A new method for the synthesis of [1,4]diazepino[6,5-*b*]indole derivatives

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Reactions of 3-[(*N*-aryl-*N*-chloroacetyl)amino]-2-formylindoles with substituted anilines gave 1,4-diaryl-2-oxo-1,2,3,6-tetrahydro[1,4]diazepino[6,5-*b*]indol-4-ium chlorides and those with 4-aminopyridine yielded 4-amino-1-(1-aryl-2-oxo-2,5-dihydro-1*H*-pyrido[3,2-*b*]indol-3-yl)pyridinium chlorides. Reduction of 1,2,3,6-tetrahydrodiazepinoindol-4-ium chlorides afforded the corresponding hexahydro derivatives. An alternative synthesis of 1-(4-nitrophenyl)-3-oxo-4-phenyl-1,2,3,4,5,6-hexahydro[1,4]diazepino[6,5-*b*]indole from 3-[*N*-(4-nitrophenyl)amino]-2-[(phenylimino)methyl]indole was developed. The method involves the following sequence of transformations: reduction, chloroacetylation, and intramolecular alkylation.

Key words: 3-[(*N*-aryl-*N*-chloroacetyl)amino]-2-formylindoles, arylamines, 4-aminopyridine, [1,4]diazepino[6,5-*b*]indoles, pyrido[3,2-*b*]indoles, 2-formyl-3-[*N*-(4-nitrophenyl)amino]indole, condensation, reduction, chloroacetylation, alkylation, Triton B.

A great number of polycyclic compounds containing the indole fragment are highly efficient drugs[1] (*e.g.*, carbidine, pyrazidol, tetrindol, incazan, dimebon, diazolin, *etc*).

Along with the indole derivatives listed above, benzo[1,4]diazepine drugs (in particular, chlozepid, phenazepam, and diazepam) are widely used in clinical practice.[2] That is why a combination of the indole and diazepine fragments in one molecule is of undoubted interest for a search for novel drugs. Some [1,4]diazepino[1,2-*a*]indole derivatives have already been found to exhibit pronounced psychotropic activity.[3—5] However, [1,4]diazepino[6,5-*b*]indoles remain poorly studied, probably because they are not easily accessible.

Recently,[6,7] we have developed a method for the synthesis of [1,4]diazepino[6,5-*b*]indole *N*-oxides by reactions of 3-[(*N*-aryl-*N*-chloroacetyl)amino]-2-formylindoles (**1a**—**c**) with hydroxylamine.

The goal of the present work was to obtain new [1,4]diazepino[6,5-*b*]indoles containing no nitrone fragment and study their biological activity. First, we carried out reactions of earlier[7] described 2-formylindoles **1a**—**c** with substituted aromatic amines (Scheme 1) with the aim of obtaining azomethines **2**, which subsequently could be subjected to intramolecular alkylation under more drastic conditions to give quaternary salts of the diazepinoindole series. We took into account that imines with *N*-aryl substituents undergo *N*-alkylation only with great difficulty.[8] However, it turned out that in reactions of aldehydes **1a**—**c** with arylamines under mild conditions, azomethines **2** undergo *in situ* cyclization into the corresponding 1,4-diaryl-2-oxo-1,2,3,6-tetrahydro[1,4]diazepino[6,5-*b*]indol-4-ium chlorides (**3a**—**e**) in high yields.

Such an easy intramolecular alkylation is probably duavoide to direct polar transition-state conjugation of the lone electron pair of the N(1) atom with the $C=N^+$ group in positions 4 and 5 of the tricycles, which stabilizes the final products, namely, quaternary salts of diazepinoindoles.

The structures of salts **3a**—**e** were proven by ^{1}H NMR spectra, which show, apart from signals for aromatic protons, signals for the NH and CH_2 protons (Table 1). The upfield shift of the signals for the H(10) protons (δ 6.3—6.5) is due to the anisotropic effect of the benzene ring of the 1-aryl substituent, which is not coplanar with the tricyclic system.

Reduction of chlorides **3a**—**e** with $NaBH_4$ occurred easily to give the corresponding hexahydro derivatives **4a**—**e** (see Scheme 1) in high yields. In the ^{1}H NMR spectra of compounds **4a**—**e**, all signals for the protons are shifted upfield compared to those in the spectra of chlorides **3a**—**e**, the singlet for the H(5) proton at δ 9.6 disappears, but a signal for $H_2C(5)$ (2 H) appears at δ 4.10—4.28.

Apart from the aforementioned aromatic amines, we also used 4-aminopyridine in reactions with 3-[(*N*-aryl-*N*-chloroacetyl)amino]-2-formylindoles **1a**—**c**. We chose

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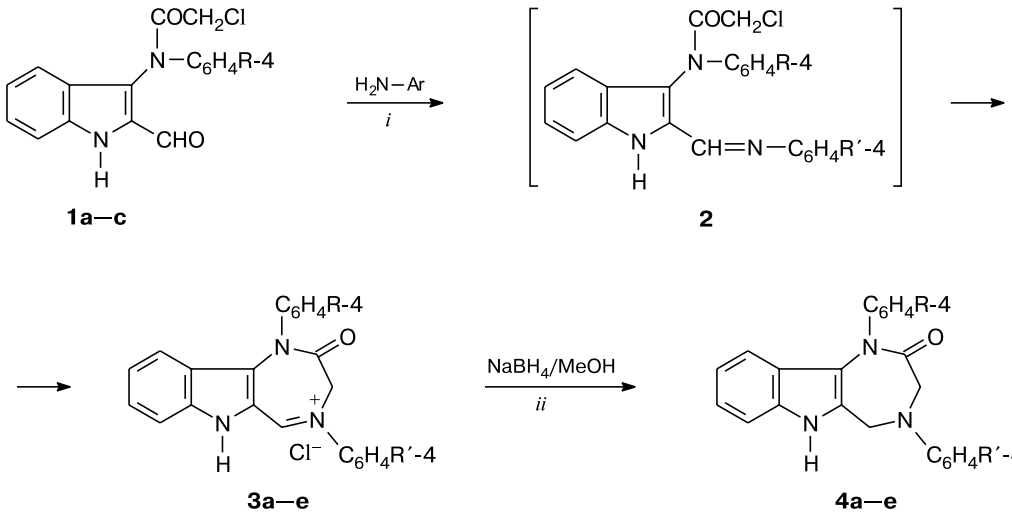
Scheme 1



1: R = NO_2 (**a**), H (**b**), OEt (**c**)

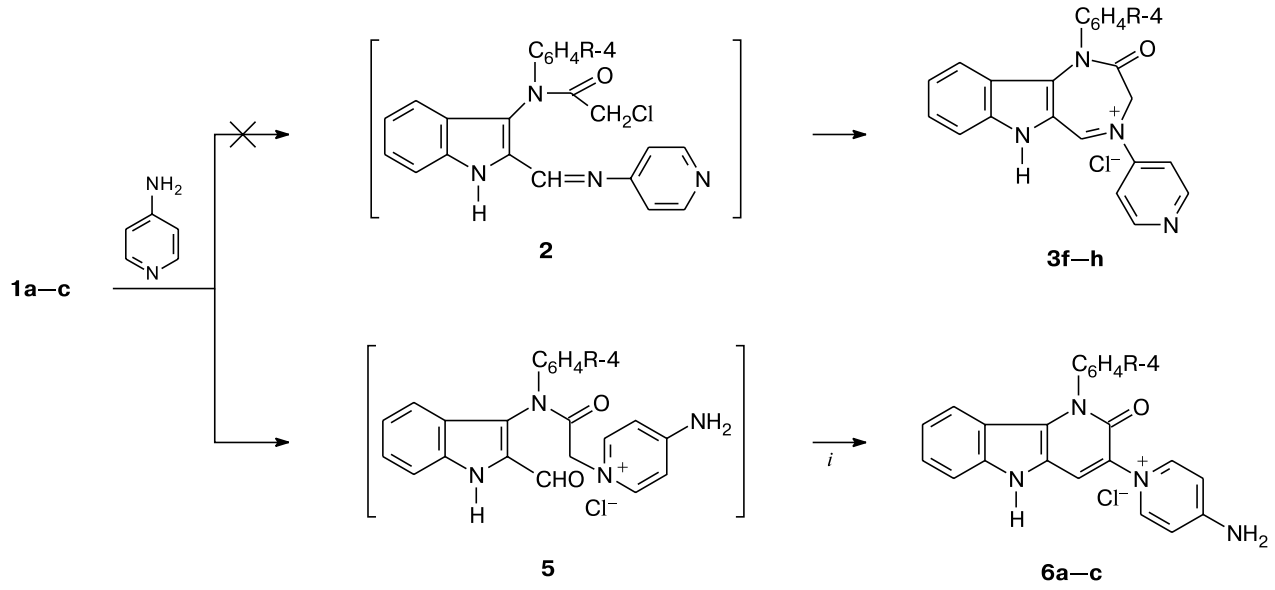
3, 4	**a**	**b**	**c**	**d**	**e**
R	NO_2	NO_2	NO_2	H	OEt
R′	H	OMe	Cl	OMe	OMe

Reagents and conditions: *i*. $ArNH_2$, Pr^iOH, 70 °C; *ii*. $NaBH_4$, MeOH, 20 °C, 1 h.

this heterocyclic amine because the resulting diazepinium salts **3f—h** containing the 4-aminopyridine fragment (Scheme 2) could exhibit anticholinesterase properties. It should be noted that the 4-aminopyridine fragment is a part of the anticholinesterase (memory-improving) drugs tacrine and amiridin.[9] It is also known[1,10] that 4-aminopyridine itself (fampridine) favors a release of acetylcholine from presynaptic terminals of motor nerves.

However, it turned out that the condensation does not lead to Schiff bases **2** with subsequent cyclization into

Scheme 2



1, 6: R = NO_2 (**a**), H (**b**), OEt (**c**)

Reagents and conditions: *i*. 4-aminopyridine, Pr^iOH, reflux, 2—4.5 h.

Table 1. ^{1}H NMR spectra (DMSO-d_6) of [1,4]diazepino[6,5-*b*]indoles **3a—e**, **4a—e**, and **13**

Compound	δ (*J*/Hz)									
	$H_2C(3)$ (s, 2 H)	$H_2C(5)$ (s, 2 H)	H(5) (s, 1 H)	H(7) (d*, 1 H)	H(8) (t*, 1 H)	H(9) (t*, 1 H)	H(10) (d*, 1 H)	N(6)H (br.s, 1 H)	4-RC_6H_4	4-R´C_6H_4
3a	5.22	—	9.85	—	7.48	6.95	6.39	13.07	7.74, 8.42 (A_2B_2 system, 4 H, $C_6\underline{H}_4NO_2$)	7.65 (m, 4 H, H(7), H(3´)—H(5´)); 7.94 (m, 2 H, H(2´), H(6´))
3b**	5.18	—	9.68	7.66	7.48	6.96	6.39	12.76	7.71, 8.39 (A_2B_2 system, 4 H, $C_6\underline{H}_4NO_2$)	7.22, 7.88 (A_2B_2 system, 4 H, $C_6\underline{H}_4$OMe); 3.89 (s, 3 H, OMe)
3c	5.19	—	9.85	7.67	7.49	6.96	6.33	12.88	7.80, 8.42 (A_2B_2 system, 4 H, $C_6\underline{H}_4NO_2$)	7.71, 7.92 (A_2B_2 system, 4 H, $C_6\underline{H}_4$Cl)
3d	5.15	—	9.66	—	7.60	6.88	6.23	12.85	7.40—7.56 (m, 6 H, Ph, H(7))	7.22, 7.91 (A_2B_2 system, 4 H, $C_6\underline{H}_4$OMe); 3.88 (s, 3 H, OMe)
3e	5.12	—	9.62	7.61	7.45	6.92	6.39	12.84	7.06, 7.33 (A_2B_2 system, 4 H, $C_6\underline{H}_4$OEt); 1.36 (t, 3 H, $OCH_2C\underline{H}_3$, *J* = 7.0); 4.10 (q, 2 H, $OC\underline{H}_2CH_3$, *J* = 7.0)	7.21, 7.88 (A_2B_2 system, 4 H, $C_6\underline{H}_4$OMe); 3.88 (s, 3 H, OMe)
4a	4.89	4.28	—	7.40	6.80	6.76	6.35	11.55	7.61, 8.23 (A_2B_2 system, 4 H, $C_6\underline{H}_4NO_2$)	7.25 (t, H(3´), H(5´), *J* = 8.4); 7.08 (t, H(4´)); 6.99 (d, 2 H, H(2´), H(6´))
4b**	4.81	4.18	—	7.40	7.08	6.80	6.37	11.50	7.60, 8.21 (A_2B_2 system, 4 H, $C_6\underline{H}_4NO_2$)	6.85, 6.96 (A_2B_2 system, 4 H, $C_6\underline{H}_4$OMe); 3.69 (s, 3 H, OMe)
4c**	4.88	4.27	—	7.41	7.08	6.80	6.38	11.49	7.61, 8.22 (A_2B_2 system, 4 H, $C_6\underline{H}_4NO_2$)	6.99, 7.27 (A_2B_2 system, 4 H, $C_6\underline{H}_4$Cl)
4d	4.78	4.13	—	—	7.02	6.71	6.30	11.37	7.18—7.45 (m, 6 H, Ph, H(7))	6.85, 6.94 (A_2B_2 system, 4 H, $C_6\underline{H}_4$OMe); 3.67 (s, 3 H, OMe)
4e**	4.75	4.10	—	7.31	7.00	6.71	6.40	11.19	6.82, 6.94 (A_2B_2 system, 4 H, $C_6\underline{H}_4$OEt); 1.37 (t, 3 H, $OCH_2C\underline{H}_3$, *J* = 7.0); 4.02 (q, 2 H, $OC\underline{H}_2CH_3$, *J* = 7.0)	6.86, 7.20 (A_2B_2 system, 4 H, $C_6\underline{H}_4$OMe); 3.70 (s, 3 H, OMe)
13***	4.96 ($H_2C(2)$)	5.50	—	7.95	7.18—7.37		6.91	—	7.02, 8.16 (A_2B_2 system, 4 H, $C_6H_4NO_2$)	7.18—7.37 (Ph)

* *J* = 8.2—8.4 Hz.

** The spectrum was recorded in DMSO—CCl_4.

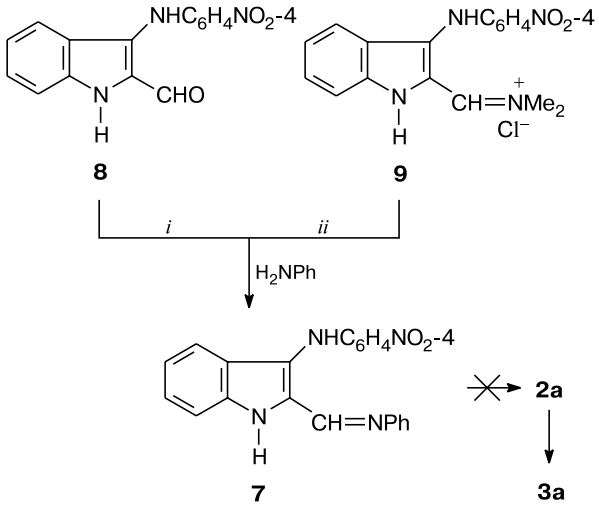
*** The spectrum also contains a signal at δ 2.79 (s, 3 H, COMe).

compounds **3f—h**. Instead, the condensation involves the pyridine N atom and the Cl atom of the chloroacetyl fragment of compounds **1a—c**. Apparently, the first-step products are pyridinium salts **5** with a substantially higher CH acidity of the CH_2 group. This favors intramolecular cyclization *via* the 2-formyl group, giving compounds of the δ-carboline structure: 4-amino-1-(1-aryl-2-oxo-2,5-dihydro-1*H*-pyrido[3,2-*b*]indol-3-yl)pyridinium chlorides (**6a—c**). In contrast to the ^{1}H NMR spectra of diazepinoindoles **3a—e**, the spectra of compounds **6a—c** show no signals for the CH_2 group but contain broadened signals (2 H) at δ 8.6—8.7 due to the NH_2 groups in the 4-aminopyridinium substituent.

Earlier,[6,11] this type of cyclization leading to δ-carboline derivatives has been observed by us in reactions of aldehydes **1a—c** with pyridine or sodium nitrite.

It was interesting to approve an alternative synthesis of [1,4]diazepino[6,5-*b*]indoles with compound **3a** as an example. For this purpose, we synthesized 3-[(4-nitrophenyl)amino]-2-[(phenylimino)methyl]indole (**7**) from aniline and 2-formyl-3-[*N*-(4-nitrophenyl)amino]indole (**8**), as well as from aniline and 2-dimethyliminiomethyl-3-[*N*-(4-nitrophenyl)amino]indole chloride (**9**) (an intermediate in the Vilsmeier synthesis of 2-formylindole **8**) (Scheme 3). We expected that chloroacetylation of phenyliminomethylindole **7** yields, through the formation of azomethine **2**, the target diazepinoindole **3a**.

Scheme 3



Reagents and conditions: *i*. Pr^{i}OH, reflux, 13.5 h; *ii*. Pr^{i}OH, reflux, 0.5 h.

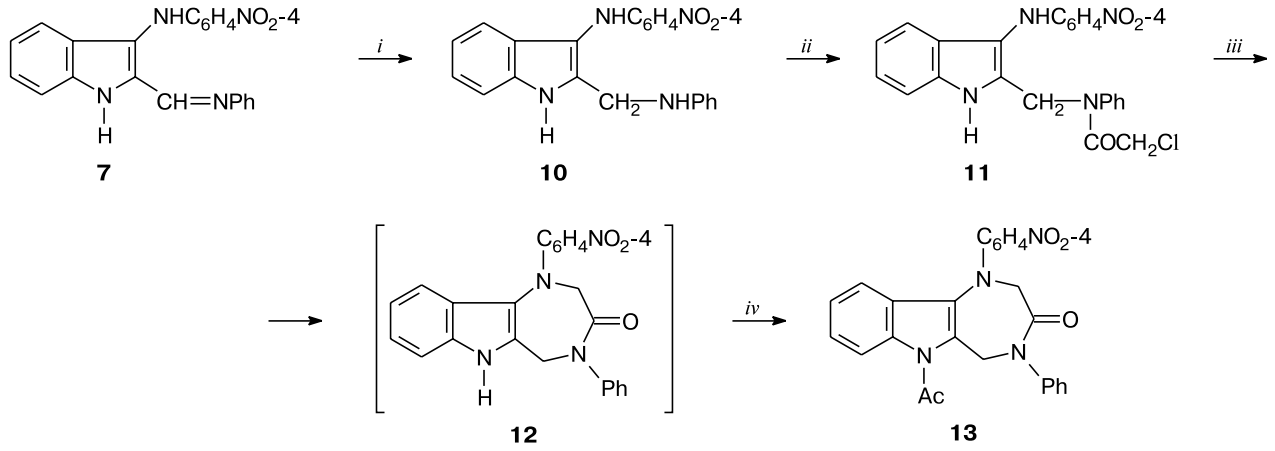
However, the chloroacetylation of compound **7** in boiling toluene in the presence of anhydrous Na_2CO_3 or in DMF with triethylamine at 20 °C gave a complex mixture of products, from which we failed to isolate individual compounds. TLC analysis showed unambiguously that diazepinoindole **3a** does not form under these conditions (see Scheme 3).

Starting from phenyliminomethylindole **7**, we developed a method for the synthesis of other [1,4]diazepino[6,5-*b*]indole derivatives. Compound **7** was reduced with $NaBH_4$ to phenylaminomethylindole **10**, which was treated with chloroacetyl chloride to give the corresponding *N*-chloroacetyl derivative **11**. Intramolecular alkylation of compound **11** on heating in methanol with Triton B (benzyltrimethylammonium hydroxide) yielded a compound whose mass spectrum (ESI) contains peaks with *m/z* 399 $[M + H]^+$, 421 $[M + Na]^+$, and 437 $[M + K]^+$ characteristic of 3-oxodiazepinoindole **12**. However, we failed to purify compound **12** for analysis by recrystallization or column chromatography. It was characterized in the form of 6-acetyl derivative **13** (Scheme 4).

Biological tests with mice revealed the low toxicity of injected compounds **3a—e** and **4a—e** (LD_{50} >1000 mg kg^{-1}). Compounds **4a—e** have no effect on the central nervous system and experimentally induced inflammation in animals. All diazepinoindole chlorides **3a—e** used in doses from 1/10 to 1/20 of LD_{50} exhibit antihypoxic activity with models of hypoxic and hypobaric hypoxia at the piracetam level.

Using a standard avoidance task procedure,[12] we studied the effect of the aminopyridinium salts of δ-carbolines (**6a—c**) on the cognitive functions (learning and memory) of non-breeded male mice (18—22 g in weight). Deficit in learning was induced by scopolamine (1 mg kg^{-1}) injected intraperitoneally as an m-choline blocking agent 15 min before learning tests. The tested low-toxicity compounds (LD_{50} > 1000 mg kg^{-1} (p.os)) were administered

Scheme 4



Reagents and conditions: *i*. $NaBH_4$, MeOH, 20 °C, 2.5 h; *ii*. $ClCH_2COCl$, C_6H_6, 25 °C, 1 h 40 min; *iii*. Triton B, Me_2CO, reflux, 1 h; *iv*. Ac_2O, reflux, 1 h.

in doses of 6—25 and 100 mg kg^{-1} p.os 40 min before learning tests. Compounds **6a—c** had a dose-dependent stimulating effect on the animal learning and memory. The positive effects of compounds **6a**, **6b**, and **6c** in a dose of 100 mg kg^{-1} were observed in 63, 83, and 72% of the animals, respectively; for a dose of 25 mg kg^{-1}, the respective percentages were 50, 40 and 60%. Because the medicinal properties of nootropic drugs are determined by their ability to boost the integrative brain activity, favor memory consolidation, and enhance cognitive functions, we compared these compounds with piracetam, the most familiar drug in this group, in efficiency. Chlorides **6a—c** proved to be more efficient than piracetam: its effect in a dose of 300 mg kg^{-1} was 70%.

Experimental

IR spectra were recorded on an FSM-1201 instrument (Nujol). Mass spectra were recorded on a Finnigan SSQ-710 mass spectrometer (EI, direct inlet probe). Mass spectra (ESI) were recorded on a Waters ZQ-2000 mass spectrometer; samples were injected without passing through a chromatography column. ^{1}H NMR spectra were recorded on Bruker AC-200 and Bruker AC-300 spectrometers in DMSO-d_6 according to the Bruker standard procedure. The course of the reactions was monitored and the purity of the products was checked by TLC on Merck 60 F_{254} plates. The yields, melting points, elemental analysis data, mass spectra, and IR spectra of the compounds obtained are summarized in Table 2. The ^{1}H NMR spectra of [1,4]diazepino[6,5-*b*]indoles **3a—e**, **4a—e**, and **13** are given in Table 1. Compounds **1a—c**,[7] **8**,[13] and **9** [7] have been characterized earlier.

1,4-Diaryl-2-oxo-1,2,3,6-tetrahydro[1,4]diazepino[6,5-*b*]indol-4-ium chlorides (3a—e) (general procedure). An appropriate arylamine (1 mmol) was added to a suspension of 2-formylindole **1a—c** (1 mmol) in Pr^iOH (10 mL). The stirred reaction mixture was heated on a water bath to 70 °C; after 15—30 min, a precipitate formed. The suspension was cooled and chloride **3a—e** was filtered off, washed with Pr^iOH and Me_2CO, and dried.

1,4-Diaryl-2-oxo-1,2,3,4,5,6-hexahydro[1,4]diazepino[6,5-*b*]indoles (4a—e) (general procedure). Sodium borohydride (5 mol) was added in portions at 20 °C to a suspension of chloride **3a—e** (1 mol) in MeOH and the reaction mixture was stirred for 1 h. The precipitate of hexahydrodiazepinoindole **4a—e** was filtered off, washed with MeOH, water, and again MeOH, and dried.

4-Amino-1-(1-aryl-2-oxo-2,5-dihydro-1*H*-pyrido[3,2-*b*]indol-3-yl)pyridinium chlorides (6a—c) (general procedure). 4-Aminopyridine (1 mmol) was added to a suspension of 2-formylindole **1a**, **1b**, or **1c** (1 mmol) in Pr^iOH (10 mL). The reaction mixture was refluxed with stirring for 2, 3.5, and 4.5 h,

Table 2. Yields, melting points, elemental analysis data, mass spectra, and IR spectra of the compounds obtained

Compound	Yield (%)	M.p./°C (solvent)	*M*	Found / Calculated (%)			Molecular formula	MS, *m/z* (I_{rel} (%))	IR, ν_{max}/cm^{-1}		
				C	H	N			NH (NH_2)	C=N$^+$	CO
3a	80	255—260 (MeOH)	432	63.73 63.80	4.26 3.95	12.88 12.94	$C_{23}H_{17}ClN_4O_3$	397 $[M - HCl + H]^+$, 369 $[M - HCl + H - CO]^+$, 419 $[M - HCl + Na]^+$	3460	1693	1626
3b	92	265—268 (MeOH)	462	62.05 62.27	4.43 4.13	11.84 12.10	$C_{24}H_{19}ClN_4O_4$	427 $[M - HCl + H]^+$, 400 $[M - HCl + H - CO]^+$, 449 $[M - HCl + Na]^+$, 465 $[M - HCl + K]^+$	3444	1690	1625
3c	75	238—240 (MeOH)	466	59.10 59.11	3.49 3.45	11.83 11.98	$C_{23}H_{16}Cl_2N_4O_3$	431 $[M - HCl + H]^+$, 403 $[M - HCl + H - CO]^+$	—	—	—
3d	85	228—230 (Pr^iOH)	417	67.76 67.55	5.13 4.95	9.84 9.74	$C_{24}H_{20}ClN_3O_2 \cdot 0.5H_2O$	382 $[M - HCl + H]^+$, 354 $[M - HCl + H - CO]^+$, 763 $[2M - 2HCl + H]^+$	3480	1687	1620
3e	90	230 (Pr^iOH)	461	66.20 66.33	5.96 5.35	8.72 8.92	$C_{26}H_{24}ClN_3O_3 \cdot 0.5H_2O$*	426 $[M - HCl + H]^+$, 398 $[M - HCl + H]^+$, 857 $[2M - 2HCl + H]^+$	—	—	—
4a	95	234—236 (EtOAc)	398	69.36 69.33	4.80 4.55	14.13 14.06	$C_{23}H_{18}N_4O_3$	398 $[M]^+$ (24), 368 $[M - NO]^+$ (12), 265 $[M - C_6H_5NCH_2CO]^+$ (25), 248 $[M - NO_2C_6H_4 - CO]^+$ (12), 232 $[M - NO_2C_6H_4NCO - H_2]^+$ (100), 218 $[C_6H_5NCH_2CO - HNO_2]^+$ (48)	3355	—	1690

(*to be continued*)

Table 2 (*continued*)

Compound	Yield (%)	M.p./°C (solvent)	*M*	Found / Calculated (%)			Molecular formula	MS, *m/z* (I_{rel} (%))	IR, ν_{max}/cm^{-1}		
				C	H	N			NH (NH_2)	C=N$^+$	CO
4b	92	208—210 (EtOAc)	428	67.43 67.28	5.09 4.70	12.91 13.07	$C_{24}H_{20}N_4O_4$	428 $[M]^+$ (12), 398 $[M - NO]^+$ (2), 262 $[M - NO_2C_6H_5NCO - H_2]^+$ (100)	—	—	—
4c	87	252—254 (decomp., MeOH—EtOAc)	432	63.91 63.82	4.13 3.96	12.92 12.95	$C_{23}H_{17}ClN_4O_3$	432 $[M]^+$ (17), 402 $[M - NO]^+$ (5), 265 $[M - ClC_6H_4NCH_2CO]^+$ (100), 248 $[M - NO_2C_6H_4 - CO]^+$ (31), 234 $[M - NO_2C_6H_4NCO]^+$ (15), 218 $[ClC_6H_4NCH_2CO - HNO_2]^+$ (78)	3335	—	1665
4d	93	208—209 (MeOH—EtOAc)	383	74.97 75.17	5.71 5.52	10.97 10.96	$C_{24}H_{21}N_3O_2$	384 $[M + H]^+$, 406 $[M + Na]^+$, 422 $[M + K]^+$, 767 $[2 M + H]^+$, 789 $[2 M + Na]^+$, 805 $[2 M + K]^+$	3295	—	1665
4e	93	223—224 (MeOH—EtOAc)	427	72.83 73.04	6.17 5.89	9.80 9.83	$C_{26}H_{25}N_3O_3$	428 $[M + H]^+$, 450 $[M + Na]^+$, 466 $[M + K]^+$, 855 $[2 M + H]^+$, 877 $[2 M + Na]^+$, 893 $[2 M + K]^+$	3120	—	1660
6a	58	>360 (EtOH—H_2O, 10 : 1.25)	451	58.13 58.48	4.05 4.02	15.28 15.50	$C_{22}H_{16}ClN_5O_3 \cdot H_2O$	398 $[M - HCl + H]^+$	3400—3100	1715	1625
6b	75	320 (decomp., EtOH—H_2O, 10 : 1.5)	415	63.15 63.54	4.84 4.85	13.27 13.47	$C_{24}H_{21}ClN_4O_2 \cdot H_2O$	353 $[M - HCl + H]^+$	3365—3075	1645	1616
6c	72	330 (decomp., EtOH—H_2O, 10 : 1)	450	63.70 63.93	5.35 5.14	12.28 12.43	$C_{22}H_{16}ClN_5O_3 \cdot 1.5H_2O$	397 $[M - HCl + H]^+$	3390—3090	1650	1620
7	80 (*A*), 75 (*B*)	114—116 (C_6H_6)	356	71.50 70.77	4.59 4.53	15.40 15.72	$C_{21}H_{16}N_4O_2$	379 $[M + Na]^+$, 395 $[M + K]^+$, 735 $[2 M + Na]^+$, 751 $[2 M + K]^+$, 1107 $[3 M + K]^+$	3302	—	—
10	70	186—188 (Pr^iOH)	358	70.33 70.38	5.03 5.06	15.27 15.63	$C_{21}H_{18}N_4O_2$	380 $[M + Na]^+$, 397 $[M + K]^+$, 755 $[2 M + K]^+$	3188, 3382	—	—
11	80	196—198 (EtOH)	434	63.30 63.52	4.63 4.40	12.90 12.88	$C_{23}H_{19}ClN_4O_5$	435 $[M + H]^+$, 457 $[M + Na]^+$, 473 $[M + K]^+$, 891 $[2 M + Na]$, 907 $[2 M + K]^+$	3296, 3329	—	1798
13	38	305—307 (DMF)	440	68.68 68.17	4.45 4.58	12.81 12.72	$C_{25}H_{20}N_4O_4$	441 $[M + H]^+$, 463 $[M + Na]^+$, 2479 $[M + K]^+$, 881 $[2 M + H]^+$, 903 $[2 M + Na]^+$, 919 $[2 M + K]^+$	—	—	1697, 1664

* Found (%): H_2O, 1.57. Calculated (%): H_2O, 1.91.

respectively (monitoring by TLC) and cooled. Chlorides **6a—c** were filtered off, washed with Pr^iOH and Me_2CO, and dried.

Chloride 6a. ^{1}H NMR, δ: 6.18 (d, 1 H, H(9), *J* = 8.2 Hz); 6.86 (t, 1 H, H(8), *J* = 8.2 Hz); 7.32 (t, 1 H, H(7)); 7.58 (d, 1 H, H(6), *J* = 8.2 Hz); 7.00, 8.34 (A_2B_2 system, 4 H, H(2′), H(6′), H(3′), H(5′)); 7.84, 8.53 (A_2B_2 system, 4 H, $C_6H_4NO_2$); 8.52 (s, 1 H, H(4)); 8.70 (br.s, 2 H, NH_2); 12.3 (br.s, 1 H, N(5)H).

Chloride 6b. ^{1}H NMR, δ: 6.00 (d, 1 H, H(9), J = 8.2 Hz); 6.83 (t, 1 H, H(8), J = 8.2 Hz); 7.32 (t, 1 H, H(7)); 7.00, 8.34 (A_2B_2 system, 4 H, H(2′), H(6′), H(3′), H(5′)); 7.50, 7.75 (both m, 3 H each, H(6) and H(2′), H(6′), H(3′)—H(5′)); 8.50 (s, 1 H, H(4)); 8.60 (br.s, 2 H, NH_2); 12.1 (br.s, 1 H, N(5)H).

Chloride 6c. ^{1}H NMR, δ: 1.40 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.0 Hz); 4.15 (q, 2 H, $OC\underline{H}_2Me$, J = 7.0 Hz); 6.18 (d, 1 H, H(9), J = 8.2 Hz); 6.86 (t, 1 H, H(8), J = 8.2 Hz); 7.32 (t, 1 H, H(7), J = 8.2 Hz); 7.58 (d, 1 H, H(6), J = 8.2 Hz), 7.00, 8.34 (A_2B_2 system, 4 H, H(2′), H(6′), H(3′), H(5′)); 7.20, 7.50 (A_2B_2 system, 4 H, C_6H_4Et); 8.52 (s, 1 H, H(4)); 8.60 (br.s, 2 H, NH_2); 12.1 (br.s, 1 H, N(5)H).

3-[*N*-(4-Nitrophenyl)amino]-2-[(phenylimino)methyl]indole (7). ***A.*** Aniline (3.24 mL, 35.6 mmol) was added to a suspension of aldehyde **8** (5 g, 17.8 mmol) in Pr^{i}OH (500 mL). The reaction mixture was refluxed with stirring for 13.5 h and evaporated to dryness. The residue was refluxed with benzene (100 mL) for 5 min. The resulting solution was cooled and the precipitate was filtered off, washed with benzene and MeOH, and dried. The yield of compound **7** was 5.07 g. ^{1}H NMR, δ: 6.81, 8.06 (m, 4 H, $C_6H_4NO_2$); 7.04, 7.33—7.17, 7.42, 7.49 (all m, 1 H, 5 H, 2 H, 1 H, H(4)—H(7), Ph); 8.57 (s, 1 H, H(1′)); 9.33 (br.s, 1 H, $N\underline{H}PhNO_2$); 11.80 (br.s, 1 H, N(1)H).

B. Aniline (0.27 mL, 3 mmol) was added to a suspension of immonium salt **9** (0.7 g, 2 mmol) in Pr^{i}OH (50 mL). The reaction mixture was refluxed with stirring for 30 min and evaporated to dryness. The residue was refluxed with benzene (20 mL) for 5 min. The resulting solution was cooled and the precipitate was filtered off, washed with benzene and MeOH, and dried. The yield of compound **7** was 0.54 g. A mixture of this compound with a sample from method ***A*** did not depress the melting point.

3-(4-Nitrophenyl)amino-2-(phenylamino)methylindole (10). Sodium borohydride (1.4 g, 38 mmol) was added in portions at 20 °C to a stirred solution of imine **7** (4.5 g, 12.6 mmol) in MeOH (100 mL). After 2.5 h, the precipitate was filtered off, washed with MeOH, and stirred for 30 min with water (150 mL) acidified with conc. HCl to pH 3. The resulting precipitate was filtered off, washed with water to pH 7 and MeOH, and dried. The yield of compound **10** was 3.22 g. ^{1}H NMR, δ: 4.27 (d, 2 H, $C\underline{H}_2NHPh$, J = 5.6 Hz); 5.96 (t, 1 H, $CH_2N\underline{H}Ph$, J = 5.6 Hz); 6.44—6.77, 6.84—7.23, 7.37, 8.01 (all m, 5 H, 5 H, 1 H, 2 H, H(4)—H(7), $C_6H_4NO_2$, Ph); 8.83 (s, 1 H, $N\underline{H}C_6H_4NO_2$); 11.17 (br.s, 1 H, N(1)H).

2-[*N*-(Chloroacetyl)-*N*-(phenyl)aminomethyl]-3-(4-nitrophenyl)aminoindole (11). Chloroacetyl chloride (0.09 mL, 1.1 mmol) and triethylamine (0.14 mL, 1 mmol) were added at 25 °C to a stirred suspension of indole **10** (0.36 g, 1 mmol) in dry benzene (5 mL). After 1 h 40 min, the precipitate was filtered off, washed with benzene, water, and MeOH, and dried. The yield of compound **11** was 0.35 g. ^{1}H NMR, δ: 4.01 (s, 2 H, $C\underline{H}_2N$); 4.98 (s, 2 H, $COCH_2Cl$); 6.28, 6.83—7.35, 7.42, 7.83 (all m, 2 H, 8 H, 1 H, 2 H, H(4)—H(7), $C_6H_4NO_2$, Ph); 8.51 (s, 1 H, $N\underline{H}PhNO_2$); 11.17 (br.s, 1 H, N(1)H).

6-Acetyl-1-(4-nitrophenyl)-3-oxo-4-phenyl-1,2,3,4,5,6-hexahydro[1,4]diazepino[6,5-*b*]indole (13). A 40% solution of Triton B (1.8 mL) in MeOH was added to a solution of chloroacetyl derivative **11** (0.8 g, 108 mmol) in anhydrous acetone (120 mL). The reaction mixture was refluxed for 1 h, cooled, and evaporated to dryness. The residue was triturated with MeOH—H_2O (2 : 1). The resulting precipitate was filtered off, washed with water, and dried. The yield of crude 1-(4-nitrophenyl)-3-oxo-4-phenyl-1,2,3,4,5,6-hexahydro-6*H*-[1,4]diazepino[6,5-*b*]indole (**12**) was 0.68 g (93%). Compound **12** (0.43 g, 1 mmol) was refluxed as obtained in acetic anhydride (6 mL) for 1 h. On cooling, the resulting precipitate was filtered off, washed with acetic anhydride and MeOH, and dried. The yield of 6-acetyl[1,4]diazepino[6,5-*b*]indole **13** was 0.18 g.

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