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

Reductive Formation of 2-(Benzoylamino)indole from 3-(2-Aminobenzyl)-5-phenyl-1,2,4-oxadiazole and Its Transformation to 6-Phenyl-8*H*-pyrimido-[1,6-*a*:4,5-*b*']diindole, a New Heterocyclic Ring System

Imre Bata[a], Dezső Korbonits*[a], Pál Kolonits[b], Benjamin Podányi[a], Tünde Takácsy-Erős[a], and Kálmán Simon[a]

Chinoin Pharmaceutical and Chemical Works[a],
H-1325 Budapest, P.O.B. 110, Hungary

Institute for Organic Chemistry, Technical University[b],
H-1521 Budapest, P.O.B. 91, Hungary

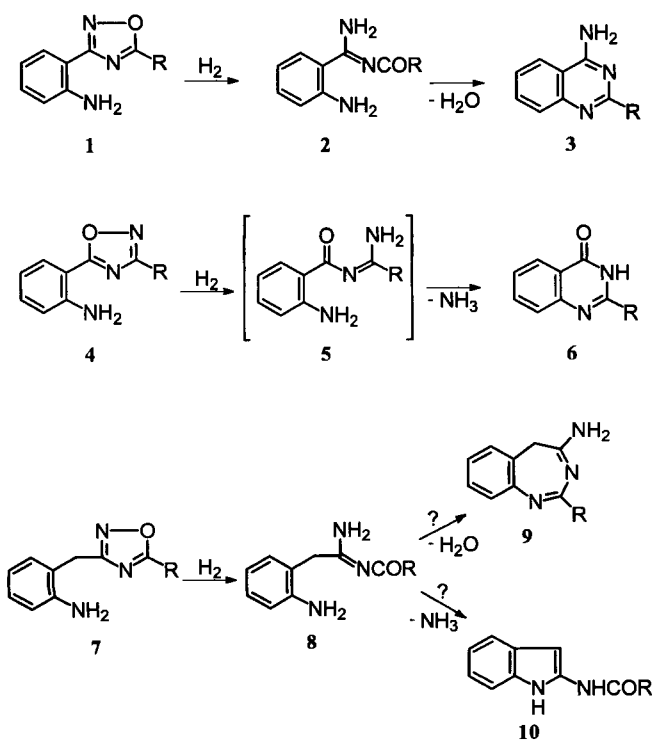
Received February 11, 1993

Key Words: 1,2,4-Oxadiazoles, 5-substituted, 3-(2-aminobenzyl)- / Indoles, 2-(acylamino)- / 8*H*-Pyrimido[1,6-*a*:4,5-*b*']diindoles, 6-aryl

Catalytic hydrogenation of 5-substituted 3-(2-aminobenzyl)-1,2,4-oxadiazoles **7** give 2-(acylamino)indoles **10**. Treatment of 2-(benzoylamino)indoles **10a–c** with acid leads to the novel 6-phenyl-8*H*-pyrimido[1,6-*a*:4,5-*b*']diindoles **19a–c**. A route for the new ring formation is proposed. Catalytic hydrogenation of **19a** (Raney nickel, 70°C, atmospheric pressure) saturates the 6-phenyl ring but leaves the pentacyclic ring system intact. The structure of **19a** is confirmed by an X-ray crystallographic analysis.

In a previous article we reported that 3-(2-aminophenyl)-1,2,4-oxadiazoles **1** as well as their heterocyclic analogs can be converted by hydrogenolysis of the N–O bond and subsequent dehydration of the intermediate acylamidines **2** to 4-aminopyrimidine derivatives **3**[2]. It has also been known that hydrogenolysis of 5-(2-aminophenyl)-1,2,4-oxadiazoles **4** is followed by elimination of ammonia to form 4-oxopyrimidines **6**[3], in contrast to the isomeric compounds **1**, which eliminate water (Scheme 1).

Scheme 1



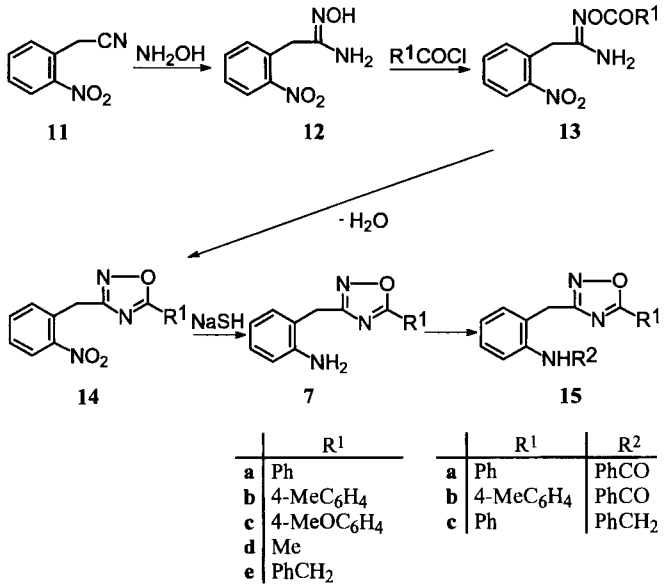
Now we became interested in finding out what would be the product of a catalytic reduction of **7**, that may be regarded as a homolog of **1**. In this case the intermediate acylamidines **8** may cyclize both by elimination of water and ammonia forming either benzodiazepines **9** or indoles **10**.

In this paper we describe these studies which resulted, among others, in the unexpected preparation of pyrimido-[1,6-*a*:4,5-*b*']diindoles, a new heterocyclic ring system.

As model compounds oxadiazoles **7a-e** and three *N*-substituted derivatives thereof (**15a-c**) were prepared. Amideoximes **12** were prepared by the reaction of (2-nitrophenyl)-acetonitrile (**11**)[4] with hydroxylamine and subsequently converted, via their *O*-acyl derivatives **13**, to oxadiazoles **14**. Reduction of the latter with sodium hydrogen sulfide gave finally 5-substituted 3-(2-aminobenzyl)-1,2,4-oxadiazoles **7a-e**. Benzoylation or benzylation of the primary amino group of compounds **7** led to the novel derivatives **15a-c** (Scheme 2).

Catalytic hydrogenation of oxadiazoles **7a-e** gave with concomitant elimination of ammonia the 2-(acylamino)indoles **10a-e**. While in the case of the ring transformation **1**→**3** the intermediate acylamidines **2** (R = Ph, Scheme 1) could be isolated, ring closure of compounds **8** occured spontaneously (Scheme 3). On reduction of the benzylamino compound **15c** cleavage of the N–O bond and hydrogenolysis of the *N*-benzyl group proceeded simultaneously and

Scheme 2

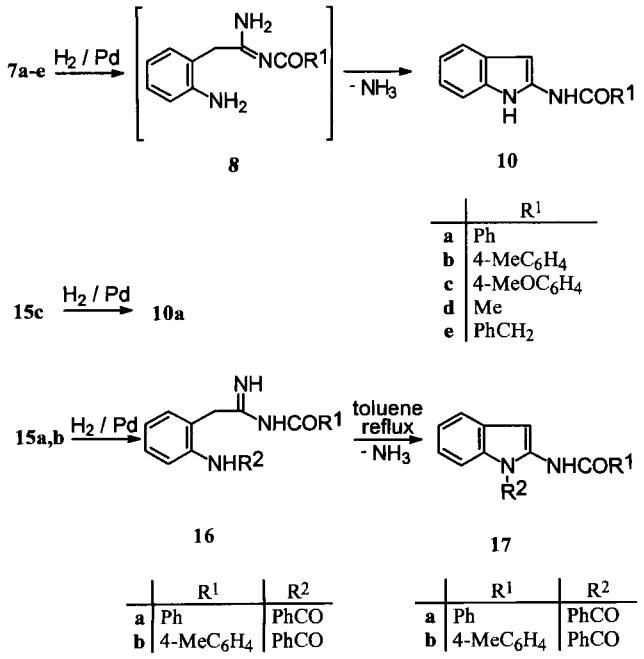


	R1
a	Ph
b	4-MeC6H4
c	4-MeOC6H4
d	Me
e	PhCH2

	R1	R2
a	Ph	PhCO
b	4-MeC6H4	PhCO
c	Ph	PhCH2

resulted in the formation of **10a**. At the same time, hydrogenolysis of the *N*-benzoyloxadiazoles **15a,b** gave the stable acylamidines **16a,b**. Their conversion to the 1-benzoyl-2-(benzoylamino)indoles **17a,b** could be performed by boiling in toluene. The different reactivity of a primary amino group and an amide group makes this difference in the conditions of cyclization understandable. The 2-(acylamino)indoles **10** could not be prepared by direct acylation of the 2-aminoindole **18**. Of compounds **10** and **17** only 2-(acetamino)indole (**10d**) has already been described[5].

Scheme 3



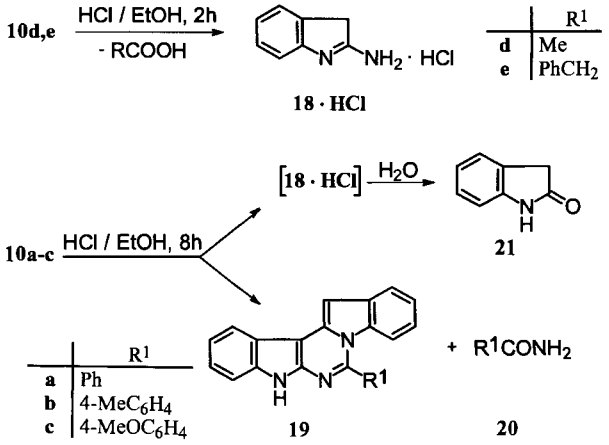
	R1
a	Ph
b	4-MeC6H4
c	4-MeOC6H4
d	Me
e	PhCH2

	R1	R2
a	Ph	PhCO
b	4-MeC6H4	PhCO

	R1	R2
a	Ph	PhCO
b	4-MeC6H4	PhCO

Attempted acid hydrolysis of the (acylamino)indoles **10** to 2-aminoindole (**18**) resulted in a novel surprising ring closure. While hydrolysis of the acetyl and phenylacetyl derivatives **10d,e** by warming in ethanolic hydrogen chloride gave the expected product **18** · HCl, the product which spontaneously crystallized following the same treatment of 2-(benzoylamino)indole (**10a**) proved to be, as shown by elementary analysis, mass and NMR spectroscopy, the first representative of a novel heterocyclic ring system, i.e. 6-phenyl-8*H*-pyrimido[1,6-*a*:4,5-*b*′) diindole (**19a**). Processing of the mother liquor gave benzamide (**20a**) and oxindole (**21**) (Scheme 4).

Scheme 4



	R1
d	Me
e	PhCH2

	R1
a	Ph
b	4-MeC6H4
c	4-MeOC6H4

In the ^{1}H-NMR spectrum of **19a**, apart from the signals of the phenyl ring and a singlet for 13-H, signals of two *ortho*-disubstituted phenyl rings could be recognized. Signal assignment was accomplished with the aid of a 2D COSY spectrum and by assuming that due to shielding by the close 6-phenyl group the signal at $\delta = 6.34$ was pertinent to 4-H. Knowing the proton assignments, we assigned the carbon signals by means of selective ^{13}C-^{1}H correlation spectra. In measuring correlations based on $^1J_{C,H}$ couplings with ^{1}H-NMR detection, selective excitation of ^{13}C signals was performed by using a chemical shift-selective filter pulse sequence[6]. Correlations based on long-range ^{13}C-^{1}H couplings were measured in selective INEPT experiments[7]. All NMR data (see Experimental) were in conformity with structure **19a**. The high value of $^2J_{12\text{-}C,13\text{-}H}$ (10.3 Hz) is remarkable.

Finally, structure **19a** was also proved by X-ray analysis (Figure 1). Analogs **10b,c** behaved similarly and were converted into the pyrimidodiindoles **19b,c**.

For the transformation **10**→**19** the pathway shown in Scheme 5 is proposed. In the first step, probably following the mechanism suggested earlier for biindole formation[8,9], the attack of cation **10** on C-3 of a non-protonated **10** leads to a hypothetic biindole **22**. While in the case of an unsubstituted indole this dimerization in protic media is accompanied by an intramolecular migration of hydrogen atoms in a reversible process[8], in the coupling of compounds **10** an irreversible reaction takes place, namely cleavage of the C—N bond and expulsion of the amide $RCONH_2$. Note that although experiments for the preparation of polycyclic com-

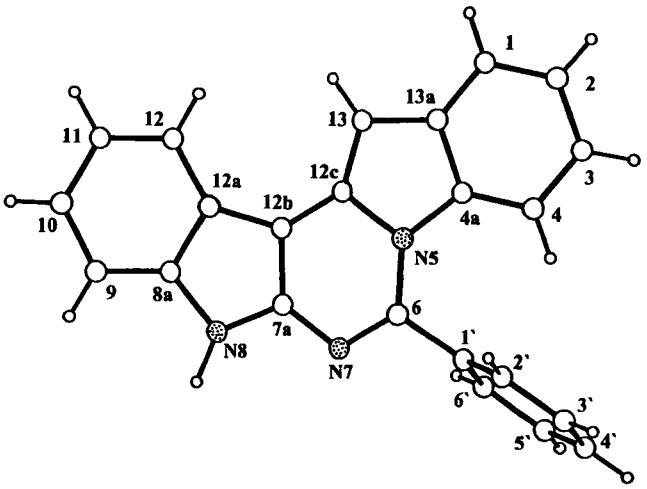
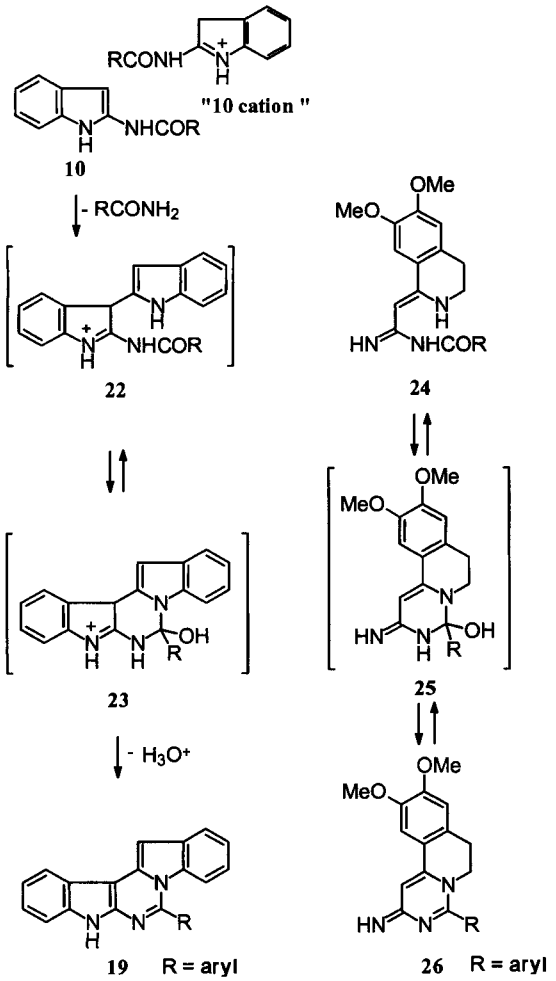


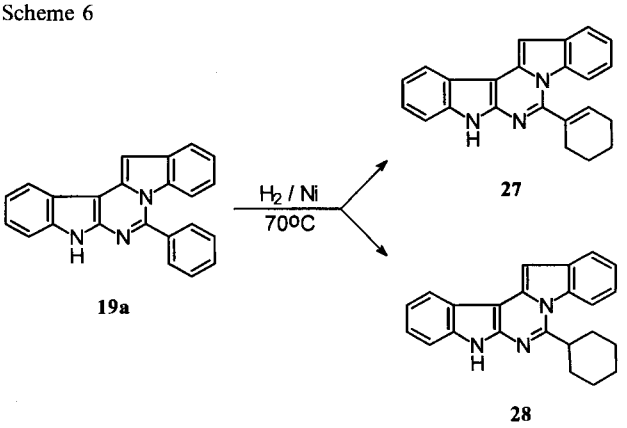
Figure 1. X-ray diagram of **19a**. Some characteristic bond lengths and bond angles: N5–C6 1.384(4), N5–C12c 1.434(4), C6–N7 1.299(4), N7–C7a 1.369(4), C7a–C12b 1.387(5), C12b–C12c 1.410(4), N8–C7a 1.369(4), N8–C8a 1.388(5), N5–C4a 1.419(4) Å; N5–C6–N7 123.2(5), C6–N7–C7a 116.3(5), C7a–C12b–C12c 118.1(5), C12b–C12c–N5 114.7(5), C12c–N5–C6 121.9(4), C7a–N8–C8a 107.7(5), C4a–N5–C12c 107.6(4)°

Scheme 5



pounds starting from 2-aminoindoles have been described[10,11], no example of the cleavage of the C(2)–N bond has been reported. Biindoles **22** are converted into pyrimidodiindoles **19** by elimination of water via the aminocarbinol **23**.

Scheme 6

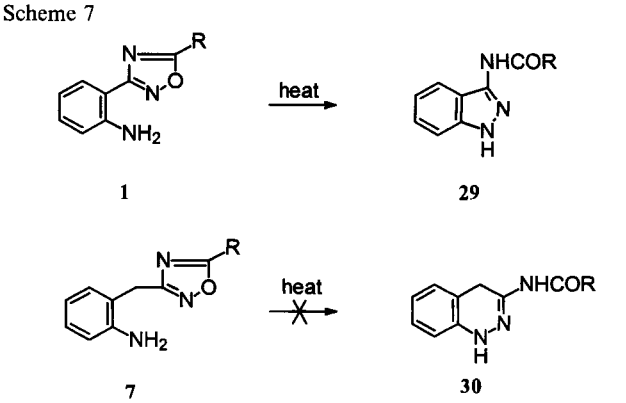


It is interesting to compare the formation of **19**, that can be regarded as a 4-aminopyrimidine derivative, with a recent synthesis of 4-aminopyrimidines **26**[12]. Analogy of pathways **22** ⇌ **23** → **19** and **24** ⇌ **25** ⇌ **26** is apparent, but an important difference is that, althoug **26** can be isolated in a crystalline form, transformation **24** ⇌ **26** is reversible, and the formation of anhydrobase **26** can be easily reverted by aqueous hydrolysis to the open-chain amide via pseudobase **25**. In contrast, **19** is stabilized by a π-electron system involving not only the five-membered ring but also the 6-phenyl group, and therefore transformation **22** → **19** becomes irreversible.

Further evidence for the stability of the ring system of **19** was the finding that on hydrogenation over Raney nickel at atmospheric pressure and 70°C the pentacyclic system remained unchanged, whereas the 6-phenyl substituent underwent partial and complete reduction to give a mixture of **27** and **28**, respectively. The products were separated by chromatography and readily identified by their ^{1}H- and ^{13}C-NMR spectra (Scheme 6).

Saturation of a phenyl ring by catalytic hydrogenation is rather well-known[13] but requires either some special catalyst or, with Raney nickel, high pressure. No example has been found either for Raney nickel-catalyzed hydrogen up-

Scheme 7



take by a phenyl ring at atmospheric pressure or for incomplete hydrogenation resulting in a 1-cyclohexenyl derivative.

Earlier we have also reported that **1** and related oxadiazoles can be readily isomerized to pyrazoles **29**[14], but attempts to rearrange compounds **7** (in analogy to the transformation **1**→**29**) to (acylamino)cinnolines **30** failed (Scheme 7). This confirms our earlier finding[15] that in the type-2 Boulton-Katritzky scheme[16] the length of the side chain plays a decisive role.

The present work is a continuation of our investigation of aminoamide oxime derivatives[1,2,12,14,15,17].

Thanks are due to Dr. *L. Pusztai* for recording the IR spectra and to Dr. *I. Remport* for performing the elementary analyses.

Experimental

IR: Zeiss Specord M-80. – ^{1}H and ^{13}C NMR: Jeol FX-100 and Bruker AC-400. – MS: Jeol JMS-D 300 and VG-TS-250. – Yields, melting points, IR spectral and analytical data are compiled in Table 1, characteristic ^{1}H-NMR data in Table 2.

2-(2-Nitrophenyl)acetamide Oxime (**12**): To a solution of **11**[4] (52.0 g, 360 mmol) in ethanol (400 ml) a solution of hydroxylamine hydrochloride (25 g, 360 mmol) and sodium hydrogen carbonate (30.2 g, 360 mmol) in water (200 ml) was added, and the mixture was refluxed for 3 h. After cooling the product crystallized (46 g, 73%), m.p. 146°C. – IR (KBr): $\tilde{\nu}$ = 3640 cm^{-1}, 3320, 1680, 1540. – ^{1}H NMR ([D$_6$]DMSO): δ = 3.69 (s, 2H, CH$_2$), 5.52 (bs, 2H, NH$_2$), 7.3–7.7 (m, 3H, Ph-4,5,6-H), 7.92 (m, 1H, Ph-3-H), 8.97 (s, 1H,

Table 1. Yields, melting points, IR spectral and analytical data of compounds **13b–e**, **14b–e**, **7b–e**, **15a–c**, **16a**, **b**, **10b–e**, **17a**, **b**, and **19b**, **c**

No	Yield (%)	M.p. (°C)	r.s.[a]	$\tilde{\nu}_{max}$(cm^{-1})	Formula	Mol. mass	Found(%) (Calcd.) C	H	N
13b	93	142	D	3490, 3385, 1725, 1625	$C_{16}H_{15}N_3O_4$	313.30	61.20 (61.33)	4.96 (4.83)	13.29 (13.41)
13c	80	164	B-P 1:1	3490, 3290, 1720, 1640	$C_{16}H_{15}N_3O_5$	329.30	58.55 (58.35)	4.50 (4.59)	12.63 (12.76)
13d	85	141	E-W 1:1	3450, 3350, 1730, 1645	$C_{10}H_{11}N_3O_4$	237.23	50.39 (50.63)	4.48 (4.68)	17.68 (17.71)
13e	69	126	D	3490, 3350, 1725, 1620	$C_{16}H_{15}N_3O_4$	313.30	61.19 (61.33)	4.78 (4.83)	13.25 (13.41)
14b	73	116	B	1600, 1555, 1530	$C_{16}H_{13}N_3O_3$	295.28	64.99 (65.08)	4.28 (4.44)	14.14 (14.23)
14c	70	117	E	1615, 1530, 1500	$C_{16}H_{13}N_3O_4$	311.28	61.62 (61.73)	4.14 (4.21)	13.33 (13.50)
14d	91	76	H	1590, 1530	$C_{10}H_9N_3O_3$	219.19	54.67 (54.79)	3.98 (4.14)	19.15 (19.17)
14e	83	62	H	1575, 1530	$C_{16}H_{13}N_3O_3$	295.28	65.13 (65.08)	4.51 (4.44)	14.31 (14.23)
7b	58	138 227[b]	M-W 1:1 EA	3405, 3320, 1635, 1615	$C_{16}H_{15}N_3O$	265.30	72.30 (72.43)	5.51 (5.70)	15.80 (15.84)
7c	45	105 221[b]	M-W 2:1 EA	3410, 3330, 1600	$C_{16}H_{15}N_3O_2$	281.30	68.27 (68.31)	5.30 (5.38)	14.48 (14.49)
7d	59	oil 182[b]	E	3425, 3370, 1630, 1580	$C_{10}H_{11}N_3O$	189.21	63.59 (63.47)	5.89 (5.86)	22.18 (22.21)
7e	30	oil 150[b]	E	3430, 3370,1625, 1570	$C_{16}H_{15}N_3O$	265.30	72.38 (72.43)	5.73 (5.70)	15.85 (15.84)
15a	77	196	W	3240, 1645, 1560	$C_{22}H_{17}N_3O_2$	355.38	74.20 (74.35)	4.70 (4.82)	12.06 (11.82)
15b	84	199	W	3240, 1650, 1525	$C_{23}H_{19}N_3O_2$	369.40	74.61 (74.78)	5.04 (5.18)	11.16 (11.38)
15c	50	91	E	3320, 1640, 1600, 1560	$C_{22}H_{19}N_3O$	341.39	77.51 (77.40)	5.42 (5.61)	12.32 (12.31)
16a[c]	81	110	E	3510, 3420, 3180, 1620	$C_{24}H_{25}N_3O_3$	403.46	71.24 (71.44)	6.15 (6.24)	10.42 (10.44)
16b[c]	82	106	E	3520, 3420, 3190, 1650	$C_{25}H_{27}N_3O_3$	417.49	72.00 (71.92)	6.41 (6.52)	10.07 (10.06)
10b	74	217	D-H 1:1	3390, 3260, 1640, 1625	$C_{16}H_{14}N_2O$	250.29	77.10 (76.77)	5.60 (5.64)	11.13 (11.20)
10c	55	221	E	3395, 3330, 1635	$C_{16}H_{14}N_2O_2$	266.29	72.10 (72.16)	5.15 (5.30)	10.40 (10.52)
10d	83	169[d]	W	3370, 3300, 1665, 1620	$C_{10}H_{10}N_2O$	174.20	68.92 (68.94)	5.68 (5.79)	15.91 (16.08)
10e	30	177	E	3380, 3190, 1630	$C_{16}H_{14}N_2O$	250.29	76.59 (76.77)	5.56 (5.64)	11.38 (11.20)
17a	31	152	D	3295, 1680, 1665	$C_{22}H_{16}N_2O_2$	340.37	77.61 (77.63)	4.68 (4.73)	8.03 (8.23)
17b	42	150	H	3290, 1670	$C_{23}H_{18}N_2O_2$	354.39	78.12 (77.95)	5.05 (5.12)	7.88 (7.91)
19b	23	330	E-W 2:1	3180, 1640, 1600	$C_{24}H_{17}N_3$	347.40	82.72 (82.97)	4.82 (4.93)	11.98 (12.09)
19c	22	325	E-W 2:1	3160, 1645, 1595	$C_{24}H_{17}N_3O$	363.40	79.18 (79.32)	4.57 (4.72)	11.70 (11.56)

[a] Recrystallization solvents: B = BuOH, D = Diethyl ether, EA = Ethyl acetate, E = ethanol, H = *n*-hexane, M = MeOH, P = 2-propanol, W = water. – [b] As hydrochloride. – [c] Crystallized with 1 mol of ethanol. – [d] ref.[5] 167°C.

Table 2. Characteristic ^{1}H-NMR data of the compounds of Table 1

13b	2.39 (s, 3H, 4`-$CH_3$), 5.46 (b, 2H, $NH_2$), 7.22 (d, 2H, 3`,5`-H), 7.90 (d, 2H, 2`,6`-H).
13c	3.87 (s, 3H, 4`-$OCH_3$), 5.30 (b, 2H, $NH_2$), 6.93 (d, 2H, 3`,5`H), 8.02 (d, 2H, 2`,6`-H).
13d	2.15 (s, 3H, CH_3), 5.26 (b, 2H, NH_2).
13e	3.74 (s, 2H, CH_2), 5.11 (b, 2H, NH_2), 7.29 (s, 5H, Ph).
14b	2.41 (s, 3H, 4`-$CH_3$), 7.28 (d, 2H, 3`,5`-H), 7.95 (d, 2H, 2`,6`-H).
14c	3.87 (s, 3H, 4`-$OCH_3$), 6.97 (d, 2H, 3`,5`-H), 8.02 (d, 2H, 2`,6`-H).
14d	2.66 (s, 3H, CH_3).
14e	4.17 (s, 2H, CH_2), 7.29 (s, 5H, Ph).
7b	2.42 (s, 3H, 4`-$CH_3$), 4.27 (br, 2H, $NH_2$), 7.29 (m, 2H, 3`,5`-H), 7.95 (m, 2H, 2`,6`-H).
7c	3.85 (bs, 5H, 4`-$OCH_3$ and $NH_2$), 6.95 (d, 2H, 3`,5`-H), 8.01 (d, 2H, 2`,6`-H).
7d[a,b]	2.67 (s, 3H, CH_3), 8.30 (br, 3H, $^+NH_3$).
7e[a]	4.42 (s, 2H, CH_2), 7.30 (m, 5H, Ph), 10.30 (vb, 3H, $^+NH_3$).
15a	7.1-7.3 (m, 5H, Ar), 7.9-8.3 (m, 9H, Ar), 10.11 (bs, 1H, NH).
15b	2.43 (s, 3H, 4`-$CH_3$), 7.31 (d, 2H, 3`,5`-H), 7.83 (d, 2H, 2`,6`-H), 10.18 (bs, 1H, NH).
15c	4.39 (s, 2H, CH_2), 5.27(b, 1H, NH), 7.0-7.5 (m, 10 H, Ar), 7.8-8.0 (m, 2H, Ar).
16a	7.0-7.5 (m, 10H, Ar), 7.8 (bs, 1H, C=NH), 7.8-8.1 (m, 4H, Ar), 10.42 (br. s, 1H, NH), 11.17 (br. s, 1H, NH).
16b	2.27 (s, 3H, 4`-$CH_3$), 6.97 (d, 2H, 3`,5`-H), 7.75 (d, 2H, 2`,6`-H), 8.23(bs, lH, C=NH), 10.30 (bs, 1H, NH), 11.40 (bs, 1H, NH).
10b	2.44 (s, 3H, 4`-$CH_3$), 6.01 (dd, 2H, 3-H), 7.32 (d, 2H, 3`,5`-H), 7.80 (d, 2H, 2`,6`-H), 8.37 (br, 1H, NH), 10.61 (br, 1H, NH).
10c[b]	3.87 (s, 3H, 4`-$OCH_3$), 6.27 (d, 1H, 3-H), 7.10 (d, 2H, 3`,5`-H), 8.05 (d, 2H, 2`,6`-H), 10.90 (br, 1H, NH), 11.05 (br, 1H, NH).
10d[b]	2.23 (s, 3H, CH_3), 6.14 (s, 1H, 3-H), 10.95 (br, 2 x NH).
10e[b]	3.78 (s, 2H, CH_2), 5.76 (dd, 1H, 3-H), 7.2-7.6 (m, 5H, Ph), 7.64 (br, 1H, NH), 10.37 (br, 1H, NH).
17a	6.32 (m,1H, 3-H), 7.4-7.6 (m, 10H, Ar), 7.9-8.1 (m, 7H, Ar), 11.29 (bs, 1H, NH).
17b	2.42 (s, 3H, 4`-$CH_3$), 6.31 (m, 1H, 3-H), 7.30 (d, 2H, 3`,5`-H) 7.4-7.8 (m, 7H, Ar), 7.81 (d, 2H, 2`,6`-H), 11.24 (bs, 1H, NH).
19b[b]	2.48 (s, 3H, CH_3), 6.48 (d, 1H, 4-H), 6.89 (dd, 1H, 3-H), 8.18 (d, 1H, 12-H), 12.16 (bs, 1H, NH).
19c[b]	3.93 (s, 3H, OCH_3), 6.56 (d, 1H, 4-H), 6.92 (dd, 1-H, 3-H), 8.17 (d, 1H, 12-H), 12.15 (bs, 1H, NH).

[a] As hydrochloride. — [b] In [D_6]DMSO, in other cases in $CDCl_3$.

OH). — $C_8H_9N_3O_3$ (195.2): calcd. C 49.23, H 4.65, N 21.53; found C 49.18, H 4.59, N 21.31.

2-(2-Nitrophenyl)acetamide (O-Benzoyloxime) (**13a**): To a solution of **12** (19.5 g, 100 mmol) and triethylamine (10.12 g, 100 mmol) in acetone (250 ml) benzoyl chloride (14.06 g, 100 mmol) was added dropwise with stirring at 20°C. After stirring for 1 h the mixture was boiled for 1 h. The suspension was filtered and the filtrate concentrated in vacuo. The product crystallized from methanol/water (4:1); yield of **13a** 25.4 g (85%), m.p. 128°C. — IR (KBr): $\tilde{\nu} = 3460$ cm^{-1}, 3280, 1715, 1630. — ^{1}H NMR ($CDCl_3$): δ = 3.87 (s, 2H, CH_2), 5.42 (bs, 2H, NH_2), 7.3—7.7 (m, 6H, Ar), 7.92 (m, 1H, Ph-3-H), 8.01 (m, 2H, Ph-2′,6′-H). — $C_{15}H_{13}N_3O_4$ (299.3): calcd. C 60.20, H 4.38, N 14.04; found C 60.35, H 4.41, N 14.04.

2-(2-Nitrophenyl)acetamide (O-Acyloximes) (**13b—e**). *General Method:* The title compounds were obtained by the reaction of **12** with the appropriate acyl chloride as described for **13a**.

3-(2-Nitrobenzyl)-5-phenyl-1,2,4-oxadiazole (**14a**): A solution of **13a** (19.5 g, 65 mmol) in butanol (200 ml) was refluxed for 3 h. After cooling the product crystallized (13.9 g, 76%), m.p. 100°C. — IR (KBr): $\tilde{\nu} = 1605$ cm^{-1}, 1560, 1520. — ^{1}H NMR ($CDCl_3$): $\delta = 4.56$ (s, 2H, CH_2), 7.3—7.7 (m, 6H, Ar), 8.08 (m, 3H, Ph-3-H and Ph-2′,6′-H). — $C_{15}H_{11}N_3O_3$ (281.3): calcd. C 64.05, H 3.94, N 14.94; found C 63.96, H 3.87, N 14.80.

5-Substituted 3-(2-Nitrobenzyl)-1,2,4-oxadiazoles (**14b—e**). *General Method:* The title compounds were obtained by boiling of **13b—e** in butanol as described for **14a**. After cooling **14b** crystallized spontaneously; in other cases, the reaction mixture was concentrated and the residue chromatographed on silica gel with toluene/ethyl acetate (1:1) in the case of **14c** or chloroform/tetrachloromethane/methanol (8:5:1) in the case of **14d, e** as the eluants.

3-(2-Aminobenzyl)-5-phenyl-1,2,4-oxadiazole (**7a**): A freshly prepared mixture of sodium hydrogen sulfide — 40.0 g (167 mmol) sodium sulfide nonahydrate, 80 ml water, 14.0 g (167 mmol) of sodium hydrogen carbonate, and 150 ml of methanol[18] — was added to a solution of **14a** (10.0 g, 35 mmol) in 150 ml of methanol, and the mixture was refluxed for 3 h. After cooling **7a** and some unreacted **14a** crystallized. Purification was performed via the hydrochloride by the addition of hydrochloric acid in ethyl acetate to the solution of the mixture in chloroform. Compound **7a** precipitated from the methanolic solution of the salt (m.p. 211°C) upon addition of sodium hydrogen carbonate; yield of **7a** 5.46 g (61%), m.p. 142°C. — IR (KBr): $\tilde{\nu} = 3440$ cm^{-1}, 3340, 1630, 1600. — ^{1}H NMR ($CDCl_3$): $\delta = 4.20$ (s, 2H, CH_2), 4.41 (bs, 2H, NH_2), 6.89 (m, 2H, Ar), 7.15—7.50 (m, 2H, Ar), 7.63 (m, 3H, Ph-3′,4′,5′-H), 8.14 (m, 2H, Ph-2′,6′-H). — $C_{15}H_{13}N_3O$ (251.3): calcd. C 71.70, H 5.21, H 16.72; found C 71.69, H 5.09, N 16.56.

5-Substituted 3-(2-Aminobenzyl)-1,2,4-oxadiazoles (**7b—e**). *General Method:* The title compounds were obtained by treatment of **14b—e** with sodium hydrogen sulfide. Compounds **7b, c** were prepared as described for **7a**, in the cases of **7d** and **7e** after boiling the solutions were concentrated, the residues triturated with water and extracted with chloroform. After removal of the solvents from the extracts purification was carried out as described for **7a**.

As shown by TLC and recovery of starting material, **7a** remained unchanged under the following conditions: a) refluxing in xylene for 8 h, in the presence of 40% sodium hydroxide in ethanol or dimethylformamide; b) keeping it in the molten state at 150 or 170°C for 3 h. Compounds **7b—e** behaved similarly.

3-[2-(Benzoylamino)benzyl]-5-aryl-1,2,4-oxadiazoles (**15a, b**). *General Method:* Compounds **15a** and **15b** were obtained by the reaction of **7a** and **7b** with benzoyl chloride as described for **13a**. The products crystallized spontaneously; the crystals were collected and washed with water.

3-[2-(Benzylamino)benzyl]-5-phenyl-1,2,4-oxadiazole (**15c**): The crude Schiff base prepared from **7a** (25.13 g, 100 mmol) and benzaldehyde (12.73 g, 120 mmol) in boiling benzene was reduced with $NaBH_4$ (5.70 g, 150 mmol) in methanol.

2-(Benzoylamino)indole (**10a**). — a) A solution of **7a** (5.0 g, 20 mmol) in ethanol (150 ml) was hydrogenated over 8% palladium/charcoal (0.5 g) at 20°C. The usual workup gave **10a** (3.36 g, 71%); m.p. 198°C (diethyl ether/*n*-hexane, 1:1). — b) Hydrogenation of **15c** (6.8 g, 20 mmol) as described under a) gave **10a** (3.07 g, 65%). — IR (KBr): $\tilde{\nu} = 3420$ cm^{-1}, 3300, 1640, 1625. — ^{1}H NMR ($CDCl_3$): $\delta = 6.04$ (s, 1H, 3-H), 7.0—7.2 (m, 2H, indole-5,6-H), 7.3—7.7 (m, 2H, indole-4,7-H), 7.8—8.0 (m, 5H, Ph), 8.43 (bs, 1H, NH), 10.61 (bs, 1H, 1-H). — ^{13}C NMR ($CDCl_3$): $\delta = 88.37$ (C-3), 111.54, 118.94, 119.56, 120.05 (C-7, -6, -5, and -4), 127.37 (C-3a), 127.86 (C-3′ and -5), 128.83 (C-2′ and -6′), 132.22 (C-4′), 132.89 (C-1′), 134.01 (C-7a), 135.53 (C-2), 164.75 (C=O). — $C_{15}H_{12}N_2O$ (236.3): calcd. C 76.24, H 5.12, N 11.86; found C 76.18, H 4.98, N 11.77.

2-(Acylamino)indoles (**10b–e** and **17a, b**): *General Method:* Compounds **10b–e** were obtained by hydrogenation of **7b–e** as described for **7a**. Compounds **17a** and **17b** were prepared by refluxing **16a** (4.84 g, 12 mmol) and **16b** (5.01 g, 12 mmol) in toluene (100 ml) for 8 h. The products were purified by chromatography on silica gel (eluant chloroform/tetrachloromethane/methanol, 8:5:1).

N-{[2-Acylamidino)methyl]phenyl}benzamides (**16a, b**). *General Method:* The title compounds were prepared by hydrogenation of **15a, b** as described for **10a** and crystallized with 1 mol of ethanol.

2-Aminoindole Hydrochloride (**18** · HCl): A solution of **10d** or **10e** (3 mmol) in a mixture of ethanol (40 ml) and 2 N HCl (20 ml) was refluxed for 2 h. After concentration of the reaction mixture the residue was crystallized from acetone; yield of **18** · HCl 0.37 g (74%), m.p. 222 °C (ref.[19] 222–224 °C). – IR (KBr): $\tilde{\nu}$ = 3200 cm^{-1}, 3020, 1690, 1625. – $C_8H_9ClN_2$ (168.6): calcd. C 56.98, H 5.38, Cl 21.02, N 16.62; found C 57.04, H 5.25, Cl 21.00, N 16.41.

Hydrolysis of **10a** *in Ethanol/Hydrochloric Acid: Formation of 6-Phenyl-8H-pyrimido[1,6-a:4,5-b']diindole* (**19a**), *Benzamide* (**20a**), *and Oxindole* (**21**): A solution of **10a** (2.84 g, 12 mmol) in a mixture of ethanol (40 ml) and 2 N HCl (20 ml) was refluxed for 8 h. After cooling **19a** crystallized spontaneously (0.56 g, 28%). Concentration of the mother liquor and chromatography of the residue on silica gel (eluant chloroform/tetrachloromethane/methanol, 8:5:1) gave **20a** (0.24 g, 33%), m.p. 128 °C (ref.[20] 128–129 °C), and **21** (0.54 g, 34%), m.p. 124 °C (ref.[19] 123–125 °C), together with impure benzoic acid.

19a: m.p. 309 °C. – IR (KBr): $\tilde{\nu}$ = 3190 cm^{-1}, 1640, 1590. – MS (70 eV), *m/z* (%): 333.1272 (100) [M^+], 229 (5) [M – C_6H_5CN–H], 166.5 (12) [M^{2+}]. – ^{1}H NMR ([D$_6$]DMSO): δ = 6.34 (d, 1H, 4-H), 6.85 (dd, $J_{3,4}$ = 8.4 Hz, 1H, 3-H), 7.17 (s, 1H, 13-H), 7.28 (t, $J_{2,3}$ = 7.5 Hz, 1H, 2-H), 7.33 (t, 1H, 11-H), 7.39 (t, $J_{10,11}$ = 7.9 Hz, 1H, 10-H), 7.60 (d, $J_{9,10}$ = 7.9 Hz, 1H, 9-H), 7.70 (m, 5H, Ph), 7.76 (d, $J_{1,2}$ = 7.7 Hz, 1H, 1-H), 8.16 (d, $J_{11,12}$ = 7.7 Hz, 1H, 12-H), 12.20 (s, 1H, NH). – ^{13}C NMR ([D$_6$]DMSO): δ = 90.0 (d, $J_{C\text{-}13,1\text{-}H}$ = 3.2 Hz, C-13), 96.9 (s, C-12b), 111.8 (d, C-9), 114.5 (d, $J_{C\text{-}4,2\text{-}H}$ = 7.7 Hz, C-4), 119.4 (d, $J_{C\text{-}3,1\text{-}H}$ = 8.0 Hz, C-3), 119.4 (d, $J_{C\text{-}1,3\text{-}H}$ = 8.2 Hz, C-1), 120.3 (d, $J_{C\text{-}12,10\text{-}H}$ = 7.6 Hz, C-12), 120.5 (d, $J_{C\text{-}11,9\text{-}H}$ = 7.9 Hz, C-11), 120.9 (s, C-12a), 123.6 (d, C-2 and -10), 128.2 (d, $J_{C\text{-}3',2'\text{-}H} = J_{C\text{-}3',4'\text{-}H}$ = 6.8 Hz, C-3′ and -5′), 129.2 (d, $J_{C\text{-}2',4'\text{-}H} = J_{C\text{-}6',4'\text{-}H}$ = 6.9 Hz, C-2′ and -6′), 129.8 (s, C-4a), 130.4 (d, $J_{C\text{-}4',2'\text{-}H} = J_{C\text{-}4',6'\text{-}H}$ = 6.9 Hz, C-4′), 131.6 (s, C-13a), 134.7 (s, $J_{C\text{-}12c,13\text{-}H}$ = 10.3 Hz, C-12c), 135.8 (s, $J_{C\text{-}1',3'\text{-}H} = J_{C\text{-}1',5'\text{-}H}$ = 7.1 Hz, C-1′), 135.8 (s, C-8a), 141.9 (s, $J_{C\text{-}7a,\ NH}$ = 2.7 Hz, C-7a), 149.5 (s, $J_{C\text{-}6,2'\text{-}H} = J_{C\text{-}6,6'\text{-}H}$ = 4.1 Hz, C-6). – $C_{23}H_{15}N_3$ (333.4): calcd. C 82.86, H 4.54, N 12.60; found C 82.66, H 4.72, N 12.71.

Crystal Data of **19a**[21]: $C_{25}H_{15}N_3$ (recrystallized from acetonitrile), M = 333.37; triclinic: a = 5.659(2), b = 12.129(2), c = 12.744(2) Å, α = 110.43(2), β = 96.48(2), γ = 90.26(2)°, space group $P\bar{1}$, Z = 2, V = 814 Å^3, D_c = 1.361 g cm^{-3}. 3325 reflections, out of which 1765 with $I > 3\sigma(I)$ were collected with an Enraf Nonius CAD4 diffractometer, crystal size 0.04 × 0.1 × 0.2 mm with Cu-K_α radiation (λ = 1.5418 Å), Θ_{range} = 1.5–75°, scan technique $\Theta/2\Theta$, μ(Cu-K_α, graphite monochromator) = 6.01 cm^{-1}. The structure was solved by direct methods and refined to R = 0.054, R_w = 0.057 for 1765 reflections [$I > 3\sigma(I)$], R = 0.083 for 3325 reflections. The unit weight was used, the number of parameters refined 235, the highest residual electron density was 0.46 e/Å^3. The N–H hydrogen atom was taken from a difference Fourier map, all C–H hydrogen atoms were calculated (C–H = 0.95 Å) in their ideal geometrical positions, and the hydrogen atoms were included into the structure factor calculations, but their positions were not refined. All calculations were carried out with an Enraf Nonius SDP Program Package.

6-Aryl-8H-pyrimido[1,6-a:4,5-b']diindoles (**19b, c**). *General Method:* **19b** and **19c** were obtained from **10b** and **10c** as described for **19a**.

Hydrogenation of **19a**: *Preparation of 6-(1-Cyclohexen-1-yl)-8H-pyrimido[1,6-a:4,5-b']diindole* (**27**) *and 6-Cyclohexyl-8H-pyrimido[1,6-a:4,5-b']diindole* (**28**): Compound **19a** (0.50 g, 1.5 mmol) was hydrogenated in dioxane with Raney nickel at 70 °C for 4 h. The solution was concentrated and the residue purified by chromatography on silica gel (eluant diethyl ether/*n*-hexane, 1:1) to give **27** (0.09 g, 18%) and **28** (0.20 g, 38%).

27: m.p. 255 °C (diethyl ether/*n*-hexane, 1:1). – IR (KBr): $\tilde{\nu}$ = 3200 cm^{-1}, 2920, 2860, 1635, 1590. – MS (70 eV), *m/z* (%): 337.175 (100) [M^+], 333.1256 (13) [M – 4H], 308.1185 (38) [M – C_2H_5], 295 (8) [M – C_3H_6], 229 (5) [M – C_6H_9CN – H], 168.5 (4) [M^{2+}]. – ^{1}H NMR ($CDCl_3$): δ = 1.98 (m, 4H, CH_2-4′,5′), 2.46 (m, 4H, CH_2-3′,6′), 6.39 (m, 1H, 2′-H), 6.98 (d, 1H, 13-H), 7.3–7.6 (m, 5H, 2,3,4,10,11-H), 7.7–7.9 (m, 1-H, 9-H), 8.0–8.2 (m, 2H, 1,12-H), 8.91 (bs, 1H, NH). – ^{13}C NMR ($CDCl_3$): δ = 21.5 (C-4′ or -5′), 22.3 (C-5′ or -4′), 25.2 (C-3′), 26.7 (C-6′), 90.7 (C-13), 98.4 (C-12b), 111.4 (C-9), 115.2 (C-4), 119.8, 119.9, 120.6, 121.2 (C-1, -3, -11, -12), 122.2 (C-12a), 124.0 (C-2, -10), 130.2 (C-4a), 131.4 (C-2′), 132.3 (C-13a), 135.0, 135.4, 135.6 (C-8a, -12c, -1′), 141.9 (C-7a), 152.3 (C-6). – $C_{23}H_{19}N_3$ (337.4): calcd. C 81.87, H 5.68, N 12.45; found C 81.60, H 5.42, N 12.39.

28: m.p. 211 °C (ethanol). – IR (KBr): $\tilde{\nu}$ = 3190 cm^{-1}, 2920, 2840, 1640, 1590. – MS (70 eV), *m/z* (%): 339.175 (100) [M^+], 295 (6) [M – C_3H_7 – H], 284.1196 (16) [M – C_4H_7], 229 (5) [M – $C_6H_{11}CN$ – H], 169.5 (5) [M^{2+}]. – ^{1}H NMR ($CDCl_3$): δ = 1.44 [m, 1H, 4′-H(ax)], 1.62 [m, 2H, 3′,5′-H(ax)], 1.89 [m, 3H, 4′-H(eq), 2′,6′-H(ax)], 2.01 [m, 2H, 3′,5′-H(eq)], 2.30 [m, 2H, 2′,6′-H(eq)], 3.74 (m, 1-H, 1′-H), 6.97 (m, 1-H, 13-H), 7.3–7.5 (m, 5H, 2,3,4,10,11-H), 7.83 (d, 1-H, 9-H), 8.04 (m, 2H, 1- and 12-H), 8.69 (bs, 1H, NH). – ^{13}C NMR ($CDCl_3$): δ = 26.2 (C-4′), 26.3 (C-3′ and -5′), 30.8 (C-2′ and -6′), 42.9 (C-1′), 90.9 (C-13), 97.8 (C-12b), 111.2 (C-9), 115.5 (C-4), 120.0, 120.1, 120.5, 121.0 (C-1, -3, -11, -12), 122.2 (C-12a), 123.7 (C-2 and -10), 129.9, 132.6 (C-4a and -13a), 135.5 (C-8a and -12c), 142.0 (C-7a), 157.3 (C-6). – $C_{23}H_{21}N_3$ · 0.5 H_2O (348.4): calcd. C 79.28, H 6.37, N 12.05; found C 79.41, H 6.22, N 12.01.

[1] Part IV.: D. Korbonits, E. Tóbiás-Héja, K. Simon, Gy. Krámer, P. Kolonits, *J. Chem. Soc., Perkin Trans. 1*, **1992**, 3069.
[2] D. Korbonits, P. Kiss, K. Simon, P. Kolonits, *Chem. Ber.* **1984**, *117*, 3183.
[3] [3a] K. Nagahara, K. Tagaki, T. Ueda, *Chem. Pharm. Bull* **1976**, *24*, 1197. – [3b] Yang-i Lin, S. A. Lang jr., *J. Heterocycl. Chem.* **1980**, *17*, 1273.
[4] V. Rousseau, H. G. Lindwall, *J. Am. Chem. Soc.* **1950**, *72*, 3049.
[5] [5a] R. Pschorr, G. Hoppe, *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 2559. – [5b] J. Kerble, K. Hoffmann, *Helv. Chim. Acta* **1956**, *39*, 116.
[6] K. Kövér et al., *J. Magn. Reson.*, in press.
[7] A. Bax, *J. Magn. Reson.* **1984**, *57*, 314.
[8] G. F. Smith, *Adv. Heterocycl. Chem.* **1963**, *2*, 300.
[9] L. R. Smith in *The Chemistry of Heterocyclic Compounds* (Eds.: A. Weissberger, E. C. Taylor), Wiley, New York, **1972**, vol. 25/2, p. 83.
[10] L. R. Smith in ref. [9], vol 25/2, p. 198.
[11] R. G. Gluskov, V. A. Volokova, O. Yu. Magidson, *Khim. Pharm. Zh.* **1967**, *1/9*, 25.
[12] D. Korbonits, G. Horváth, P. Kiss, K. Simon, P. Kolonits, *Chem. Ber.* **1990**, *123*, 493.
[13] [13a] F. Asinger, H. H. Vogel, *Methoden Org. Chem. (Houben – Weyl)*, **1970**, vol 5/1 a, p. 62. – [13b] H. J. Rimek, *Methoden Org. Chem. (Houben – Weyl)*, **1980**, vol. 4/1 c, p. 168. – [13c] M. Freifelder, *Practical Catalytic Hydrogenation*, Wiley, New York–London–Sidney–Toronto, **1971**, p. 544.
[14] [14a] D. Korbonits, I. Kanzel-Szvoboda, K. Horváth, *J. Chem. Soc., Perkin Trans 1*, **1982**, 759. – [14b] D. Korbonits, E. M. Bakó, K. Horváth, *J. Chem. Res.* **1979**, *(S)* 64; *(M)* 0801. – [14c] I. Bata, G. Héja, P. Kiss, D. Korbonits, *J. Chem. Soc., Perkin Trans 1*, **1986**, 9.
[15] [15a] D. Korbonits, Cs. Gönczi, K. Horváth, J. Tamás, *Acta Chim. Acad. Sci. Hung.* **1984**, *117*, 239. – [15b] K. Horváth, D. Korbonits, G. Náray-Szabó, K. Simon, *J. Mol. Struct. (Theochem)* **1986**, *136*, 215.
[16] [16a] A. J. Boulton, A. R. Katritzky, A. Majid Hamid, *J. Chem. Soc. C* **1967**, 2005. – [16b] A. J. Boulton, *Lectures Heterocycl. Chem.* **1974**, *2*, 45. – [16c] A. Sultan Afridi, A. R. Katritzky, C. A. Ramsden, *J. Chem. Soc., Perkin Trans. 1*, **1976**, 315. – [16d] M. Ruccia, N. Vivona, D. Spinelli, *Adv. Heterocycl. Chem.* **1981**, *29*, 141.

[17] [17a] D. Korbonits, E. Tóbiás-Héja, K. Simon, P. Kolonits, *Chem. Ber.* **1991**, *124*, 2065. – [17b] D. Korbonits, P. Kiss, I. Bata, G. Héja, K. Simon, P. Kolonits, *Chem. Ber.* **1987**, *120*, 1039. – [17c] D. Korbonits, K. Simon, P. Kolonits, *Tetrahedron Lett.* **1983**, *24*, 5763. – [17d] D. Korbonits, P. Kolonits, *J. Chem. Soc., Perkin Trans. 1*, **1986**, 2163. – [17e] D. Korbonits, P. Kolonits, *J. Chem. Res.* **1988**, *(S)* 109; *(M)* 1652. – [17f] D. Korbonits, I. Kanzel-Szvoboda, Cs. Gönczi, K. Simon, P. Kolonits, *Chem. Ber.* **1989**, *122*, 1107. – [17g] D. Korbonits, P. Kolonits, *Acta Chim. Acad. Sci. Hung.* **1990**, *127*, 795. – [17h] D. Korbonits, E. Tóbiás-Héja, P. Kolonits, *Chem. Ber.* **1991**, *124*, 1199. – [17i] E. M. Bakó, K. Horváth, E. Pálosi, D. Korbonits, *Chem. Ber.* **1988**, *121*, 723. – [17j] D. Korbonits, K. Simon, P. Kolonits, *Chem. Ber.* **1991**, *124*, 111.

[18] [18a] G. Pallazo, U. S. Pat. 3,270,029, **1966**; *Chem. Abstr.* **1966**, *65*, 20139b. – [18b] H. H. Hodgson, E. R. Ward, *J. Chem. Soc.* **1948**, 242.

[19] H. Rinderknecht, H. Koechlin, C. Niemann, *J. Org. Chem.* **1953**, *18*, 971.

[20] B. Prager, P. Jakobson, P. Schmidt, D. Stern in *Beilsteins Handbuch der Organischen Chemie*, **1926**, *9*, 195.

[21] Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen, on quoting the depository number CSD-57181, the names of authors, and the journal citation.

[52/93]