Synthesis of 4-Aminopyrimidines from 1,2,4-Oxadiazoles, II[1]

A General Method for the Preparation of 4-Substituted 6,7-Dihydro-9,10-dialkoxy-2*H*-pyrimido[6,1-*a*]isoquinolin-2-imine Hydrochlorides

Dezső Korbonits*[a], Pál Kiss[a], Imre Bata[a], Gergely Héja[a], Kálmán Simon[a], and Pál Kolonits[b]

Chinoin Research Centre[a], P.O.B. 110, H-1325, Budapest, Hungary
Institute of Organic Chemistry, Technical, University[b], P.O.B. 91, Budapest, Hungary

Received January 19, 1987

5'-Substituted 1-[(1,2,4-oxadiazol-3-yl)methyl]-3,4-dihydroisoquinolines (7) were reduced by $NaBH_4$ selectively to give the corresponding tetrahydroisoquinolines (8) which underwent ring isomerization to pyrazolo[5,1-*a*]isoquinolines[4] (9). Catalytic hydrogenation of 7 in the presence of hydrogen chloride, in turn, gave by reductive cleavage of the N–O bond of the 1,2,4-oxadiazole ring and subsequent dehydration, quite generally, 4-substituted pyrimido[6,1-*a*]isoquinolin-2-imine hydrochlorides (11).

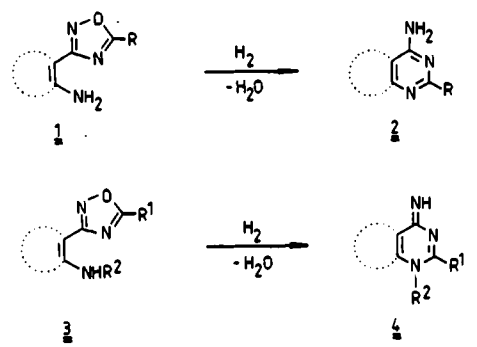
Synthese von 4-Aminopyrimidinen aus 1,2,4-Oxadiazolen, II[1]. – Eine allgemeine Methode zur Herstellung von 4-substituierten 6,7-Dihydro-9,10-dialkoxy-2*H*-pyrimido[6,1-*a*]isochinolin-2-imin-hydrochloriden

Während die Reduktion von 5'-substituierten 1-[(1,2,4-Oxadiazol-3-yl)methyl]-3,4-dihydroisochinolinen (7) mit $NaBH_4$ selektiv zu den entsprechenden Tetrahydroisochinolinen 8 und durch nachfolgende Ringisomerisierung zu Pyrazolo[5,1-*a*]isochinolinen 9 führte[4], ergab die katalytische Hydrierung von 7 in Anwesenheit von Chlorwasserstoff durch reduktive Spaltung der N–O-Bindung des 1,2,4-Oxadiazolringes und nachfolgende spontane Dehydratisierung ganz allgemein 4-substituierte Pyrimido[6,1-*a*]isochinolin-2-imin-hydrochloride (11).

Earlier we have reported the synthesis of some 2- and 4-unsubstituted pyrimido[6,1-*a*]isoquinolines[2a,b] among which several compounds with a hypotensive action were found[2c]. According to the recent literature 2-iminopyrimido[6,1-*a*]isoquinolin-4-ones have valuable pharmacological properties. In these compounds the 2-imino or 2-amino groups have been elaborated by transforming pyrimido[6,1-*a*]isoquinolin-2-ones into the corresponding 2-halides followed by amination of this function[3].

The purpose of the present study was to extend our method for the preparation of condensed 4-aminopyrimidines (2, 4) by hydrogenolysis of 3-(2-aminoaryl)-1,2,4-oxadiazoles (1, 3)[1] to the synthesis of 4-substituted 2-iminopyrimido[6,1-*a*]isoquinolines (11). In this procedure the amino or imino group is formed by an intramolecular reductive condensation (Scheme 1).

Scheme 1



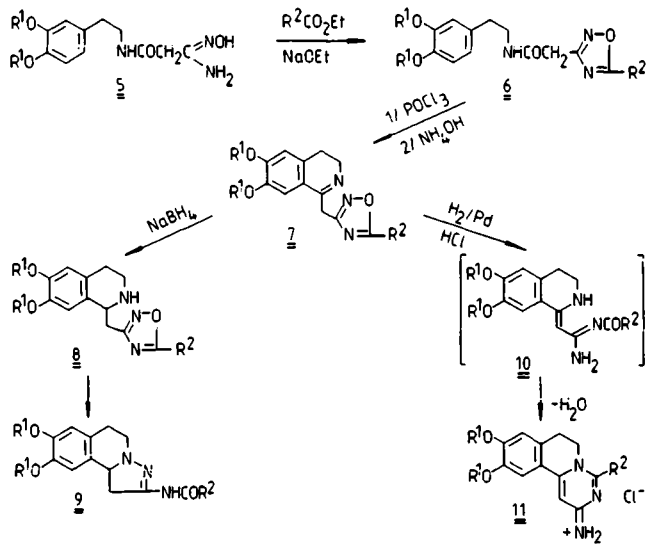
Recently we described[4] the $NaBH_4$ reduction of 1-[(1,2,4-oxadiazol-3-yl)methyl]-3,4-dihydroisoquinolines 7, readily avaible via the amides 5 and 6[5]. This involves the uptake of 1 mol of hydrogen to give the tetrahydroisoquinolines 8, which undergo spontaneously or on brief heating ring isomerization to 2-(acylamino)pyrazolo[5,1-*a*]isoquinolines (9). This reaction is analogous to the ring isomerization of the related 1,2,4-oxadiazoles[6]. It has to be noted, that, according to NMR (taken in DMSO), 7 as a base is present in solution in the enamine form containing an exocyclic double bond, while the salts of 7 exist as protonated imines.

According to our present study the reduction of 7 can be carried out with a chemo selectivity quite different from that reported earlier[4]. If the oxadiazoles **7a–z** are subjected to catalytic hydrogenation in dilute ethanolic hydrogen chloride over palladium-carbon, first the N–O bond of the 1,2,4-oxadiazol ring suffers hydrogenolysis followed in a second step by immediate cyclization and spontaneous dehydration of the intermediate acylamidines (10) to give the 4-substituted 6,7-dihydro-9,10-dialkoxy-2*H*-pyrimido[6,1-*a*]-isoquinolin-2-imine hydrochlorides **11a–z**[7].

For compounds 11 several other tautomeric forms can be envisaged, but under aqueous acidic conditions they exist probably as 2-amino-6,7-dihydro-9,10-dialkoxypyrimido-[6,1-*a*]isoquinolinium chlorides. The relative stability of the aromatic pyrimidinium ring may explain the fact that whereas catalytic hydrogenation of the related pyrimido[6,1-*a*]isoquinolines according to our previous experiences resulted, in the saturation of the pyrimidine ring[2a], in the transformation 7→11 and under the present conditions hydrogen uptake stopped after the consumption of one mol.

  0009–2940/87/0606–1039 $ 02.50/0

Scheme 2



	R¹	R²		R¹	R²
a	Me	Me	**n**	Et	*n*-heptyl
b	Me	$PhCH_2$	**o**	Et	2-morpholinoethyl
c	Me	$3,4\text{-}(MeO)_2C_6H_3CH_2$	**p**	Et	cyclohexyl
d	Me	Ph	**q**	Et	$3,4\text{-}(MeO)_2C_6H_3CH_2$
e	Me	$4\text{-}MeC_6H_4$	**r**	Et	Ph
f	Me	$4\text{-}MeOC_6H_4$	**s**	Et	$4\text{-}MeC_6H_4$
g	Me	$3,4,5\text{-}(MeO)_3C_6H_2$	**t**	Et	$4\text{-}MeOC_6H_4$
h[+]	Me	$4\text{-}R^3OC_6H_4$	**u**	Et	$3,4,5\text{-}(MeO)_3C_6H_2$
i	Me	3-pyridyl	**v**[+]	Et	$4\text{-}R^3OC_6H_4$
j	Me	4-pyridyl	**w**	Et	1-naphthyl
k	Et	Me	**x**	Et	2-pyridyl
l	Et	Et	**y**	Et	3-pyridyl
m	Et	*n*-pentyl	**z**	Et	4-pyridyl

[+] For **6h**, **v** and **7h**, **v** $R^3 = PhCH_2$, for **11h**, **v** $R^3 = H$

By variation of the ester component (R^2CO_2Et) serving to elaborate the 1,2,4-oxadiazole ring of the amide **6**, the key intermediates **7** not only permit the preparation of the pyrazolo[5,1-*a*]isoquinolines **9** by simple reduction and ring transformation[4], but as shown here, modification of the reduction provides a selective method for the preparation of pyrimido[6,1-*a*]isoquinolines of type **11** containing a broad variety of R^2 groups.

The present results extend the scope of our investigations on 4-aminopyrimidines, condensed pyrimidines, and on the ring transformation of 1,2,4-oxadiazoles[1,2,4,6,8].

Thanks are due to Miss *V. Harangozó* for technical assistance, to Dr. *V. Kovács* for recording the IR spectra, and to Dr. *I. Remport* for elemental analyses.

Experimental

IR spectra: Unicam SP-100 and Spectromom 2000 in KBr. – ^1H- and ^{13}C-NMR spectra: Jeol FX-100 at 100 and 25 MHz, respectively. In the Tables only characteristic ^1H-NMR data are quoted. Melting points were not corrected.

5-Substituted 3-{[2-(3,4-Dialkoxyphenyl)ethyl]carbamoylmethyl}-1,2,4-oxadiazoles (**6**) (General method)[4,5]: To a solution of 2-{[2-(3,4-dialkoxyphenyl)ethyl]carbamoyl}acetamide oxime (**5**) (75 mmol) in dry ethanol (300 ml) the appropriate carboxylic ester (150 mmol) and a solution of sodium (1.72 g, 75 mmol) in ethanol (75 ml) was added. After refluxing for 4 h the mixture was cooled, the product separated, washed with water (300 ml), and dried. Compounds **6m** and **6n** were recrystallized from hexane, all the others from ethanol. M.p.'s, yields, IR spectroscopic data, and elementary analyses see Table 1, ^1H-NMR data Table 4.

Table 1. Yields, melting points, IR spectral and analytical data of compounds **6a–c** and **6g–z**. The data of **6d–f** were given earlier[4]

No	Yield (%)	M.p. (°C)	ν_{max}/cm^{-1}	Formula Mol. Wt.	Found(%) (Required) C	H	N
6a	63	127	3295, 1652	$C_{15}H_{19}N_3O_4$ 305.32	59.96 (59.00)	6.25 (6.27)	13.72 (13.76)
6b	39	152[a]	3180, 1635	$C_{21}H_{23}N_3O_4$ 381.41	66.00 (66.13)	6.02 (6.08)	10.97 (11.02)
6c	67	124	3290, 1660	$C_{23}H_{27}N_3O_6$ 441.47	62.65 (62.57)	6.08 (6.16)	9.31 (9.51)
6g	55	152	3220, 1640	$C_{23}H_{27}N_3O_7$ 457.47	60.21 (60.38)	5.84 (5.73)	9.29 (9.18)
6h	56	144	3340, 1662, 1620	$C_{27}H_{27}N_3O_5$ 473.51	68.31 (68.48)	5.60 (5.75)	8.80 (8.87)
6i	63	131	3295, 1645	$C_{19}H_{20}N_4O_4$ 368.36	61.98 (61.94)	5.40 (5.47)	15.15 (15.21)
6j	52	162	3340, 1658	$C_{19}H_{20}N_4O_4$ 368.36	62.30 (61.94)	5.46 (5.47)	15.23 (15.21)
6k	71	99	3320, 2950, 1652	$C_{17}H_{23}N_3O_4$ 333.37	61.10 (61.24)	6.70 (6.95)	12.55 (12.60)
6l	40	106	3310, 3000, 1650	$C_{18}H_{25}N_3O_4$ 347.40	62.50 (62.23)	7.16 (7.25)	12.05 (12.10)
6m	80	77 (from hexane)	3300, 2910, 1650	$C_{21}H_{31}N_3O_4$ 389.49	64.52 (64.76)	7.95 (8.02)	10.63 (10.79)
6n	72	76 (from hexane)	3400, 2900, 1630	$C_{23}H_{35}N_3O_4$ 417.53	66.03 (66.16)	8.32 (8.45)	10.01 (10.06)
6o	71	89 (from hexane)	3265, 2975, 1640	$C_{22}H_{32}N_4O_5$ 432.51	61.05 (61.09)	7.43 (7.46)	12.91 (12.95)
6p	45	109	3310, 2950, 1650	$C_{22}H_{31}N_3O_4$ 401.49	65.86 (65.01)	7.66 (7.70)	10.60 (10.47)
6q	74	121	3320, 1655	$C_{25}H_{31}N_3O_6$ 469.52	63.90 (63.95)	6.56 (6.66)	8.97 (8.95)
6r	71	137	3290, 1642	$C_{22}H_{25}N_3O_4$ 395.44	67.03 (66.82)	6.40 (6.37)	10.89 (10.63)
6s	61	152	3340, 1665	$C_{23}H_{27}N_3O_4$ 409.47	67.38 (67.46)	6.73 (6.65)	10.29 (10.26)
6t	78	142	3300, 1650	$C_{23}H_{27}N_3O_5$ 425.47	65.10 (64.92)	6.50 (6.40)	9.72 (9.88)
6u	49	148	3360, 1638	$C_{25}H_{31}N_3O_7$ 485.52	61.23 (61.04)	6.33 (6.64)	8.70 (8.66)
6v	47	141	3320, 1662, 1620	$C_{29}H_{31}N_3O_5$ 501.56	69.14 (69.44)	6.02 (6.23)	8.36 (8.38)
6w	62	160	3320, 1658	$C_{26}H_{27}N_3O_4$ 445.50	70.00 (70.09)	6.13 (6.11)	9.07 (9.43)
6x	47	128	3300, 1655	$C_{21}H_{24}N_4O_4$ 396.43	63.70 (63.62)	6.15 (6.10)	14.15 (14.13)
6y	59	129	3295, 1650	$C_{21}H_{24}N_4O_4$ 396.43	63.45 (63.62)	6.00 (6.10)	14.05 (14.13)
6z	37	136	3320, 1652	$C_{21}H_{24}N_4O_4$ 396.43	63.42 (63.62)	5.95 (6.10)	14.21 (14.13)

[a] Ref.[5] 153°C.

5'-Substituted 3,4-Dihydro-6,7-dialkoxy-1-[(1,2,4-oxadiazol-3-yl)methyl]isoquinolines (**7**) (General method)[4,5]: To a hot solution of oxadiazole **6** (60 mmol) in chloroform (200 ml) phosphoryl chloride (55.2 g, 33 ml, 360 mmol) was added dropwise. Boiling was continued for another 3 h. Then excess reagent was distilled off, the residue dissolved in chloroform, and the solution made alkaline with conc. ammonium hydroxide under cooling. The solution was thoroughly extracted with water, evaporated and the residue crystallized. M.p.'s., solvents of crystallization, yields, IR spectroscopic data, and elementary analyses were compiled in Table 2, ^1H-NMR data in Table 5.

Table 2. Yields, melting points, IR spectral and analytical data of compounds **7a–c** and **7g–z**. The data of **7d–f** were given earlier[4]

No	Yield (%)	M.p.(°C) r.s.[a]	ν_{max}/cm^{-1}	Formula Mol. Wt.	Found(%) (Required) C	H	N
7c	71	122 E	3335, 1640, 1620	$C_{15}H_{17}N_3O_3$ 287.31	62.73 (62.70)	6.00 (5.97)	14.60 (14.63)
7h	61	145[b] E	3295, 1630, 1622	$C_{21}H_{21}N_3O_3$ 363.40	69.56 (69.40)	5.75 (5.82)	11.60 (11.56)
7i	70	145 E	3300, 1630, 1610	$C_{23}H_{25}N_3O_5$ 423.45	65.36 (65.23)	5.97 (5.95)	9.95 (9.92)
7k	56	150 E	3295, 1630	$C_{23}H_{25}N_3O_6$ 439.45	62.83 (62.85)	5.70 (5.73)	9.60 (9.56)
7l	58	195 A	3350, 1640, 1620	$C_{27}H_{25}N_3O_4$ 455.49	71.08 (71.19)	5.40 (5.53)	9.30 (9.22)
7m	41	169 A	3360, 1630, 1610	$C_{19}H_{10}N_4O_3$ 350.36	65.11 (65.13)	5.04 (5.10)	15.00 (15.99)
7n	56	172 A	3345, 1625, 1605	$C_{19}H_{10}N_4O_3$ 350.36	65.02 (65.13)	5.30 (5.10)	15.02 (15.99)
7o	72	134 E	3305, 1622, 1604	$C_{17}H_{21}N_3O_3$ 315.36	64.70 (64.74)	6.59 (6.71)	13.27 (13.32)
7q	83	93 E	3350, 1630, 1612	$C_{10}H_{23}N_3O_3$ 329.38	65.65 (65.63)	7.16 (7.04)	12.73 (12.76)
7r	64	171[c] EA 1610	2960, 2560, 1663	$C_{21}H_{29}N_3O_3$·HCl 407.93	62.00 (61.83)	7.50 (7.41)	10.30[d] (10.30)
7p	57	151[c] EA 1612	2950, 2560, 1660	$C_{23}H_{33}N_3O_3$·HCl 435.98	63.50 (63.36)	8.01 (7.86)	9.40[e] (9.64)
7s	60	141 A	3320, 1640, 1595	$C_{22}H_{30}N_4O_4$ 414.49	64.00 (63.75)	7.23 (7.30)	13.46 (13.52)
7t	79	101 E	3375, 2950, 1630	$C_{22}H_{29}N_3O_3$ 383.47	68.90 (68.90)	7.49 (7.62)	10.90 (10.96)
7u	34	163 A	3350, 2950, 1635 1612	$C_{25}H_{29}N_3O_5$ 451.50	66.45 (66.50)	6.43 (6.47)	9.28 (9.31)
7v	74	137 A	3355, 1640, 1617	$C_{22}H_{23}N_3O_3$ 377.42	70.28 (70.01)	6.13 (6.14)	11.20 (11.13)
7w	77	154 A	3400, 1640, 1622	$C_{23}H_{25}N_3O_3$ 391.45	70.28 (70.57)	6.61 (6.44)	10.95 (10.74)
7x	79	131 A	3350, 1630, 1618	$C_{23}H_{25}N_3O_4$ 407.45	67.36 (67.79)	6.12 (6.18)	10.49 (10.31)
7y	71	158 A	3350, 1642, 1615	$C_{25}H_{29}N_3O_6$ 467.50	64.68 (64.22)	6.30 (6.25)	8.75 (8.99)
7z	51	150 A	3320, 1630, 1612	$C_{29}H_{29}N_3O_4$ 483.54	71.93 (72.03)	5.99 (6.05)	8.72 (8.69)
7aa	77	150 A	3355, 1636, 1616	$C_{26}H_{25}N_3O_3$ 427.48	72.83 (73.05)	5.92 (5.89)	9.92 (9.83)
7ab	62	139 A	3325, 1625, 1605	$C_{21}H_{22}N_4O_3$ 378.42	66.49 (66.65)	5.82 (5.86)	14.63 (14.81)
7ac	58	169 A	3305, 1630, 1605	$C_{21}H_{22}N_4O_3$ 378.42	66.35 (66.65)	5.85 (5.86)	14.57 (14.81)
7ad	57	166 A	3370, 1640, 1618	$C_{21}H_{22}N_4O_3$ 378.42	66.77 (66.65)	5.78 (5.86)	14.78 (14.81)

[a] Recrystallization solvents: E = EtOH, EA = EtOAc, A = CH_3CN. – [b] Ref.[5] 145°C. – [c] As monohydrochloride. – [d] Cl Found 8.80 (required 8.69). – [e] Cl Found 8.02 (required 8.13).

6,7-Dihydro-9,10-dimethoxy-4-methyl-2H-pyrimido[6,1-a]isoquinolin-2-imine Hydrochloride (**11a**)[7]: **7a** (2.87 g, 10 mmol) was hydrogenated over 8% palladiumcarbon (0.2 g) in a mixture of ethanol (200 ml) and 10% hydrochloric acid (10 ml). The uptake of hydrogen was complete within 30 min. Filtration, evaporation, and crystallization of the residue from water gave **11a** (2.34 g, 72%), m.p. 275°C (dec.). – IR: 3400 cm^{-1}, 3200, and 1630. – ^{1}H NMR ([D$_6$]DMSO): δ = 2.68 (s, 3H, CH_3), 3.06 (t, *J* = 6.5 Hz, 2H, 7-H), 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.24 (t, *J* = 6.5 Hz, 2H, 6-H), 7.09 (s, 1H, 8-H), 7.24 (s, 1H, 11- or 1-H), 7.38 (s, 1H, 1- or 11-H), 8.70 (bs, 1H, NH-2 or NH-3), 8.72 (bs, 1H, NH-3 or NH-2). – ^{13}C NMR ([D$_6$]DMSO): δ = 23.36 (CH_3), 26.10 (C-7), 45.99 (C-6), 56.14 (2 OCH_3), 97.50 (C-7), 109.00 (C-11), 111.13 (C-8), 117.51 (C-11a), 130.55 (C-7a), 148.60 (C-9 or C-10), 149.80 (C-10 or C-9), 153.05 (C-11b), 162.82 (C-4 or C-2), 163.26 (C-2 or C-4).

$C_{15}H_{18}ClN_3O_2 \cdot H_2O$ (325.8)
Calcd. C 55.29 H 6.19 Cl 10.88 N 12.90
Found C 55.32 H 6.08 Cl 10.94 N 12.75

6,7-Dihydro-9,10-dimethoxy-4-phenyl-2H-pyrimido[6,1-a]isoquinolin-2-imine Hydrochloride (**11d**): **7d**[5] (3.49 g, 10 mmol) was hydrogenated as described for **11a** to give **11d** (3.02 g, 78%), m.p. 232°C (from H_2O). – IR: 3380 cm^{-1}, 3210, 1655. – ^{1}H NMR ([D$_6$]DMSO): δ = 3.03 (m, 2H, 7-H), 3.87 (s, 6H, 2 OCH_3), 4.12 (m, 2H, 6-H), 7.09 (s, 1H, 8-H), 7.64 (s, 1H, 11- or 1-H), 7.58 (s, 1H, 1- or 11-H), 7.6–7.9 (m, 5H, Ph), 8.96 (bs, 1H, NH-2 or NH-3), 9.23 (bs, 1H, NH-3 or NH-2). – ^{13}C NMR ([D$_6$]DMSO): δ = 23.36 (C-7), 48.59 (C-6), 56.20 (OCH_3), 56.26 (OCH_3), 98.55 (C-1), 109.00 (C-11), 111.19 (C-8), 117.95 (C-11a), 128.86 (C-2′ or C-3′), 128.95 (C-3′ or C-2′), 130.79 (C-7a), 131.26 (C-4′), 133.16 (C-1′), 148.63 (C-9 or C-10), 150.07 (C-10 or C-9), 153.05 (C-11b), 162.06 (C-4 or C-2), 163.26 (C-2 or C-4).

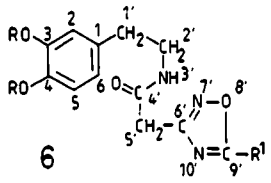
$C_{20}H_{20}ClN_3O_2 \cdot H_2O$ (387.9)
Calcd. C 61.93 H 5.72 Cl 9.14 N 10.83
Found C 61.73 H 5.81 Cl 9.00 N 10.90

Table 3. Yields, melting points, IR spectral and analytical data of compounds **11b, c, e–z**

No	Yield (%)	M.p.(°C) r.s.[a]	ν_{max}/cm^{-1}	Formula Mol. Wt.	Found(%) (Required) C	H	N	Cl
11b	64	252 E–W 1:1	3300, 3200, 1630	$C_{21}H_{21}N_3O_2$·HCl·H_2O 401.88	62.62 (62.76)	6.32 (6.01)	10.48 (10.45)	8.07 (8.82)
11c	48	223 E	3340, 3110, 1650	$C_{23}H_{25}N_3O_4$·HCl·H_2O 461.93	59.65 (59.80)	6.10 (6.11)	8.81 (9.10)	7.65 (7.68)
11e	72	255 W	3420, 3270, 1660	$C_{21}H_{21}N_3O_2$·HCl·H_2O 401.88	62.90 (62.76)	5.95 (6.02)	10.35 (10.46)	9.01 (8.82)
11f	69	248 W	3420, 3220, 1630	$C_{21}H_{21}N_3O_3$·HCl·H_2O 417.88	60.21 (60.35)	5.80 (5.79)	10.17 (10.06)	8.37 (8.49)
11g	60	259 W	3320, 3140, 1625	$C_{23}H_{25}N_3O_5$·HCl·H_2O 478.03	58.16 (57.80)	5.65 (5.90)	8.96 (8.79)	7.47 (7.42)
11h	63	297 E	3360, 3150, 1660	$C_{20}H_{19}N_3O_3$·HCl·H_2O 305.84	61.99 (62.25)	5.36 (5.22)	10.68 (10.89)	9.07 (9.19)
11i	44	246 E	3360, 3100, 1660	$C_{19}H_{10}N_4O_2$·2HCl·2H_2O 443.32	51.72 (51.47)	5.31 (5.46)	12.63 (12.64)	
11j	82	270 E	3410, 3250, 1670	$C_{19}H_{10}N_4O_2$·2HCl 407.29	56.24 (56.03)	5.07 (4.95)	13.67 (13.76)	17.43 (17.41)
11k	70	285 W 1625	3420, 3270, 1672	$C_{17}H_{21}N_3O_2$·HCl·H_2O 353.84	57.51 (57.70)	6.83 (6.84)	12.07 (11.88)	9.95 (10.02)
11l	50	243 A	3400, 3200, 1640	$C_{18}H_{23}N_3O_2$·HCl·H_2O 367.87	58.70 (58.76)	7.15 (7.12)	11.35 (11.42)	9.82 (9.64)
11n	61	244 P	3300, 3100, 2950 1640	$C_{21}H_{29}N_3O_2$·HCl·H_2O 409.95	61.70 (61.52)	8.16 (7.87)	9.97 (10.25)	8.49 (8.65)
11p	48	225 E–D 1:3	3300, 3100, 2920 1640	$C_{23}H_{33}N_3O_2$·HCl·H_2O 438.00	62.99 (63.07)	8.39 (8.29)	9.50 (9.59)	8.02 (8.10)
11q	86	195 E–D 1:6	3200, 3100, 2850 1635	$C_{22}H_{30}N_4O_3$·2HCl·2H_2O 507.45	52.14 (52.07)	7.00 (7.15)	11.10 (11.04)	14.05 (13.97)
11r	65	228 E	3300, 3150, 2920 1640	$C_{22}H_{29}N_3O_2$·HCl 403.95			10.30 (10.40)	8.69 (8.78)
11s	56	250 E	3320, 3050, 1660	$C_{25}H_{29}N_3O_4$·HCl 471.97	63.19 (63.62)	6.49 (6.41)	8.99 (8.90)	7.21 (7.51)
11t	80	260 W	3420, 3350, 1660	$C_{22}H_{23}N_3O_2$·HCl·H_2O 415.91	63.12 (63.53)	6.40 (6.30)	9.97 (10.10)	8.50 (8.53)
11u	41	250 W	3290, 3095, 1645	$C_{23}H_{25}N_3O_2$·HCl·H_2O 429.93	64.29 (64.25)	6.71 (6.56)	9.32 (9.77)	8.25 (8.25)
11v	41	276 W	3460, 3350, 1645	$C_{23}H_{25}N_3O_3$·HCl·H_2O 445.93	62.18 (61.94)	6.33 (6.33)	9.69 (9.42)	8.10 (7.95)
11w	85	253 E	3360, 3150, 1650	$C_{25}H_{29}N_3O_5$·HCl·H_2O 506.00	59.25 (59.34)	6.35 (6.38)	8.40 (8.30)	7.30 (7.01)
11x	51	305 E	3300, 3100, 1640	$C_{22}H_{23}N_3O_3$·HCl 413.89	64.05 (63.84)	6.08 (5.84)	10.30 (10.15)	8.72 (8.57)
11y	51	255 E	3400, 3300, 1650	$C_{26}H_{25}N_3O_2$·HCl·H_2O 465.96	66.71 (66.37)	6.06 (5.70)	9.02 (9.10)	
11z	63	247 E	3400, 3290, 1658	$C_{21}H_{22}N_4O_2$·HCl 398.88	62.91 (63.23)	6.04 (5.81)	14.12 (14.05)	8.65 (8.89)
11aa	60	275 E	3460, 3300, 1625	$C_{21}H_{22}N_4O_2$·2HCl 435.35	57.70 (57.93)	5.65 (5.56)	13.02 (12.87)	16.02 (16.29)
11ab	61	244 E	3350, 3200, 1660	$C_{21}H_{22}N_4O_2$·2HCl·2H_2O 471.39	53.35 (53.50)	5.78 (5.99)	12.07 (11.89)	15.00 (15.04)

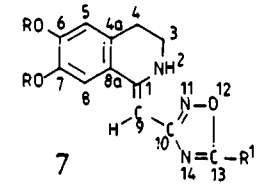
[a] Recrystallization solvents: E = EtOH, W = water, A = CH_3CN, P = 2-propanol, D = diethyl ether.

Table 4. ^{1}H-NMR data of **6a–z** (δ ppm, [D$_6$]DMSO)



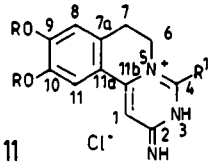
	2-H = 6.79–6.85 ; 5-H = 6.82–6.87 ; 6-H = 6.68–6.75 ; 1'-H = 2.62–2.70 ; 2'-H = 3.26–3.35 ; 3'-H = 8.24–8.41 ; 5'-H = 3.56–3.77 , $J_{2,6}$ = 1.5–2 Hz ; $J_{5,6}$ = 8–8.5 Hz ; a) R = Me, CH_3: 3.69–3.70 ; b) R = Et, CH_3: 1.28–1.31 ; CH_2 = 3.93–4.01		
	R^1		
a	2.56 (s,3H,CH_3)		
b	4.33 (s,2H,CH_2); 7.34 (s,5H,Ph)		
c	3.72 (s,3H,OCH_3); 3.74 (s,3H,OCH_3); 4.25 (s,2H,CH_2); 6.8–7.0 (m,3H,Ar)		
d	7.5–7.8 (m,3H,Ph-3',4',5'H); 8.0–8.2 (m,2H,Ph-2',6'H)		
e	2.41 (s,3H,CH_3); 7.44 (d,2H,Ph-3',5'H); 7.98 (d,2H,Ph-2',6'H)		
f	3.87 (s,3H,OCH_3); 7.16 (d,2H,Ph-3',5'H); 8.03 (d,2H,Ph-2',6'H)		
g	3.77 (s,3H,OCH_3); 3.89 (s,6H,2xOCH_3); 7.34 (s,2H,Ph-2',6'H)		
h	5.24 (s,2H,OCH_2); 7.25 (d,2H,Ph-3',5'H); 7.44 (m,5H,Ph'); 8.04 (d,2H,Ph-2',6'H)		
i	7.68 (m,1H,Py-5'H); 8.47 (m,1H,Py-6'H); 8.86 (m,1H,Py-4'H); 9.25 (m,1H,Py-2'H)		
j	8.01 (m,2H,Py-2',6'H); 8.90 (m,2H,Py-3',5'H)		
k	2.56 (s,3H,CH_3)		
l	1.27 (t,3H,CH_3); 2.91 (q,2H,CH_2)		
m	0.86 (t,3H,CH_3); 1.30 (m,4H,2xCH_2); 1.69 (m,2H,CH_2); 2.88 (t,2H,CH_2)		
n	0.85 (t,3H,CH_3); 1.31 (m,8H,4xCH_2); 1.70 (m,2H,CH_2); 2.89 (t,2H,CH_2)		
o	2.40 (m,4H,2xCH_2(N)); 2.71 (t,2H,CH_2-C); 3.09 (t,2H,CH_2-N); 3.54 (m,4H,2xCH_2(O))		
p	1.2–2.0 (m,10H,5xCH_2); 3.00 (m,1H,cyclohexyl-1'H)		
q	3.73 (s,6H,2xOCH_3); 4.24 (s,2H,CH_2); 6.8–7.0 (m,3H,Ar)		
r	7.5–7.8 (m,3H,Ph-3',4',5'H); 8.0–8.2 (m,2H,Ph-2',6'H)		
s	2.42 (s,3H,CH_3); 7.45 (d,2H,Ph-3',5'H); 7.98 (d,2H,Ph-2',6'H)		
t	3.87 (s,3H,OCH_3); 7.17 (d,2H,Ph-3',5'H); 8.04 (d,2H,Ph-2',6'H)		
u	3.77 (s,3H,OCH_3); 3.90 (s,6H,2xOCH_3); 7.34 (s,2H,Ph-2',6'H)		
v	5.23 (s,2H,OCH_2); 7.25 (d,2H,Ph-3',5'H); 7.3–7.5 (m,5H,Ph'); 8.04 (d,2H,Ph-2',6'H)		
w	7.5–7.8 (m,2H,Ar); 8.0–8.3 (m,4H,Ar); 8.80 (m,1H,naphthyl-1'H)		
x	7.72 (m,1H,Py-4'H); 8.09 (m,1H,Py-5'H); 8.24 (m,1H,Py-6'H); 8.84 (m,1H,Py-3'H)		
y	7.68 (m,1H,Py-5'H); 8.47 (m,1H,Py-6'H); 8.86 (m,1H,Py-4'H); 9.25 (m,1H,Py-2'H)		
z	8.01 (dd,2H,Py-2',6'H); 8.89 (dd,2H,Py-3',5'H)		

Table 5. ^{1}H-NMR data of **7a–z** (δ ppm, [D$_6$]DMSO)



	2-H = 7.31–7.53 ; 3-H = 3.40–3.49 ; 4-H = 2.76–2.84 ; 5-H = 6.84–6.88 ; 8-H = 7.26–7.35 ; 9-H = 5.45–5.64 ; a) R = Me, CH_3: 3.79–3.86 ; b) R = Et, CH_3: 1.32–1.35 ; CH_2 = 4.06–4.12		
	R^1		
a	2.55 (s,3H,CH_3)		
b	4.29 (s,2H,CH_2); 7.35 (m,5H,Ph)		
c	3.74 (s,3H,OCH_3); 3.75 (s,3H,OCH_3); 4.20 (s,2H,CH_2); 6.8–7.0 (m,3H,Ar)		
d	7.5–7.7 (m,3H,Ph-3',4',5'H); 8.0–8.2 (m,2H,Ph-2',6'H)		
e	2.42 (s,3H,CH_3); 7.44 (d,2H,Ph-3',5'H); 8.03 (d,2H,Ph-2',6'H)		
f	3.87 (s,3H,OCH_3); 7.16 (d,2H,Ph-3',5'H); 8.07 (d,2H,Ph-2',6'H)		
g	3.77 (s,3H,OCH_3); 3.89 (s,6H,2xOCH_3); 7.36 (s,2H,Ph-2',6'H)		
h	5.25 (s,2H,OCH_2); 7.24 (d,2H,Ph-3',5'H); 7.43 (m,5H,Ph'); 8.07 (d,2H,Ph-2',6'H)		
i	7.66 (m,1H,Py-5'H); 8.49 (m,1H,Py-6'H); 8.85 (m,1H,Py-4'H); 9.31 (m,1H,Py-2'H)		
j	8.03 (dd,2H,Py-2',6'H); 8.87 (dd,2H,Py-3',5'H)		
k	2.53 (m,3H,CH_3)		
l	1.29 (t,3H,CH_3); 2.88 (q,2H,CH_2)		
m	0.86 (t,3H,CH_3); 1.26 (bs,4H,2xCH_2); 1.73 (m,2H,CH_2); 2.76 (t,2H,CH_2)		
n	0.84 (t,3H,CH_3); 1.26 (bs,8H,4xCH_2); 1.71 (m,2H,CH_2); 2.76 (t,2H,CH_2)		
o	2.41 (m,4H,2xCH_2(N)); 2.75 (m,2H,CH_2-N); 3.06 (m,2H,CH_2-C); 3.55 (m,4H,2xCH_2(O))		
p	1.3–2.1 (m,10H,5xCH_2); 2.97 (m,1H,cyclohexyl-1'H)		
q	3.73 (s,3H,OCH_3); 3.74 (s,3H,OCH_3); 4.20 (s,2H,CH_2); 6.7–7.0 (m,3H,Ar)		
r	7.5–7.8 (m,3H,Ph-3',4',5'H); 8.0–8.2 (m,2H,Ph-2',6'H)		
s	2.42 (s,3H,CH_3); 7.44 (d,2H,Ph-3',5'H); 8.02 (d,2H,Ph-2',6'H)		
t	3.87 (s,3H,OCH_3); 7.16 (d,2H,Ph-3',5'H); 8.07 (d,2H,Ph-2',6'H)		
u	3.77 (s,3H,OCH_3); 3.90 (s,6H,2xOCH_3); 7.36 (s,2H,Ph-2',6'H)		
v	5.23 (s,2H,OCH_2); 7.24 (d,2H,Ph-3',5'H); 7.3–7.6 (m,5H,Ph'); 8.07 (d,2H,Ph-2',6'H)		
w	7.6–7.8 (m,2H,Ar); 8.0–8.3 (m,4H,Ar); 8.80 (s,1H,naphthyl-1'H)		
x	7.67 (m,1H,Py-4'H); 8.07 (m,1H,Py-5'H); 8.27 (m,1H,Py-6'H); 8.81 (m,1H,Py-3'H)		
y	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)		
z	8.05 (dd,2H,Py-2',6'H); 8.88 (dd,2H,Py-3',5'H)		

Table 6. ^{1}H-NMR data of **11a–z** (δ ppm, [D$_6$]DMSO). Structure in [D$_6$]DMSO



	1-H = 7.34–7.58 ; 2-NH = 8.60–9.20 ; 3-H = 8.72–9.23 ; 6-H = 4.09–4.32 ; 7-H = 2.96–3.06 ; 8-H = 7.04–7.09 ; 11-H = 7.13–7.43 ; a) R = Me, CH_3: 3.85–3.89 ; b) R = Et, CH_3: 1.36–1.39 ; CH_2 = 4.08–4.15		
	R^1		
a	2.68 (s,3H,CH_3)		
b	4.42 (s,2H,CH_2); 7.33 (s,5H,Ph)		
c	3.73 (s,3H,OCH_3); 3.74 (s,3H,OCH_3); 4.34 (s,2H,CH_2); 6.77 (dd,1H,Ph-6'H); 6.92 (d,1H,Ph-5'H); 6.96 (d,1H,Ph-2'H)		
d	7.6–7.9 (m,5H,Ph)		
e	2.42 (s,3H,CH_3); 7.42 (d,2H,Ph-3',5'H); 7.64 (d,2H,Ph-2',6'H)		
f	3.87 (s,3H,OCH_3); 7.16 (d,2H,Ph-3',5'H); 7.72 (d,2H,Ph-2',6'H)		
g	3.76 (s,3H,OCH_3); 3.82 (s,6H,2xOCH_3); 7.08 (s,2H,Ph-2',6'H)		
h	7.00 (d,2H,Ph-3',5'H); 7.59 (d,2H,Ph-2',6'H); 10.5 (bs,1H,OH)		
i	7.78 (dd,1H,Py-5'H); 8.35 (m,1H,Py-6'H); 8.89 (dd,1H,Py-4'H); 9.01 (m,1H,Py-2'H)		
j	7.92 (dd,2H,Py-2',6'H); 8.96 (dd,2H,Py-3',5'H)		
k	2.67 (s,3H,CH_3)		
l	1.25 (t,3H,CH_3); 3.00 (q,2H,CH_2)		
m	0.90 (t,3H,CH_3); 1.36 (bs,4H,2xCH_2); 1.73 (m,2H,CH_2); 2.97 (t,2H,CH_2)		
n	0.87 (t,3H,CH_3); 1.30 (bs,8H,4xCH_2); 1.72 (m,2H,CH_2); 2.97 (t,2H,CH_2)		
o	3.60 (bs,6H,3xCH_2); 3.98 (m,6H,3xCH_2); 11.70 (b,1H,NH$^+$)		
p	1.4–2.0 (m,10H,5xCH_2); 3.17 (m,1H,cyclohexyl-1'H)		
q	4.33 (s,2H,CH_2); 6.77 (dd,1H,Ph-6'H); 6.91 (d,1H,Ph-5'H); 6.95 (d,1H,Ph-2'H)		
r	7.65 (m,5H,Ph)		
s	2.42 (s,3H,CH_3); 7.41 (d,2H,Ph-3',5'H); 7.63 (d,2H,Ph-2',6'H)		
t	3.86 (s,3H,OCH_3); 7.25 (d,2H,Ph-3',5'H); 7.72 (d,2H,Ph-2',6'H)		
u	3.76 (s,3H,OCH_3); 3.82 (s,6H,2xOCH_3); 7.07 (s,2H,Ph-2',6'H)		
v	6.97 (d,2H,Ph-3',5'H); 7.58 (d,2H,Ph-2',6'H); 10.2 (vb,1H,OH)		
w	7.5–7.9 (m,3H,Ar); 8.0–8.2 (m,3H,Ar); 8.35 (bs,1H,naphthyl-1'H)		
x	7.69 (m,1H,Py-4'H); 7.93 (m,1H,Py-6'H); 8.15 (m,1H,Py-5'H); 8.78 (m,1H,Py-3'H)		
y	7.85 (dd,1H,Py-5'H); 8.43 (m,1H,Py-6'H); 8.94 (dd,1H,Py-4'H); 9.06 (d,1H,Py-2'H)		
z	7.99 (dd,2H,Py-2',6'H); 8.88 (dd,2H,Py-3',5'H)		

4-Substituted 6,7-Dihydro-9,10-dialkoxy-2H-pyrimido[6,1-a]isoquinolin-2-imine Hydrochlorides (**11b, c, e–z**) (General method): A solution of the oxadiazole **7** (10 mmol) in a mixture of ethanol (200 ml) and 10% hydrochloric acid (10 ml) was hydrogenated over 8% palladium/carbon catalyst (0.2 g) until the uptake of hydrogen stopped. If the hydrochloride of the product precipitated hydrogenolysis was continued at 60°C and the catalyst filtered off at this temperature. The solvent was evaporated in vacuo and the residue crystallized to constant m.p. The [(benzyloxy)phenyl]oxadiazoles **7h** and **7v** absorbed two mol of hydrogen and gave the corresponding hydroxyphenyl compounds **11h** and **11v**. Yields, m.p.'s, solvents of crystallization, IR data, and elementary analyses were given in Table 3, ^{1}H-NMR data in Table 6.

CAS Registry Numbers

5a: 105361-71-5 / **5k**: 107301-08-6 / **6a**: 107300-85-6 / **6b**: 107300-86-7 / **6c**: 107300-87-8 / **6d**: 105361-45-3 / **6e**: 105361-47-5 / **6f**: 105361-46-4 / **6g**: 107300-88-9 / **6h**: 107300-89-0 / **6i**: 107300-90-3 / **6j**: 107300-91-4 / **6k**: 107300-92-5 / **6l**: 107300-93-6 / **6m**: 107300-94-7 / **6n**: 107300-95-8 / **6o**: 107300-96-9 / **6p**: 107300-97-0 / **6q**: 107300-98-1 / **6r**: 107300-99-2 / **6s**: 107301-00-8 / **6t**: 107301-01-9 / **6u**: 107301-02-0 / **6v**: 107301-03-1 / **6w**: 107301-04-2 / **6x**: 107301-05-3 / **6y**: 107301-06-4 / **6z**: 107301-07-5 / **7a**: 107301-11-1 / **7b**: 107301-12-2 / **7c**: 107301-13-3 / **7d**: 107301-58-6 / **7e**: 107301-09-7 / **7f**: 107301-10-0 / **7g**: 107301-14-4 / **7h**: 107301-15-5 / **7i**: 107301-16-6 / **7j**: 107301-17-7 / **7k**: 107301-18-8 / **7l**: 107301-19-9 / **7m**: 107301-20-2 / **7n**: 107301-21-3 / **7o**: 107301-22-4 / **7p**: 107301-23-5 / **7q**: 107301-24-6 / **7r**: 107301-25-7 / **7s**: 107301-26-8 / **7t**: 107301-27-9 / **7u**: 107301-28-8 / **7v**: 107301-29-1 / **7w**: 107301-30-4 / **7x**: 107301-31-5 / **7y**: 107301-32-6 / **7z**: 107301-33-7 / **11a**: 83733-79-3 / **11b**: 107301-34-8 / **11c**: 107301-35-9 / **11d**: 107301-59-7 / **11e**: 107301-36-0 / **11f**: 107301-37-1 / **11g**: 107301-38-2 / **11h**: 107301-39-3 / **11i**: 107301-40-6 /

11j: 107301-41-7 / **11k**: 107301-42-8 / **11l**: 107301-43-9 / **11m**: 107301-44-0 / **11n**: 107301-45-1 / **11o**: 107301-46-2 / **11p**: 107301-47-3 / **11q**: 107301-48-4 / **11r**: 107301-49-5 / **11s**: 107301-50-8 / **11t**: 107301-51-9 / **11u**: 107301-52-0 / **11v**: 107301-53-1 / **11w**: 107301-54-2 / **11x**: 107301-55-3 / **11y**: 107301-56-4 / **11z**: 107301-57-5 / $MeCO_2Et$: 141-78-6 / $PhCH_2CO_2Et$: 101-97-3 / $3,4\text{-}(MeO)_2\text{-}C_6H_3CH_2CO_2Et$: 18066-68-7 / $PhCO_2Et$: 93-89-0 / $4\text{-}MeC_6H_4CO_2Et$: 94-08-6 / $4\text{-}MeOC_6H_4CO_2Et$: 94-30-4 / $3,4,5\text{-}(MeO)_3\text{-}C_6H_2CO_2Et$: 6178-44-5 / $4\text{-}PhCH_2OC_6H_4CO_2Et$: 56441-55-5 / $EtCO_2Et$: 105-37-3 / $Me(CH_2)_4CO_2Et$: 123-66-0 / $Me(CH_2)_6CO_2Et$: 106-32-1 / $4\text{-}HOC_6H_4CO_2Et$: 120-47-8 / R^2CO_2Et (R^2 = 3-pyridyl): 614-18-6 / R^2CO_2Et (R^2 = 4-pyridyl): 1570-45-2 / R^2CO_2Et (R^2 = 2-morpholinoethyl): 20120-24-5 / R^2CO_2Et (R^2 = cyclohexyl): 3289-28-9 / R^2CO_2Et (R^2 = 1-naphthyl): 3007-97-4 / R^2CO_2Et (R^2 = 2-pyridyl): 2524-52-9

[1] Part I.: D. Korbonits, P. Kiss, K. Simon, P. Kolonits, *Chem. Ber.* **117** (1984) 3183.

[2] [2a] P. Kiss, S. Holly, *Chem. Ber.* **114** (1981) 61. – [2b] K. Harsányi, P. Kiss, D. Korbonits, *J. Heterocycl. Chem.* **10** (1973) 435. – [2c] P. Kiss, E. Pálosi, J. Szegi, J. Szentmiklósi, *VIIth. Int. Symp. on Medicinal Chemistry*, Torremolinos, Spain 1980, Abstr. p. 71.

[3] [3a] B. Lal, A. N. Dohadwalla, N. K. Dadkar,. A. D'Sa, N. Y. De Souza, *J. Med. Chem.* **27** (1984) 1470. – [3b] A. Kaiser, F. Kienzle, *Eur.-Pat. Appl.* 124.893 (5. May 1983) [*Chem. Abstr.* **102** (1984) P 78909x].

[4] I. Bata, G. Héja, P. Kiss, D. Korbonits, *J. Chem. Soc., Perkin Trans. 1*, **1986**, 9.

[5] Chinoin Gyógyszer és Vegyészeti Termékek Gyára R. T., Ger. Offen. 2,332,860 (30 June 1972) [*Chem. Abstr.* **80** (1974) P133434t].

[6] [6a] D. Korbonits, E. M. Bakó, K. Horváth, *J. Chem. Research.* **1979** (S) 64; (M) 0801. – [6b] D. Korbonits, I. Kanzel-Szvoboda, K. Horváth, *J. Chem. Soc., Perkin Trans. 1*, **1982**, 759. – [6c] K. Horváth, D. Korbonits, G. Náray-Szabó, K. Simon, *J. Mol. Struct. (Theochem.)* **136** (1986) 215.

[7] This name was based on the Chemical Abstracts name of **11a** [*Chem. Abstr.* **98** (1983) Formula Index, 1370 F]. **11a** is the only representative of its type found in the literature (V. G. Granik, V. F. Knyazeva, I. V. Persianova, N. P. Solo'veva, R. G. Glushkov, *Khim. Geterosikl. Soedin.* **1982**, 1095 [*Chem. Abstr.* **98** (1983) 4513r]). No spectral data were reported and the quoted m.p. (> 300°C) is not in accord with our finding [275°C (dec.)].

[8] [8a] D. Korbonits, K. Simon, P. Kolonits, *Tetrahedron Lett.* **24** (1983) 5763. – [8b] D. Korbonits, P. Kolonits, *J. Chem. Soc., Perkin Trans. 1*, **1986**, 2163. – [8c] R. Szebeni, D. Korbonits, *Tetrahedron Lett.* **1978**, 2049, and references cited therein.

[11/87]