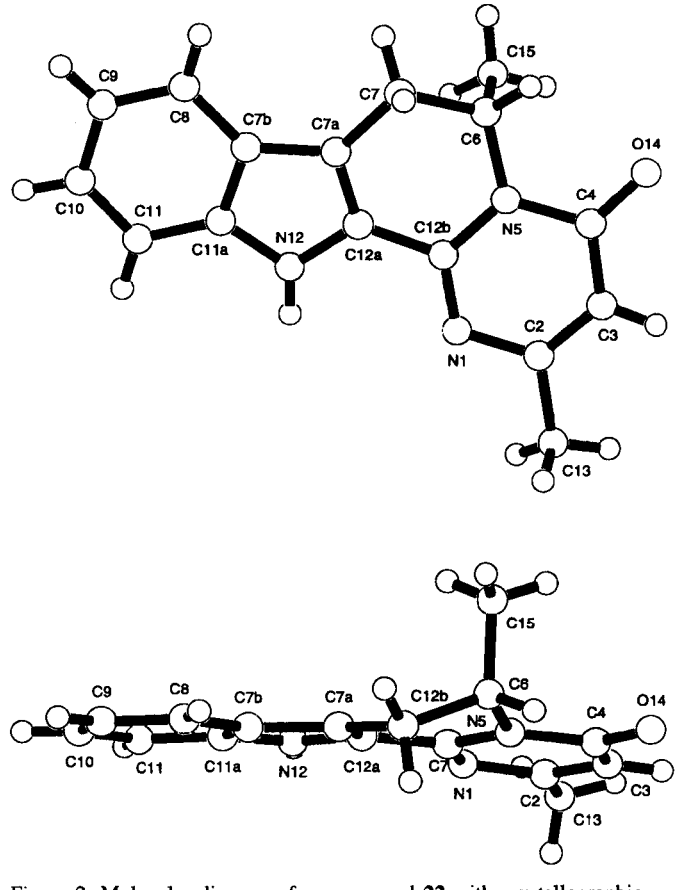


Figure 2. Molecular diagrams for compound **22** with crystallographic atomic numbering.

Table 7

Crystal Data and Structure Refinement for **22**

Empirical formula	$C_{16}H_{15}N_3O$	
Formula weight	265.31	
Temperature	293(2) K	
Wavelength	1.54180 Å	
Crystal system	Orthorhombic	
Space group	P c c n	
Unit cell dimensions	a = 14.791(3) Å	alpha = 90 deg
	b = 15.317(5) Å	beta = 90 deg
	c = 11.946(7) Å	gamma = 90 deg
Volume	2706(2) $Å^3$	
Z	8	
Density (calculated)	1.302 g/cm^3	
Absorption coefficient	0.671 mm^{-1}	
F(000)	1120	
Crystal size	0.20 x 0.20 x 0.10 mm/from $CHCl_3$	
Theta range for data coll.	4.15 to 75.44 deg	
Index	0<=h<=17, 0<=k<=19, 0<=1<=15	
Reflections collected	2649	
Independent reflections	2649	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	2636/0/185	
Goodness-of-fit on F^2	1.016	
Final R indices [I>2σ(I)]	R1 = 0.0685, wR2 = 0.1502	
Extinction coefficient	0.0033(4)	
Largest diff. peak and hole	0.466 and -0.462 $e.Å^{-3}$	

by ring D (N1, C2, C3, C4, N5, C12b) and its connected atoms C6, C12a, C13 and O14 (r.m.s. = 0.015 Å) as well as the plane of rings A and B (C7a, C7b, C8, C9, C10, C11, C11a, N12, C12a) along with their connected atoms C7 and C12b (r.m.s. = 0.011 Å) form an angle of 8.8 deg. C6 is in a distance of 0.27(1) Å as well as 0.54(1) Å while C15 is in a distance of 1.77(1) Å as well as 2.06(1) Å from the first and the second planes, respectively.

The bond length shows in accordance with the structural formula that delocalisation characterises the whole ring system apart from the three bonds including atoms N5-C6-C7-C7a (Table 3). The lone pair of N12 is also delocalized that leads to shortening of the corresponding N12-C11a and N12-C12a bonds to 1.36 Å as opposed to the somewhat unusual value of 135.7(8) deg. A similar argument applies to the bond angles C7-C7a-C7b, N12-C12a-C12b and N12-C11a-C11.

A hydrogen bond is formed in the crystal structure by the following three atoms. N12-H12...O14_$1, where $1 is meant to show that the atom in question belongs to a neighbouring molecule that is produced from the original one by the following symmetry relation $1 = X-0.5, 1-Y, 0.5-Z. The N12..O14_$1 bridgehead distance is 2.838 (9) Å, while the N12-H12...O14_$1 angle is 145.6 (0.3) deg.

Table 8

Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters (A^2 x 10^3) for Compound **22**.

	x	y	z	U(eq)
N(1)	9659(4)	4791(5)	1997(5)	41(2)
C(2)	9936(7)	4232(6)	1165(7)	48(3)
C(3)	10816(6)	4049(7)	988(7)	57(3)
C(4)	11512(6)	4393(7)	1630(7)	51(3)
N(5)	11214(5)	4954(5)	2483(6)	41(2)
C(6)	11888(6)	5485(6)	3081(7)	49(2)
C(7)	11628(5)	5685(6)	4306(7)	44(2)
C(7a)	10657(5)	5958(5)	4338(6)	32(2)
C(7b)	10160(5)	6432(5)	5163(6)	37(2)
C(8)	10376(6)	6895(6)	6154(7)	50(2)
C(9)	9700(7)	7292(6)	6729(7)	55(3)
C(10)	8802(7)	7265(6)	6341(8)	55(3)
C(11)	8565(6)	6826(5)	5383(7)	47(2)
C(11a)	9255(6)	6426(5)	4792(7)	40(2)
N(12)	9219(5)	5959(4)	3823(5)	40(2)
C(12a)	10067(5)	5680(6)	3559(7)	38(2)
C(12b)	10296(6)	5124(5)	2623(6)	33(2)
C(13)	9186(6)	3858(7)	446(7)	65(3)
O(14)	12334(4)	4268(5)	1513(5)	81(2)
C(15)	12100(6)	6305(6)	2420(7)	69(3)

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Table 9

Bond Lengths and Angles for Compound **22**

Bond Lengths (Å)

N(1)-C(12b)	1.307(9)	C(7a)-C(12a)	1.344(10)
N(1)-C(2)	1.375(10)	C(7a)-C(7b)	1.428(10)
C(2)-C(3)	1.349(12)	C(7b)-C(11a)	1.409(10)
C(2)-C(13)	1.516(11)	C(7b)-C(8)	1.417(11)
C(3)-C(4)	1.388(11)	C(8)-C(9)	1.356(11)
C(4)-O(14)	1.238(10)	C(9)-C(10)	1.407(11)
C(4)-N(5)	1.405(10)	C(10)-C(11)	1.374(11)
N(5)-C(12b)	1.391(9)	C(11-C(11a)	1.385(10)
N(5)-C(6)	1.472(10)	C(11a)-N(12)	1.362(9)
C(6)-C(15)	1.516(10)	N(12)-C(12a)	1.362(10)
C(6)-C(7)	1.543(10)	C(12a)-C(12b)	1.447(10)
C(7)-C(7a)	1.496(10)		

Bond Angles [deg]

C(12b)-N(1)-C(2)	116.2(7)	C(11a)-C(7b)-C(8)	118.7(8)
C(3)-C(2)-N(1)	122.0(9)	C(11a)-C(7b)-C(7a)	105.6(7)
C(3)-C(2)-C(13)	22.6(9)	C(8)-C(7b)-C(7a)	135.7(8)
N(1)-C(2)-C(13)	115.3(8)	C(9)-C(8)-C(7b)	118.7(8)
C(2)-C(3)-C(4)	23.4(9)	C(8)-C(9)-C(10)	121.1(9)
O(14)-C(4)-C(3)	127.4(9)	C(11)-C(10)-C(9)	122 0(9)
O(14)-C(4)-N(5)	119.0(9)	C(10)-C(11)-C(11a)	116 9(8)
C(3)-C(4)-N(5)	113.6(8)	N(12)-C(11a)-C(11)	129.5(9)
C(12b)-N(5)-C(4)	120.5(7)	N(12)-C(11a)-C(7b)	108.0(8)
C(12b)-N(5)-C(6)	120.0(7)	C(11)-C(11a)-C(7b)	122.5(8)
C(4)-N(5)-C(6)	118.5(8)	C(12a)-N(12)-C(11a)	108.9(7)
N(5)-C(6)-C(15)	110.2(7)	C(7a)-C(12a)-N(12)	109.8(7)
N(5)-C(6)-C(7)	113.6(7)	C(7a)-C(12a)-C(12b)	124.7(8)
C(15)-C(6)-C(7)	112.4(7)	N(12)-C(12a)-C(12b)	125.4(8)
C(7a)-C(7)-C(6)	108.6(7)	N(1)-C(12b)-N(5)	124.2(7)
C(12a)-C(7a)-C(7b)	107.7(7)	N(1)-C(12b)-C(12a)	120.2(8)
C(12a)-C(7a)-C(7)	121.1(8)	N(5)-C(12b)-C(12a)	115.6(7)
C(7b)-C(7a)-C(7)	130.8(7)		

Table 10

Selected Torsion Angles [deg] for Compound **22**

O(14)-C(4)-N(5)-C(12b)	178.6(9)
C(3)-C(4)-N(5)-C(6)	-168.7(8)
C(12b)-N(5)-C(6)-C(15)	-85.6(9)
C(4)-N(5)-C(6)-C(15)	83.0(10)
C(12b)-N(5)-C(6)-C(7)	41.5(10)
C(4)-N(5)-C(6)-C(7)	-149.9(8)
N(5)-C(6)-C(7)-C(7a)	-45.2(10)
C(15)-C(6)-C(7)-C(7a)	80.8(9)
C(6)-C(7)-C(7a)-C(12a)	27.1(11)
C(6)-C(7)-C(7a)-C(7b)	-160.2(8)
C(7)-C(7a)-C(7b)-C(8)	8(2)
C(6)-N(5)-C(12b)-N(1)	168.1(7)
C(6)-N(5)-C(12b)-C(12a)	-14.3(11)
N(12)-C(12a)-C(12b)-N(1)	-5.2(12)
C(7a)-C(12a)-C(12b)-N(5)	-7.0(12)

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EXPERIMENTAL

Melting points were uncorrected. Yields were not optimized. The uv spectra were recorded on a Unicam SP-800 spectrophotometer, the cd spectrum of **17** was recorded on a JobinYvon CD Dichrograph Mark VI instrument in ethanol. The ^{1}H nmr spectra were measured on a Bruker WP-80 or a AC-400 spectrometer at 80.0 and 400.132 MHz respectively, and ^{13}C nmr spectra were measured on a Bruker AC-400 spectrometer at 100.614 MHz. Chemical shifts are given on scale, and TMS was used as internal standard.

The X-ray intensities were measured on a Rigaku AFC6S diffractometer. The structure was solved by direct methods (SHELXS-86) and refined with full matrix least-squares against F^2 of all data with anisotropic thermal parameters for the nonhydrogen atoms (SHELXL-93). Hydrogen atoms were generated and kept in a constrained distance form their parent atoms. Their isotropic thermal motion parameters were refined in chemically similar groups. Further details of the crystal structure analysis are available on request from the authors.

Preparation of 9-Arylhydrazono-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones.

The appropriate starting 9-arylhydrazono-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrido[1,2-*a*]pyrimidin-4-ones **3-7**, **11** and **14** were prepared according to the literary method [16a,17].

9-Phenylhydrazono-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones.

Phenyldiazonium chloride was prepared by the usual procedure [21] from the appropriate aniline (10 mmoles) in 1:1 diluted hydrochloride acid (10 ml) at 0° with a solution of sodium nitrite (0.69 g, 10 mmoles) in water (5 ml). To a solution of phenyldiazonium chloride and sodium acetate trihydrate (6 g) was added dropwise a solution of the required 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one [18] (10 mmoles) at 0° in water (10 ml) or in a 2:1 mixture of water and ethanol (30 ml, in the case of 2,6-dimethyl-3-ethyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one). The reaction mixture was stirred at 0° for 24 hours, then the precipitated crystals were filtered off, dried, and recrystallized. If the hydrochloride salt of 9-arylhydrazono-6,7,8,9-tethrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was obtained, then the hydrochloride was first treated with 5% aqueous sodium carbonate solution to give free base which then was recrystallized.

2-Methyl-9-phenylhydrazono-6,7,8,9-tetrahydro-4*H*-pyrido-[1,2-*a*]pyrimidin-4-one (**10**) Hemi Hydrate.

This compound was obtained in a yield 52%, mp 191-192° (ethanol); uv (ethanol): 374 (ε 20900), 288 (3810), 249 nm (15200).

Anal. Calcd. for $C_{15}H_{16}N_4O \cdot 1/2H_2O$: C, 64.96; H, 6.18; N, 20.20. Found: C, 64.94; H, 6.02; N, 20.13.

3-Methyl-9-phenylhydrazono-6,7,8,9-tetrahydro-4*H*-pyrido-[1,2-*a*]pyrimidin-4-one (**9**).

This compound was obtained in a yield 72%, mp 158-161° (ethanol); uv (ethanol): 368 (ε 24000), 288 (6460), 239 nm (16200); ^{1}H-nmr (deuteriochloroform): *Z* 100%; δ 2.10 (2H, m, 7-H_2), 2.12 (2H, s, 3-Me), 2.82 (2H, m, 8-H_2), 4.02 (2H, t, 6-H_2), 6.80-7.45 (5H, m, Ph), 7.85 (1H, d, 2-H), 13.92 (1H, s, NH); ^{1}H-nmr (DMSO-d_6): *E*:*Z* = 20:80; 9.90 (0.2H, s, NH_E) and 13.98 (0.8H, s, NHz).

Anal. Calcd. for $C_{15}H_{16}N_4O$: C, 67.14, H, 6.01, N, 20.88. Found: C, 67.20; H, 5.96; N, 21.02.

6-Methyl-9-[4-chlorophenyl)hydrazono]-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-4-one (**8**).

This compound was obtained in a yield of 84%, mp 140-141° (ethanol).

Anal. Calcd. for $C_{15}H_{15}ClN_4O$: C, 59.50; H, 4.99; N, 18.51; Cl, 11.71. Found: C, 59.45; H, 5.15; N, 18.58; Cl, 11.51.

2,6-Dimethyl-9-phenylhydrazono-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one (**12**).

This compound was obtained in a yield of 59%, mp 160° (ethyl acetate); uv (ethanol): 378 (ε 19500), 288 (2950), 250 (12100).

Anal. Calcd. for $C_{16}H_{18}N_4O$: C, 68.07; H, 6.43; N, 19.84. Found: C, 67.78; H, 6.33; N, 19.54.

2,6-Dimethyl-3-ethyl-9-phenylhydrazono-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-one (**13**).

This compound was obtained in a yield of 67%; mp 135-137° (ethyl acetate); ^{1}H-nmr (deuteriochoroform): *E*:*Z* = 23:77; δ 1.09 (t, E, 3-CH_2CH_3; 0.69H), 1.10 (t, *Z* 3-CH_2CH_3, 2.31H), 1.27 (d, *E* 6-Me_E, 0.69H), 1.33 (d, *Z* 6-Me, 2.31H), 1.66-3.13 (m, 7-H_2, 8-H_2, 2-Me, 3-CH_2, 9H), 5.00 (m, *Z* 6-H, 0.77H), 5.24 (m, *E* 6-H 0.23H), 6.75-7.45 (m, Ph, 5H), 7.80 (s, *E* NH, 0.23), 14.48 (s, *Z* NH, 0.77).

Anal. Calcd. for $C_{18}H_{22}N_4O$: C, 69.95; H, 7.14; N, 18.05. Found: C, 69.34; H, 7.06; N, 17.93.

Fischer Indolization.

Method A.

9-Arylhydrazono-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (10 g) was heated in 85% phosphoric acid (100 g) at

180-185° for the reaction period given in Table 1. After cooling to ambient temperature the reaction mixture was diluted with water (100 ml), then after 30 minutes strirring the *p*H of the aqueous solution was adjusted to 6.5-7.0 with 25% aqueous ammonium hydroxide solution. The precipitated product was filtered off and dissolved in chloroform (200 ml). The chloroformic solution was filtered, then it was treated with 5% aqueous sodium hydroxide (2 x 20 ml), then with water (2 x 30 ml). The dried (sodium sulfate) organic solution was evaporated to dryness *in vacuo*, and residue was recrystallized to give pyrimidopyridoindole (see Table 1).

Method B.

9-Phenylhydrazono-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido-[1,2-*a*]pyrimidin-3-carboxylic acid (1 g) was heated in polyphosphoric acid (Fluka) (15 g) at 180° for reaction period given in Table 1. Then the reaction mixture was treated with water (100 ml) and *p*H of the aqueous solution was adjusted to *p*H 5-7 with 25% aqueous ammonium hydroxide solution. After 1 hour stiring the precipitated crystalls were filtered off, washed with water, dried and recrystallized to give pyrimidopyridoindole (see Table 1).

Reactions.

Method C.

To a solution of 6-methyl derivative **16** (6.02 g, 24 mmoles) and triethylamine in chloroform (60 ml) was added dropwise bromine (3.84 g, 24 mmoles) in chloroform (40 ml) at ambient temperature. The reaction mixture was stirred for 2 hours, and then it was allowed to stand overnight. The reaction mixture was diluted with chloroform (100 ml) and it was extracted with 5% aqueous hydrochloric acid (2 x 100 ml), then with water (2 x 100 ml). The dried (sodium sulfate) organic solution was evaporated to dryness *in vacuo*. The residue was crystallized to give 3-bromo-6-methyl derivative **25** (see Table 3).

Method D.

A mixture of 3-bromo-6-methyl derivative **25** (1.2 g, 4 mmoles) and cyclic secondary amine (6 g) was gently refluxed under nitrogen. The reaction period was 8 hours for pyrrolidine, 6 hours for piperidine, 12 hours for morpholine, 7 hours for piperazine and 10 hours for 1-methylpiperazine. Then the reaction mixture was poured into water (60 ml) and the precipitated crystals were filtered off, washed with water, dried and recrystallized to give 2-amino derivatives **26-30** (see Table 3).

Method E.

To a solution of 6-methyl derivative **16** (1.0 g, 4 mmoles) in dimethylformamide (10 ml) was dropwise added phosphoryl chloride (0.7 g, 4.6 mmoles) at 0° then the reaction mixture was stirred at 60° for 3 hours. The cooled reaction mixture was treated dropwise with 5% aqueous solution of sodium carbonate. The aqueous phase was carefully decanted above the precipitation, which was crystallized by the treatment with methanol. The crystals were filtered off, washed with methanol, dried and recrystallized to give 12-formyl-6-methyl derivative **31** (see Table 3).

Method F.

To a solution of 6-methyl derivative **16** (0.5 g, 2 mmoles) in dimethylformamide (5 ml) was added dropwise prosphoryl chloride. Then the reaction mixture was streared at 100° for 5 hours. The reaction mixture was poured into saturated aqueous sodium, hydrogen carbonate solution and strirred for 1 hours at ambient temperature. The precipated crystals were filtered off, it was treated with 10% aqueous hydrogen chloride at 100° for 10 minutes. After cooling to room temperature crystals were filtered off, washed with water, dried and recrystallized to give 3,12-diformyl derivative **32** (see Table 3).

Method G.

To a suspension of 3,12-diformyl compound **32** (0.89 g, 3 mmoles) in 5% aqueous solution of sodium hydroxide at 60° aqueous potassium permanganate solution (0.95 g, 6 mmoles in 5 ml of water) was added dropwise. Then the reaction mixture was stirred at 60° for 3 hours. Isopropyl alcohol (2 ml) was added to the reaction mixture to destroy the excess of potassium permanganate. The precipitated mangane dioxide was filtered off and washed with 10% aqueous sodium hydroxide solution (2 x 10 ml). The *p*H of the combined aqueous solution was adjusted to 7 with 20% aqueous hydrochloric acid. The precipitated crystals were filtered off, and washed with water then methanol, dried and crystallized to give 3-carboxylic acid **33** (see Table 3).

Method H.

To a suspension of 6-methyl derivative **16** (5.02 g, 20 mmoles) in toluene (100 ml) was added dimethyl sulfate (3.53 g, 28 mmoles). The suspension was refluxed. During the heating the reaction mixture became clear and in about 30 minutes crystal precitipitation started. After 10 hours the crystals were filtered off, washed with ethyl acetate, dried and recrystallized from acetonitrile to give metosulfate **35** (see Table 3).

Method I.

The *p*H of the aqueous solution of quaternary salt **35** (0.4 g, 1.06 mmoles) in water (20 ml) was adjusted to 9 with 3% aqueous sodium hydroxide solution (*ca.* 5 ml). The aqueous reaction mixture was extracted with chloroform (2 x 10 ml), then the combined and dried (over sodium sulfate) organic phase was evaporated to dryness *in vacuo*. The residue was treated wiht ethyl acetate (3 ml), then crystals were filtered off, which were a 1:1:1 mixture of compound **16** and *E* and *Z* izomers of ring opened product **38** (80 mg). From the filtrate, after evaporation, ring opened product **38** was obtained (see Table 3).

REFERENCES AND NOTES

[1] Nitrogen Bridgehead Compounds. **85**. I. Hermecz, I. Szilágyi, L. Őrffi, J. Kökösi and Gy. Szász, *J. Heterocyclic Chem.*, **30**, 1413 (1993).

[2] J. Kökösi, I. Hermecz, Gy. Szász and Z. Mészáros, *Tetrahedron Letters*, **22**, 4861 (1981).

[3] J. Kökösi, I. Hermecz, B. Podányi, Gy. Szász and Z. Mészáros, *J. Heterocyclic Chem.*, **22**, 1373 (1985).

[4] I. Hermecz, J. Kökösi, Á. Horváth, B. Podányi, L. Vasvári-Debreczy, Gy. Szász and Z. Mészáros, *J. Heterocyclic Chem.*, **24**, 1045 (1987).

[5] J. Kökösi, I. Hermecz, B. Podányi, Gy. Szász and Z. Mészáros, *J. Heterocyclic Chem.*, **21**, 1301 (1984).

[6] B. Robinson, The Fischer Indole Synthesis, John Wiley and Sons, New York, 1982.

[7] J. Bergman, *Alkaloids (N.Y.)*, **21** (Chap 2), 29 (1983).

[8] J. Bergman and S. Bergman, *J. Org. Chem.*, **50**, 1246 (1985).

[9] L. M. Yang, C. F. Chen and K. H. Lee, *Bioorg. Med. Chem. Letters*, **5**, 465 (1995).

[10] C. Kaneko, T. Chiba, K. Kasai and C. Miwa, *Heterocycles*, **23**, 1385 (1985).

[11] J. Kökösi, Gy. Szász and I. Hermecz, *Tetrahedron Letters*, **33**, 2995 (1992).

[12] J. H, Chu, *Sci. Rec. (China)*, **4**, 279 (1951); *Chem. Abstr.*, **46**, 11589 (1952).

[13] Ming-Tao Li and Ho-I Huang, *Yao Hsueh Hsueh Pao*, **13**, 265 (1966); *Chem. Abstr.*, **65**, 3922 (1966).

[14] Y. Asahina, Acta Phytochim., **1**, 67 (1923).

[15a] Raymond-Hamet, *Compt. Rend.*, **220**, 792 (1945); [b] Raymond-Hamet, *Compt. Rend.*, **255**, 1152 (1962); [c] Y.C. Kong and C. L. King, *Recent Adv. Nat. Prod. Res., Proc. Int. Symp.*, 1979, 104 (Pub.1980); [d] C. L. King, Y. C. Kong, N. S. Wong, H. W. Yeung, H. H. S. Fong and U. Sankawa, *J. Nat. Prod.*, **43**, 577 (1980); [e] Y. C. Kong, *Adv. Pharm. Ther.*, **6**, 239 (1982); [f] J. Ruyun, *Drugs Future*, **10**, 556 (1985); [g] N. Shoji, A. Umeyama, T. Takemoto, A. Kajiwara and Y. Ohizumi, *J. Pharm. Sci.*, **75**, 612 (1986); [h] J. Yamahara, T. Yamada, T. Kitani, Y. Naitoh and H. Fujimura, *Chem. Pharm. Bull.*, **37**, 1820 (1989); [i] J. Yamahara, T. Yamada, T. Kitani, Y. Naitoh and H. Fujimura, *J. Ethnophamacol.*, **27**, 185 (1989); [j] M. Gillner, J. Bergman, C. Cambillau and J. Gustafsson, *Carcinognesis* (London), **10**, 651 (1989); [k] Y. Kano, Q. Zong and K. Komatsu, *Chem. Pharm. Bull.*, **39**, 690 (1991).

[16a] I. Herrnecz, T. Breining, Z. Mészáros, Á. Horváth, L. Vasvári-Debreczy, F. Dessy, C. DeVos and L. Rodriguez, *J. Med. Chem.*, **25**, 1140 (1982); [b] C. DeVos, F. Dessy, I. Hermecz, Z. Mészáros and T. Breining, *Int. Arch. Allergy Appl. Immunol.*, **67**, 362 (1982); [c] I. Hermecz, T. Breining, Z. Mészáros, J. Kökösi, L. Mészáros, F. Dessy and C. DeVos, *J. Med. Chem.*, **26**, 1126 (1983).

[17] G. Tóth, Á. Szöllősy, A. Almásy, B. Podányi, I. Hermecz, T. Breining and Z. Mészáros, *Org Magn. Reson.*, **21**, 687 (1983).

[18] G. Tóth, K. Horváth-Dora, O. Clauder and H. Duddeck, *Liebigs Ann. Chem.*, 529 (1977); [b] Z. Pál, K. Horváth-Dora, G. Tóth, J. Tamás and O. Clauder, *Acta Chim. Acad. Sci. Hung.*, **99**, 43 (1979); [c] Z. Pál, K. Horváth-Dora, G. Tóth, O. Clauder and J. Tamás, *Acta Chim. Acad. Sci. Hung.*, **102**, 127 (1979).

[19a] G. Náray-Szabó, I. Hermecz and Z. Mészáros, *J. Chem. Soc. Perkin Trans. 1*, 1753 (1974); [b] F. Fülöp, I. Hermecz, Z. Mészáros, Gy. Dombi and G. Bernáth, *J. Heterocyclic Chem.*, **16**, 457 (1979); [c] H. L. Yale and E. R. Spitzmiller, *J. Heterocyclic Chem.*, **13**, 797 (1976); [d] Á. Horváth, I. Hermecz, L. Vasvári-Debreczy, K. Simon, M. Pongor-Csákvári, Z. Mészáros and G. Tóth, *J. Chem. Soc. Perkin Trans. 1*, 369 (1983).

[20a] J. Kökösi, I. Hermecz, Gy. Szász, Z. Mészáros, G. Tóth and M. Csákvári-Pongor, *J. Heterocyclic Chem.*, **19**, 909 (1982); [b] I. Hermecz, in *Heterocyclic Bio-Org. Chem.*, [Proc. Fed. Eur. Chem. Soc. FECHEM Conf.] 6th, 1990, (Publ. 1991) p 187, Cambridge, UK.

[21] A. I. Vogel, Practical Organic Chemistry, Longman Group Ltd., London, 1974, pp 590-619.

[22] J. J. P. Stewart, *QCPE Bulletin*, **9**, 10 (1989).

[23] M. W. Schmidt, K. K. Baldridge, J. A. Boatz, S. T. Elbert, M. S. Gordon, J. H. Jensen, S. Koseki, N. Matsunaga, K. A. Nguyen, S. J. Su, T. L. Windus, M. Dupuis and J. A. Montgomery, *J. Comput. Chem.*, **14**, 1347 (1993).

[24a] K. Fukui, T. Yonezawa, C. Nagata and H. Shingu, *J. Chem. Phys.*, **22**, 1433 (1954); [b] R. E. Brown and A. M. Simas, *Theor. Chim. Acta*, **62**, 1 (1982).

[25a] I. Bitter, B. Pete, G. Tóth, I. Hermecz, K. Simon and Z. Mészáros, *Heterocycles*, **24**, 69 (1986); [b] I. Bitter, B. Pete, G. Tóth, A. Almásy, I. Hermecz and Z. Mészáros, *Heterocycles*, **23**, 2289 (1985); [c] I. Bitter, B. Pete, G. Tóth, I. Hermecz and Z. Mészáros, *Heterocycles*, **23**, 2549 (1985); [d] I. Bitter, G. Tóth, B. Pete, I. Hermecz, K. Simon, G. Náray-Szabó and Z. Mészáros, *Heterocycles*, **20**, 1891 (1983); [e] I. Bitter, G. Tóth, B. Pete, I. Hermecz, K. Simon and Z. Mészáros, *Heterocycles*, **20**, 579 (1983).

[26a] H. Takayama, R. Yamamoto, M. Kurihara, M. Katajima, N. Aimi, L. Mao and S. Sakai, *Tetrahedron Letters*, **35**, 8813 (1994), [b] L. Mao, L. Xin and Y. Dequan, *Planta Med.*, **50**, 459 (1984).

[27] M. S. Morales-Rios, J. Espiñeira and P. Joseph-Nathan, *Magn. Reson. Chem.*, **25**, 377 (1987).

[28] F. Johnson, *Chem. Rev.*, **68**, 375 (1968).

[29] K. Nagarajan, R. K. S. Shah, H. Fuhrer, R. T. Puckett, M. R. Narasimhamurthy and K. Venkatesan, *Helv. Chim. Acta*, **61**, 1246 (1978).

[30] G. Tóth, I. Hermecz, and Z. Mészáros, *J. Heterocyclic Chem.*, **16**, 1181 (1979).

[31] H. O. Kalinowski and H. Kessler, *Top. Stereochem.*, **7**, 295 (1973).

[32] J. Sandström, *Top. Stereochem.*, **14**, 83 (1981).