Synthesis and study of some properties of 1-aryl-2-oxo-1,2,3,6-tetrahydro[1,4]diazepino[6,5-*b*]indole 4-oxides

*S. Yu. Ryabova, N. A. Rastorgueva, E. A. Lisitsa, L. M. Alekseeva, and V. G. Granik**

The State Scientific Center "Scientific Research Institute of Organic Intermediates and Dyes," 1, building 4, ul. Bolshaya Sadovaya, 123995 Moscow, Russian Federation. Fax: +7 (095) 254 6574. E-mail: makar-cl@ropnet.ru

A number of 1-aryl-2-oxo-1,2,3,6-tetrahydro[1,4]diazepino[6,5-*b*]indole 4-oxides were synthesized based on 3-[*N*-aryl-*N*-(chloroacetyl)amino]-2-formylindoles. The nature of the substituent in the 1-aryl fragment has a pronounced influence on the course of reactions throughout the whole sequence of transformations during the synthesis of diazepinoindoles. The reduction of 4-oxides by formamidinosulfinic acid, hydrogen in the presence of Pd/C, and sodium bisulfite was studied. The structures of the reaction products were confirmed using IR and ^{1}H NMR spectroscopy and mass spectrometry.

Keywords: 3-[*N*-aryl-*N*-(chloroacetyl)amino]-2-formylindoles, 3-arylamino-2-formylindoles, [1,4]diazepino[6,5-*b*]indole 4-oxides, deoxygenation, formamidinosulfinic acid.

Research into the synthesis, properties, and transformations of benzo[1,4]diazepine derivatives, the group of compounds comprising, in particular, the most efficient tranquilizers, attracts considerable attention.[1—4] The scope of investigation of compounds of this type can be extended by including the synthesis and the study of properties of systems in which the diazepine ring is annelated to various heterocycles. Data on the preparation of such compounds exhibiting biological activities have already been obtained.[5—7]

Recently, we developed a new approach to the synthesis of [1,4]diazepino[6,5-*b*]indoles.[8] This work continues studies dealing with the synthesis and properties of compounds of this series. As the starting compounds, we used *N*-acetylindoxyl (**1**) and *para*-R-derivatives of aniline **2a—e**. It was found that the nature of the substituent R influences substantially the course of the reactions, this influence remaining significant throughout the whole sequence of transformations involved in the synthesis and further conversions of diazepinoindoles (Scheme 1), despite the remoteness of the substituent R from the reaction center.

As follows from the previous publication,[9] pure compound **3a** cannot be isolated upon the reaction of indoxyl **1** with aniline; it was identified as a chloroacetyl derivative **4a**. A similar situation is also observed for another arylamine, *p*-phenetidine (**2b**), having an electron-donating group in the *para*-position.

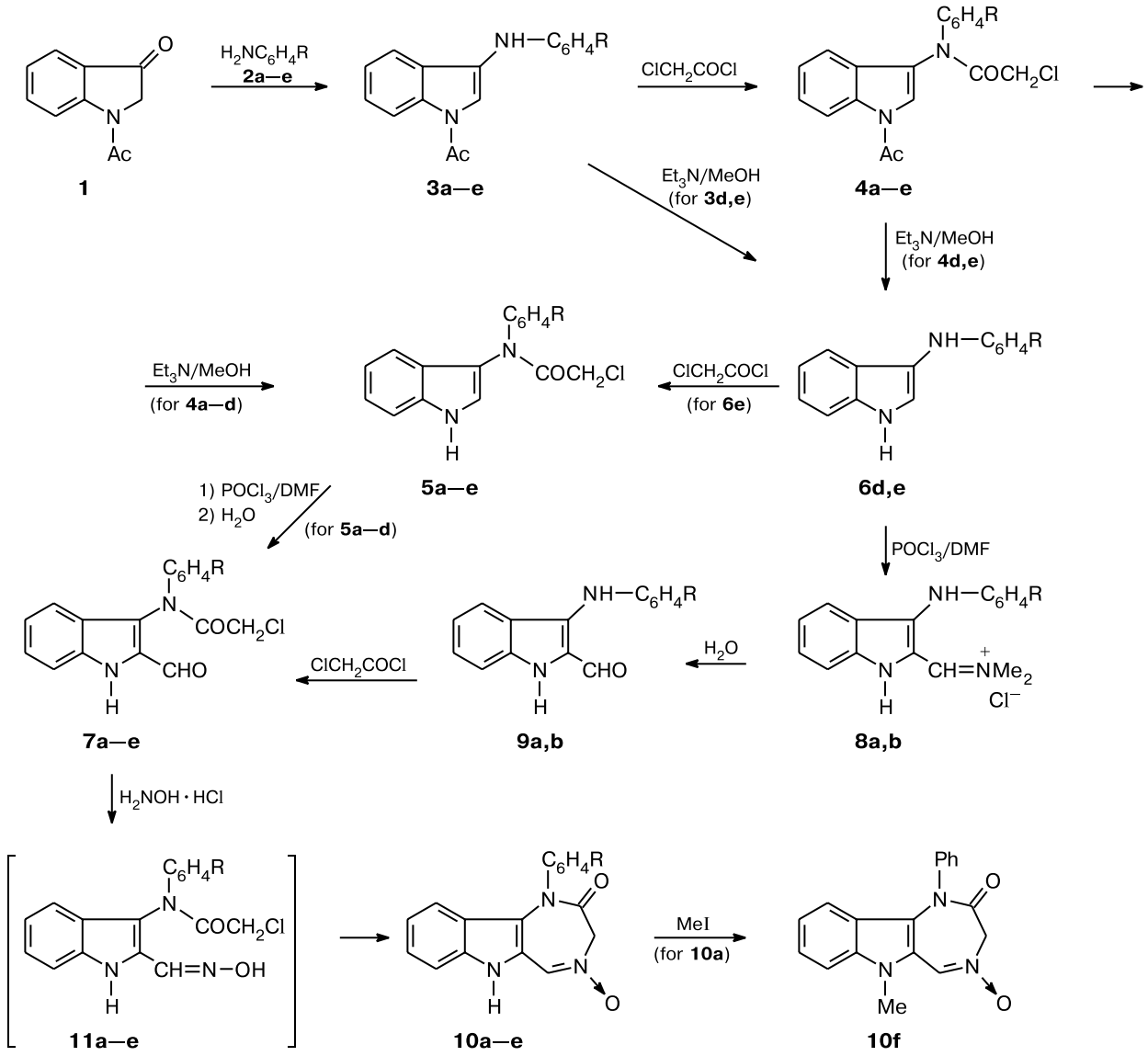
The condensation **1** + **2b** was immediately followed, without isolation of intermediate 1-acetyl-3-[*N*-(4-ethoxyphenyl)amino]indole (**3b**), by chloroacetylation leading to *N*′-chloroacetyl derivative **4b**. The other compounds **3c**[9],**3d**, and **3e**[9] were isolated in a pure state, so were their diacyl derivatives **4c**[9], **4d**, and **4e**.[9] As has already been noted,[9] *N*,*N*′-diacyl-substituted 3-arylaminoindoles do not undergo the Vilsmeier reaction due to the pronounced decrease in the electron density in position 2 of the indole ring. Therefore, it was necessary to remove selectively one *N*-acetyl group or both acyl groups. For compounds **4a—d**, *N*(1)-deacetylation yielding *N*′-chloroacetyl derivatives **5a—d** was acxcomplished by treatment with triethylamine in methanol. It is noteworthy that, whereas for **4a—c** this reaction proceeded smoothly on refluxing the reaction mixture, in the case of **4d**, partial abstraction of the chloroacetyl group is also observed under these conditions due to the presence of the electron-withdrawing cyano group in the *para*-position of the benzene ring, the reaction resulting in a mixture of compounds **5d** and **6d**. Selective elimination of the acetyl fragment from **4d** giving rise to pure **5d** could be performed only by conducting this reaction at a low temperature (5—7 °C). Keeping a mixture of reactants (**4d**, Et_3N, MeOH) at 20 °C for 72 h afforded completely deacylated indole **6d** in 35% yield. The same reaction involving a 3-arylaminoindole with a stronger acceptor (NO_2) in the *para*-position of the *N*′-phenyl group, *viz.*, compound **4e**, caused elimination of both acyl groups to furnish compound **6e**.[9] Attempts to carry out regioselective chloroacetylation of this compound at the exocyclic NH group showed that this is possible with small batches; in this case, compound **5e** was obtained in good yields. However, in larger-scale experiments this product was formed as a mixture with 2,*N*′-bis(chloroacetyl) derivatives **12**, which could not be separated by crystallization.

Thus, depending on the substituent R, one can prepare either *N*(1)- or *N*(1),*N*′-deacylated compounds **5** and **6**.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 6, pp. 1312—1323, June, 2003.

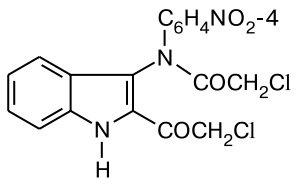
1066-5285/03/5206-1386 $25.00

Scheme 1



2—7, 10,11: R = H (**a**), 4-OEt (**b**), 4-Cl (**c**), 4-CN (**d**), 4-NO_2 (**e**)
8, 9: R = 4-CN (**a**), 4-NO_2 (**b**)

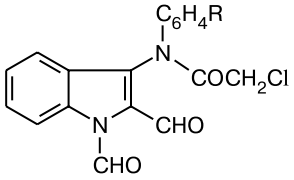
3-[*N*-Aryl-*N*-(chloroacetyl)amino]-2-formylindoles (**7a—e**) are key compounds of the diazepine cyclization. In view of the above discussion, these compounds are synthesized using different approaches. In the case of chloroacetyl derivatives **5a—c**, direct Vilsmeier C(2)-formylation can be carried out. When the aryl nucleus contains an NO_2 group, compound **5e** becomes poorly accessible; therefore, compound **6e** was subjected to formylation with subsequent chloroacetylation. For CN derivatives of 3-(arylamino)indole, the corresponding 2-formylindole **7d** can be prepared both from **5d** and from **9a**.



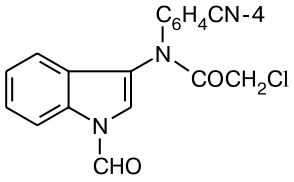
12

Thus, formylation of **5a—d** gave rise to 2-formylindoles **7a—d**. It was established that the optimal **5** to Vilsmeier complex ratio for compounds **5a—c** is 1 : 1, but not 1 : 3, as has been proposed previously.[9] This conclusion was based on a study of the ^{1}H NMR spectrum of the crude product obtained by the reaction of compound **5a** with

the Vilsmeier reagent (1 : 3). This product was shown to be a mixture of compound **7a** and 1,2-diformyl derivative **13a** in a ratio of 2 : 1. The ^{1}H NMR spectrum exhibits the following signals, δ: 4.30 (s, 2 H, $COCH_2Cl$), 10.08 (s, 1 H, 2-CHO), 12.23 (br.s, 1 H, N(1)H) (**7a**) and 4.43 (s, 2 H, $COCH_2Cl$), 8.42 (d, 1 H, H(7), $J_{7,6}$ = 8.2 Hz), 9.97 (s, 1 H, 1-CHO), 10.31 (s, 1 H, 2-CHO) (**13a**). (The signals of the benzene rings for these compounds occur in the range of δ 7.00—7.85.) Meanwhile, when **5a** and the Vilsmeier complex were taken in 1 : 1 ratio, aldehyde **7a** was formed in 80% yield. Conversely, the formylation of **5d** requires a threefold excess of the complex (with 1 : 1 ratio the reaction does not proceed). However, judging by the ^{1}H NMR spectrum, the mixture formed in this case contains 1,2-diformyl- (**13b**) and 1-formyl-substituted (**14**) derivatives apart from the target 2-formylindole **7d** (see Experimental). Since the Vilsmeier formylation of *N*(1),*N*′-diacyl derivatives of 3-(arylamino)indoles does not occur under these conditions,[9] 1,2-diformylindoles **13a,b** are formed upon further formylation of aldehydes **7a,d** rather than compound **14**.



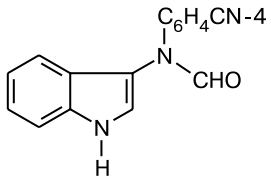
13a,b



14

R = H (**a**), 4-CN (**b**)

Deacylated derivatives **6d,e**, which can be conveniently prepared by hydrolysis of compounds **3d**,**e**, were introduced into the Vilsmeier reaction. In the case of **6e**, a threefold excess of the Vilsmeier complex was used and for **6d**, the components were taken in 1 : 1 ratio. After these reactions, immonium salts **8a,b** were isolated. Without further purification,* these products were hydrolyzed to 2-formyl-3-arylaminoindoles (**9a,b**).[9] Treatment of the mother liquor left after separation of the immonium salt **8a** with water made it possible to isolate the side product, 3-[*N*-formyl-*N*-(4-cyanophenyl)amino]indole (**15**), which could not be purified to form an analytical grade specimen; however, its structure was indicated unambiguously by the data of IR, mass, and ^{1}H NMR spectra (see Experimental).



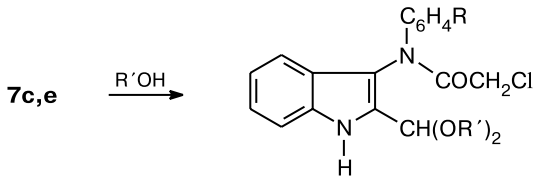
15

On heating with chloroacetyl chloride in the presence of sodium carbonate, compounds **9a,b** were smoothly transformed into the corresponding *N*′-chloroacetyl derivatives **7d,e**. In this case, too, one can clearly follow the influence of the 4-R-substituent. Indeed, acylation of 4-nitro derivative **9b** requires a higher temperature (refluxing in toluene) than that of 4-cyano derivative **9a** (refluxing in benzene).

The resulting aldehydes **7a—e** react with hydroxylamine to give 4-oxides **10a—e**; one of these compounds, **10a**, was subjected to methylation under conditions of phase transfer catalysis, which resulted in 6-methyl derivative **10f**. Note that oximes **11** are intermediate compounds in the synthesis of 4-oxides **10a—e**.[8]

On treatment with alcohols, some aldehydes **7** are quite readily converted into the corresponding acetals **16a**,[9] **16b**, and **16c**, which were isolated and identified for compounds **7c,e** (Scheme 2).

Scheme 2



16a—c

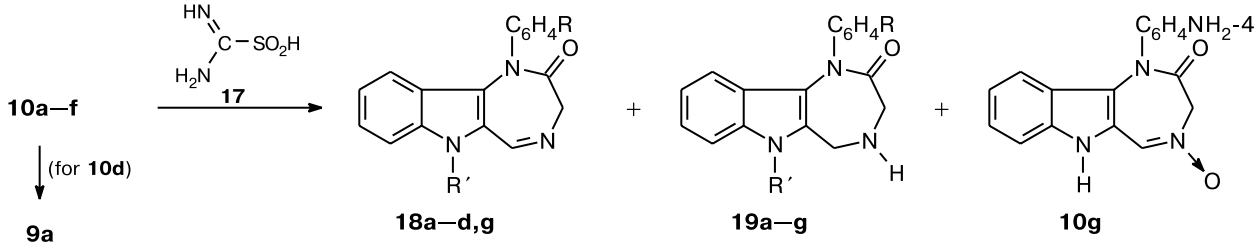
R = 4-Cl, R′ = Me (**a**); R = 4-NO_2, R′ = Pr^i (**b**), Et (**c**)

Previously, we have shown[8] that 2-oxo-1-phenyl-1,2,3,6-tetrahydro[1,4]diazepino[6,5-*b*]indole 4-oxide (**10a**) can be deoxygenated using formamidinosulfinic acid (**17**). It was found[8] that the reduction of the 4-oxide group to give tetrahydro[1,4]diazepino[6,5-*b*]indole **18a** is followed by reduction of the C=N bond, hexahydro derivative **19a** being formed as the major reaction product.

It is worth noting that reagent **17** has been used previously for the reduction of carbonyl, nitro, and azo com-

* As was to be expected, salt **8b** was easily hydrolyzed to aldehyde **9b**: the chromatogram of **8b** on a Silufol plate showed a small spot of aldehyde **9b** in addition to the spot for the salt (at the start). The FAB mass spectrum of salt **8b** shows a peak with m/z 309 $[M + H]^+$; the compound does not melt and decomposes at a temperature of >200 °C, unlike aldehyde **9b**, which has m.p. 237—238 °C.

Scheme 3



18,19	a	b	c	d	e	f	g
R	H	4-OEt	4-Cl	4-CN	4-NO_2	H	4-NH_2
R´	H	H	H	H	H	Me	H

pounds and disulfides,[10,11] but, apparently, it has never been used to reduce nitrones to which 4-oxides **10** belong.

In this study, we attempted such reduction. 4-Oxides **10b—f** were treated with a four-fold excess of formamidinosulfinic acid in aqueous alkali, *i.e.*, under conditions similar to those employed to reduce compound **10a** [8] (Scheme 3). In most cases, the reduction gave mixtures of tetra- and hexahydro derivatives **18** and **19** (no **18f** is formed, only compound **19f** being isolated, see below).

The structures of compounds in the mixtures thus obtained were determined by ^{1}H NMR spectroscopy (Tables 1 and 2). The following signals are the most characteristic in the spectra of 4-oxides and the reduction products, δ: 8.13—8.48 (H(5)) and 4.71—4.74 (2 H(3))

Table 1. ^{1}H NMR spectra of 1-aryl-2-oxo[1,4]diazepino[6,5-*b*]indole derivatives **10b,d—f, 18b, 19b—d,f,g,** and **20**

Compound	δ (*J*/Hz)						
	2 H(3) (s)	H(5) (s)	2 H(5) (s)	N(6)H (br.s)	H(9) (t)	H(10) (d)	H(8), H(7), C_6H_4R and other signals
10b	4.71	8.13	—	11.43	6.80 ($J_{9,8} = J_{9,10} = 8.4$)	6.42 ($J_{10,9} = 8.4$)	1.34 (t, 3 H, $OCH_2C\underline{H}_3$, $J = 7.5$); 4.05 (q, 2 H, $OC\underline{H}_2CH_3$); 6.96 (m, 2 H, H(2´), H(6´)); 7.15 (m, 3 H, H(5´), H(3´), H(8)); 7.39 (d, 1 H, H(7), $J_{7,8} = 8.2$)
10d	4.78	8.18	—	12.00	6.85 ($J_{9,8} = J_{9,10} = 8.2$)	6.33 ($J_{10,9} = 8.2$)	7.18 (t, 1 H, H(8), $J_{8,7} = J_{8,9} = 8.2$); 7.44 (d, 1 H, H(7), $J_{7,8} = 8.2$); 7.50, 7.92 (AA´XX´, 4 H, C_6H_4CN)
10e	4.83	8.21	—	11.63	6.86 ($J_{9,8} = J_{9,10} = 8.4$)	6.39 ($J_{10,9} = 8.4$)	7.21 (t, 1 H, H(8), $J_{8,7} = J_{8,9} = 8.4$); 7.47 (d, 1 H, H(7), $J_{7,8} = 8.4$); 7.59, 8.32 (AA´XX´, 4 H, $C_6H_4NO_2$)
10f	4.74	8.48	—	—	6.82 ($J_{9,8} = J_{9,10} = 8.4$)	6.39 ($J_{10,9} = 8.4$)	3.80 (s, 3 H, N(6)CH_3); 7.09—7.65 (m, 7 H, H(7), H(8), C_6H_5)
18b	4.42	8.78	—	11.6	6.85 ($J_{9,8} = J_{9,10} = 8.2$)	6.42 ($J_{10,9} = 8.2$)	1.34 (t, 3 H, $OCH_2C\underline{H}_3$, $J = 7.5$); 4.05 (q, 2 H, $OC\underline{H}_2CH_3$); 6.94, 7.12 (AA´XX´, 4 H, $C_6\underline{H}_4OEt$); 7.20 (t, 1 H, H(8), $J_{8,7} = J_{8,9} = 8.2$); 7.47 (d, 1 H, H(7), $J_{7,8} = 8.2$)
19b	4.22	—	3.43	11.02	6.70 ($J_{9,8} = J_{9,10} = 8.2$)	6.39 ($J_{10,9} = 8.2$)	1.33 (t, 3 H, $OCH_2C\underline{H}_3$, $J = 7.5$); 4.02 (q, 2 H, $OC\underline{H}_2CH_3$); 6.88—7.29 (m, 6 H, H(7), H(8), $C_6\underline{H}_4OEt$)
19c	4.24	—	3.45	11.13	6.75 ($J_{9,8} = J_{9,10} = 8.4$)	6.39 ($J_{10,9} = 8.4$)	7.00 (t, 1 H, H(8), $J_{8,7} = J_{8,9} = 8.4$); 7.29—7.43 (m, 5 H, H(7), C_6H_4Cl)
19d	4.24	—	3.47	11.16	6.76 ($J_{9,8} = J_{9,10} = 8.4$)	6.33 ($J_{10,9} = 8.4$)	6.99 (t, 1 H, H(8), $J_{8,7} = J_{8,9} = 8.4$); 7.33 (d, 1 H, H(7), $J_{7,8} = 8.4$); 7.52, 7.81 (AA´XX´, 4 H, C_6H_4CN)
19f	4.27	—	3.43	—	6.73 ($J_{9,8} = J_{9,10} = 8.4$)	6.40 ($J_{10,9} = 8.4$)	3.70 (s, 3 H, N(6)CH_3); 7.06 (t, 1 H, H(8), $J_{8,7} = J_{8,9} = 8.4$); 7.15 – 7.56 (m, 6 H, H(7), C_6H_5)
19g	4.20	—	3.40	10.89	6.70 ($J_{9,8} = J_{9,10} = 8.4$)	*	4.97 (br.s, 2 H, NH_2); 6.53 (m, 3 H, H(10), H(2´), H(6´)); 6.96 (m, 3 H, H(8), H(3´), H(5´); 7.25 (d, 1 H, H(7), $J_{7,8} = 8.4$)
20	4.83, 5.00	—	4.20, 4.23	11.33, 11.44	6.73, 6.78 ($J_{9,8} = J_{9,10} = 8.4$)	6.37, 6.48 ($J_{10,9} = 8.4$)	7.02, 7.06 (both t, 1 H each, H(8), $J_{8,7} = J_{8,9} = 8.4$); 7.15—7.51 (m, 6 H, H(7), C_6H_5); 8.31, 8.34 (both s, 1 H each, N(4)CHO)

* The signal of H(10) falls in the aromatic region of benzene ring protons.

Table 2. ^{1}H NMR spectra of mixtures obtained by the reduction of 4-oxides with formamidinosulfinic acid

Mixture	Compound*	δ (*J*/Hz)				
		2 H(3) (s)	2 H(5) (s)	H(5) (s)	N(6)H	H(7)—H(10), C_6H_4R
18b—19b	**18b** (60)	4.41	—	8.77	11.62	1.32 (t, $OCH_2C\underline{H}_3$, J = 7.5); 4.03 (q, 2 H, $OC\underline{H}_2CH_3$); 6.37 (d, 1 H, H(10), $J_{10,9}$ =8.2); 6.79 (t, 1 H, H(9), $J_{9,8} = J_{9,10}$ = 8.2); 7.41 (d, 1 H, H(7), $J_{7,8}$ = 8.2); 6.85—7.25 (m)**
	19b (40)	4.21	3.42	—	11.05	1.32 (t, $OCH_2C\underline{H}_3$, J = 7.5); 4.03 (q, 2 H, $OC\underline{H}_2CH_3$); 6.37 (d, 1 H, H(10), $J_{10,9}$ = 8.2); 6.70 (t, 1 H, H(9), $J_{9,8} = J_{9,10}$ = 8.2); 7.26 (d, 1 H, H(7), $J_{7,8}$ = 8.2); 6.85—7.25 (m)**
18c—19c	**18c** (30)	4.45	—	8.81	11.65	6.39 (br.d, 1 H, H(10), $J_{10,9}$ = 8.2); 6.50—7.90 (m)**
	19c (70)	4.24	3.46	—	11.08	6.39 (br.d, 1 H, H(10), $J_{10,9}$ = 8.2); 6.50—7.90 (m)**
10d—18d—19d	**10d** (76)	4.66	—	8.05	11.49	6.22 (d, 1 H, H(10), $J_{10,9}$ = 8.0); 6.72 (t, 1 H, H(9), $J_{9,8} = J_{9,10}$ = 8.0); 7.06 (t, 1 H, H(8), $J_{9,8} = J_{9,10}$ = 8.0); 7.32 (d, 1 H, H(7), $J_{7,8}$ = 8.2); 7.38—7.78 (m, 4 H, C_6H_4CN-4)
	18d (8)	4.35	—	8.70	11.53	6.40—8.00 (m)
	19d (16)	4.12	3.34	—	11.01	6.40—8.00 (m)
10g—18g—19g	**10g** (3.0)	4.68	—	8.12	11.40	5.15 (br.s, 2 H, NH_2); 6.55—7.20 (m)
	18g (85)	4.38	—	8.74	11.52	5.15 (br.s, 2 H, NH_2); 6.50 (d, 1 H, H(10), $J_{10,9}$ = 8.2); 7.18 (t, 1 H, H(8), $J_{9,8} = J_{9,10}$ = 8.2); 7.39 (d, 1 H, H(7), $J_{7,8}$ = 8.2); 6.55—7.20 (m)**
	19g (12)	4.21	3.40	—	11.00	5.15 (br.s, 2 H, NH_2); 6.50 (d, 1 H, H(10), $J_{10,9}$ = 8.2); 7.28 (d, 1 H, H(7), $J_{7,8}$ = 8.2); 6.55—7.20 (m)**

* The contents of compounds (%) are given in parentheses.
** This region contains signals that cannot not be resolved.

(for **10**); 8.70—8.78 (H(5)) and 4.35—4.45 (2 H(3)) (for **18**); 4.20—4.27 (2 H(3)) and 3.40—3.47 (2 H(5)) (for **19**). The ratio of the products was found based on the intensity of the signals for the methylene protons (see Table 2). The **18b** : **19b** and **18c** : **19c** ratios of the products obtained in the reduction of 4-oxides **10b** and **10c** were found to be 60 : 40 and 30 : 70, respectively. Note that the terahydrogenated derivative **18b** was isolated as an analytical grade sample by recrystallization of a **18b**—**19b** mixture.

The reduction of 4-oxide **10d**, containing a CN group, *i.e.*, a stronger electron acceptor than Cl, in the *para*-position of the 1-benzene ring, under similar conditions (the **10d** : **17** : NaOH ratio was 1 : 4 : 7.5) resulted unexpectedly in predominant cleavage of the seven-membered ring, 3-(*N*′-4-cyanophenyl)amino-2-formylindole **9a** being formed as the major product. This was due to the presence of a large amount of alkali in the reaction mixture. It was shown independently that heating of 4-oxide **10d** in an aqueous solution of alkali yields pure 2-formylindole **9a**. Therefore, we studied the reduction of 4-oxide **10d** in the presence of a smaller amount of alkali (with a **10d** : **17** : NaOH ratio of 1 : 4 : 4). In this case, cleavage of the diazepine ring did not take place, but the reduction was markedly hampered and the isolated mixture consisted of the starting 4-oxide **10d** and tetrahydro-(**18d**) and hexahydrodiazepinoindoles (**19d**) in 76 : 8 : 16 ratio, *i.e.*, the amount of hexahydro derivative **19d** was twice as large as that of tetrahydro derivative **18d**.

It has been noted earlier that reagent **17** easily reduces nitro compounds.[11] Nevertheless, it could be suggested that reduction of 4-oxide **10e** (R = NO_2) might proceed as initial deoxygenation followed by reduction of the C=N bond giving tetrahydro- and hexahydrodiazepinoindoles **18e** and **19e**, respectively. Then reduction of the NO_2 group in compounds **18e** and **19e** should take place to give amino derivatives **18g** and **19g**. Therefore, in this case, we used a seven-fold excess of acid **17**. However, it was found that during the reduction of nitro derivative 4-oxide **10e**, the $NO_2 \rightarrow NH_2$ process was the first to take place, *i.e.*, the reaction gave initially 4-oxide **10g** containing an electron-releasing substituent (NH_2 group) in the *para*-position of the 1-phenyl substituent, and this compound underwent further reduction. As a result, the reaction gave a mixture that consisted, according to ^{1}H NMR data, of 4-oxide **10g** and tetrahydro- (**18g**) and hexahydrodiazepinoindoles (**19g**) in 3 : 85 : 12 ratio, respectively. Thus, the reduction of 4-oxides with formamidinosulfinic

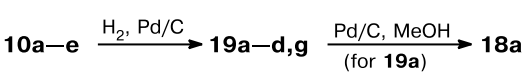
acid, depending on the electronic properties of the 1-(4-R-phenyl) substituent, can be described qualitatively in the following way: electron-withdrawing groups (Cl, CN) favor the reduction of the C=N bond in the diazepine ring, while electron-releasing groups (OEt, NH_2), conversely, impede this process. The content of tetrahydrodiazepinoindoles with respect to hexahydrodiazepinoindoles in the isolated mixtures increases with enhancement of the donor properties of the substituent (NH_2 > OEt) (**18g** > **18b**). This pronounced effect of the substituent rather remote from the reaction center can be explained in terms of the known positive bridge effect,[12,13] typical of compounds in which two aromatic rings (here, the benzene and the indole rings) are linked by an O, S, or N (our case) bridge capable of efficient p—π-conjugation.[12,13] The essential influence of the electron density on the —HC=N→O reaction center on the course of reduction is indicated by the fact that the reaction between reagent **17** and 6-methyldiazepinoindole **10f** 4-oxide proceeds unambiguously, giving rise to hexahydro derivative **19f**, *i.e.*, no tetrahydro derivative **18f** is produced. This was to be expected, as the reduction with formamidinosulfinic acid **17** was carried out in a highly alkaline medium in which 6-unsubstituted diazepinoindoles are largely ionized, which hampers the reduction compared to that of 6-methyl derivative **10f**.

The structures of the synthesized compounds and the mixtures under study were proved by spectroscopic methods, first of all, by ^{1}H NMR spectroscopy. The results are given in Tables 1 and 2 and also in Experimental.

Since the use of reagent **17** did not always allowed us to perform targeted reduction of the synthesized diazepinoindole 4-oxides, we also studied other approaches to the synthesis of hydrogenated representatives of this tricyclic system. For this purpose, we studied the catalytic hydrogenation of compounds **10b—e** in ethanol over Pd/C in the presence of hydrochloric acid and showed that, under these conditions, the reaction proceeded to completion to give hexahydro derivatives **19b—d,g**. Hydrogenation of 4-oxide **10a** to **19a** was performed in DMF.

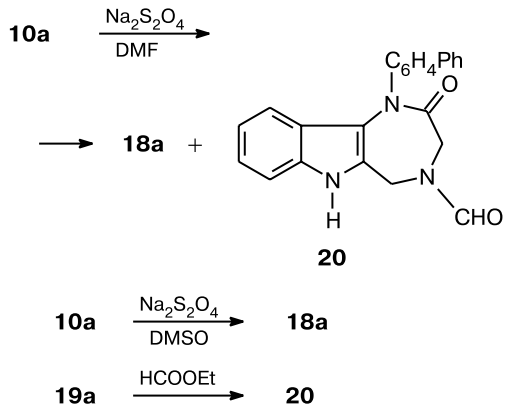
For compound **19a** as an example, the N(4)—C(5) dehydrogenation was accomplished by long-term heating of the compound in methanol in the presence of Pd/C; this gave tetrahydro derivative **18a** as the only product (Scheme 4).

Scheme 4



Previously, we showed[8] that the reduction of 4-oxide **10a** with sodium bisulfite in aqueous DMF affords tetrahydrodiazepinoindole **18a**, which was isolated in 46% yield. More detailed investigation of this reaction showed that the reduction gives one more compound, which was identified as 4-formyl-2-oxo-1-phenyl-1,2,3,4,5,6-hexahydro[1,4]diazepino[6,5-*b*]indole (**20**) on the basis of analysis of the ^{1}H NMR spectrum of the crude product, a mixture of **18a** and **20** (Scheme 5). The doubling of most signals in the spectrum, CHO at δ 8.31 and 8.34, NH at δ 11.33 and 11.44, 2 H(3) at δ 4.83 and 5.00, and 2 H(5) at δ 4.20 and 4.23, is due to the amide isomerism possible for this structure. It should be noted that this formylation of hexahydrodiazepinoindole **19a** (the final product of reduction of 4-oxide **10a** under the reaction conditions) appeared rather unusual. To prove unambiguously the structure of **20**, this compound was prepared by an alternative synthetic protocol, namely, by the reaction between compound **19a** and ethyl formate, in a yield of 74%. The ^{1}H NMR spectrum of 4-formyldiazepinoindole **20** is identical to the spectrum of this compound recorded for its mixture with **18a**. The reduction of 4-oxide **10a** with sodium bisulfite was also carried out in DMSO; this gave tetrahydro derivative **18a**.

Scheme 5



Thus, as a result of this study, we developed a general method for the synthesis of 1-aryl[1,4]diazepino[6,5-*b*]indole 4-oxide derivatives that were previously inaccessible. The outcome of reduction of these compounds with formamidinosulfinic acid was found to depend on the nature of the substituent in the 1-aryl fragment.

Experimental

Infrared spectra of compounds were recorded on a Perkin—Elmer 457 instrument in mineral oil and in KBr pellets (for compounds **19b,d**). Mass spectra were recorded on a JSQ-900 mass spectrometer with direct sample injection into the ion source. ^{1}H NMR spectra were measured in DMSO-d_6 on a Bruker AC-200 spectrometer. The reactions were monitored and the purity of the compounds was checked using Silufol

UV-254 plates and elution by chloroform (for compounds **3d—6d**), a 10 : 1 chloroform—methanol mixture (for compounds **3d,e, 4a—e, 5a,e, 6e, 7a—e, 9a,b, 16b,s,** and **20**), and a 6 : 2.5 : 1.4 : 0.1 ethyl acetate—hexane—ethanol—ammonia mixture (for compounds **10, 18,** and **19**). The ^{1}H NMR spectra of compounds **10b,d—f, 18b, 19b—d,f,g,** and **20** are given in Table 1. The physicochemical characteristics and the yields of substances are listed in Table 3. Compounds **3c,e, 4a,c,e, 5a,c, 6e,** and **9b**[9] and **10a,c, 18a,** and **19a**[8] were recorded previously. Commercial (Lancaster) benzyltriethylammonium chloride (TEBAC) and formamidinosulfinic acid **17** were used.

4-Nitrobenzonitrile. Hydroxylamine hydrochloride (10.4 g, 150 mmol) and Ac_2O (40 mL, 40 mmol) were added to a solution of 4-nitrobenzaldehyde (15 g, 100 mmol) in 150 mL of Py, the mixture was stirred for 2 h with heating on a boiling water bath, cooled, and poured into a five-fold volume of water. The resulting mixture was acidified with concentrated HCl. The precipitate was filtered off, washed with water, and dried to give 10.5 g (71%) of 4-nitrobenzonitrile, m.p. 148—150 °C (*cf.* Ref. 14, m.p. 149 °C). IR, ν/cm^{-1}: 2231 (CN).

4-Aminobenzonitrile (2d). Cast iron chips (18.48 g) and 16 mL of water were added with vigorous stirring to 21 mL of a saturated solution of NH_4Cl in water, the mixture was heated to

Table 3. Physicochemical characteristics of the synthesized compounds **3d, 4b,d, 5b,d,e, 7b,d,e, 9a, 10b,d—f, 15, 16b,c, 18b, 19b—d,f,g,** and **20**

Compound	Yield (%)	M.p./°C (solvent)	M	Found / Calculated (%)				Molecular formula	Mass spectrum, m/z (I_{rel} (%))	IR, ν_{max}/cm^{-1}		
				C	H	N	Cl			NH (NH_2)	CO	CN
3d	63	218—220 (EtOH)	275	73.65 74.16	4.71 4.76	15.23 15.26	—	$C_{17}H_{13}N_3O$	—	3317	1709	2214
4b	59	142—144 (Pr^iOH)	370	64.33 64.78	5.14 5.16	7.40 7.56	9.51 9.56	$C_{20}H_{19}N_2O_3Cl$	—	—	1707, 1669	—
4d	73	180—182 (MeCN)	351	64.56 64.87	4.02 4.01	11.93 11.95	10.04 10.07	$C_{19}H_{14}N_3O_2Cl$	—	—	1702	2211
5b	90	164—165 (Pr^iOH)	328	65.24 65.75	5.29 5.21	8.43 8.52	10.71 10.78	$C_{18}H_{17}N_2O_2Cl$	—	3310	1669	—
5d	56	195.5—196.5 (Pr^iOH)	309	65.86 65.92	3.89 3.91	13.45 13.57	11.82 11.45	$C_{17}H_{12}N_3OCl$	—	3325	1681	2226
5e	45	219—220 (Pr^iOH)	329	57.98 58.27	3,73 3.67	12.75 12.74	10.46 10.75	$C_{16}H_{12}N_3O_3Cl$	329 $[M]^+$ (67), 252 $[M - COCH_2Cl]^+$ (80), 222 $[M - COCH_2Cl - NO]^+$ (67), 205 $[M - COCH_2Cl - HNO_2]^+$ (100)	3334, 3282	1680	—
7b	79	183—184 (toluene)	356	64.30 63.96	4.87 4.80	7.51 7.85	9.97 9.94	$C_{19}H_{17}N_2O_3Cl$	—	3229 1665	1681,	—
7d	62	190—192 (Pr^iOH)	337	63.91 64.01	3.58 3.58	12.35 12.44	10.50 10.50	$C_{18}H_{12}N_3O_2Cl$	337 $[M]^+$ (33), 285 $[M - Cl - OH]^+$ (78), 261 $[M - ClCHCO]^+$ (100), 232 $[M - ClCHCO - HCO]^+$ (25), 205 $[M - HCO - C_6H_5CN]^+$ (5)	3330	1679, 1661	2227
7e	98	212—214 (Pr^iOH)	357	56.71 57.07	3.46 3.38	11.67 11.75	9.82 9.91	$C_{17}H_{12}N_3O_4Cl$	357 $[M]^+$ (40), 281 $[M - ClCHCO]^+$ (100), 234 $[M - C_6H_5NO_2]^+$ (56), 205 $[M - HCO - C_6H_5NO_2]^+$ (67)	3286	1689, 1672	—
9a	55 (*A*), 24 (*B*), 23 (*C*)	243—244 (MeOH)	261	—	—	15.82 16.08	—	$C_{16}H_{11}N_3O$	261 $[M]^+$ (100), 232 $[M - HCO]^+$ (29), 205 $[M - HCO - HCN]^+$ (12), 159 $[M - C_6H_4CN]^+$ (5)	3312, 3286	1646	2212
10b	65	268 (decomp.) (DMF—Me_2CO, 1 : 1)	335	68.25 68.05	5.30 5.11	12.55 12.53	—	$C_{19}H_{17}N_3O_3$	335 $[M]^+$ (58), 319 $[M - O]^+$ (54), 290 $[M - O - HCO]^+$ (100), 262 $[M - O - HCO - C_2H_4]^+$ (43), 248 $[M - OEt]^+$ (33), 219 $[M - O - HCO - HCN - OEt]^+$ (33), 170 $[M - O - CO - C_6H_4OEt]^+$ (43)	—	1665	—

(*to be continued*)

Table 3 (*continued*)

Compound	Yield (%)	M.p./°C (solvent)	M	Found / Calculated (%)				Molecular formula	Mass spectrum, *m/z* (I_{rel} (%))	IR, ν_{max}/cm^{-1}		
				C	H	N	Cl			NH (NH_2)	CO	CN
10d	60	279—280 (decomp.) (DMF—Me_2CO, 1 : 1)	316	68.48 68.35	3.93 3.82	17.36 17.71	—	$C_{18}H_{12}N_4O_2$	316 $[M]^+$ (2), 300 $[M - O]^+$ (71), 271 $[M - O - HCO]^+$ (100), 244 $[M - O - HCO - HCN]^+$ (20), 170 $[M - O - CO - C_6H_4CN]^+$ (25)	3197	1667	2227
10e	84 (*A*), 60 (*B*), 55 (*C*)	284 (decomp.) (DMF—Me_2CO, 1 : 1)	336	—	—	16.75 16.66	—	$C_{17}H_{12}N_4O_4$	336 $[M]^+$ (6), 320 $[M - O]^+$ (71), 291 $[M - O - HCO]^+$ (100), 261 $[M - O - HCO - NO]^+$ (64), 245 $[M - O - HCO - NO_2]^+$ (77), 218 $[M - O - HCO - NO_2 - HCN]^+$ (30), 170 $[M - O - CO - C_6H_4NO_2]^+$ (52)	3224	1670	—
10f	68	263—264 (AcOEt)	305	70.90 70.81	4.90 4.95	13.78 13.76	—	$C_{18}H_{15}N_3O_2$	305 $[M]^+$ (57), 289 $[M - O]^+$ (92), 261 $[M - O - CO]^+$ (80), 260 $[M - O - HCO]^+$ (100), 233 $[M - O - HCO - HCN]^+$ (54), 184 $[M - O - HCO - C_6H_5]^+$ (56)	—	1678	—
15	9	155—156 (Me_2CO)	261	—	—	—	—	$C_{16}H_{11}N_3O$*	261 $[M]^+$ (100), 233 $[M - CO]^+$ (90), 205 $[M - HCO - HCN]^+$ (64)	3278 3296	1660 1687	2227 —
16b	47	147—149 (Pr^iOH)	459	59.78 60.06	5.45 5.70	9.33 9.14	7.58 7.71	$C_{23}H_{26}N_3O_5Cl$	399 $[M - Pr^iOH]^+$ (15), 357 $[M - Pr^i_2 - O]^+$ (46), 281 $[M - Pr^i_2O - ClCHCO]^+$ (100)			
16c	82 (*A*), 42 (*B*)	187—189 (EtOH)	431	—	—	9.55 9.73	8.00 8.21	$C_{21}H_{22}N_3O_5Cl$	431 $[M]^+$ (38), 385 $[M - EtOH]^+$ (92), 366 $[M - Cl - NO]^+$ (66), 340 $[M - EtOH - EtO - NO - H]^+$ (59), 281 $[M - Et_2O - ClCHCO]^+$ (100)	3265	1685	—
18b	18	255—257 (MeOH)	319	—	—	13.20 13.16	—	$C_{19}H_{17}N_3O_2$	319 $[M]^+$ (83), 290 $[M - HCO]^+$ (100), 262 $[M - HCO - C_2H_4]^+$ (78), 235 $[M - HCO - C_2H_4 - HCN]^+$ (54), 170 $[M - CO - C_6H_4OEt]^+$ (68)	3476, 3413	1663	—
19b	47	239—240 (EtOH)	321	71.31 71.01	5.90 5.96	13.06 13.08	—	$C_{19}H_{19}N_3O_2$	321 $[M]^+$ (4), 319 $[M - H_2]^+$ (22), 290 $[M - H_2 - HCO]^+$ (22), 265 $[M - HCO - HCN]^+$ (100), 235 $[M - H_2 - HCO - C_2H_4 - HCN]^+$ (70), 170 $[M - H_2 - CO - C_6H_4OEt]^+$ (48)	3403, 3284	1647	—
19c	20	240—242 (EtOH)*	311	—	—	—	—	$C_{17}H_{14}N_3OCl$	311 $[M]^+$ (85), 309 $[M - H_2]^+$ (79), 282 $[M - HCO]^+$ (51), 280 $[M - H_2 - HCO]^+$ (97), 255 $[M - HCO - HCN]^+$ (62), 219 $[M - H_2 - CO - Cl - HCN]^+$ (100), 170 $[M - H_2 - CO - C_6H_4Cl]^+$ (59)	3312, 3140	1675	—

(*to be continued*)

Table 3 (*continued*)

Compound	Yield (%)	M.p./°C (solvent)	M	Found / Calculated (%)				Molecular formula	Mass spectrum, *m/z* (I_{rel} (%))	IR, ν_{max}/cm^{-1}		
				C	H	N	Cl			NH (NH_2)	CO	CN
19d	10	234—236 **	302	—	—	17.33 17.49	—	$C_{18}H_{14}N_4O$	302 $[M]^+$ (51), 300 $[M - H_2]^+$ (78), 271 $[M - H_2 - HCO]^+$ (92), 244 $[M - H_2 - HCO - HCN]^+$ (100), 170 $[M - H_2 - CO - C_6H_4CN]^+$ (81)	3406, 3291	1679	2228
19f	70	238—240 (dioxane)	291	74.53 74.20	5.87 5.88	14.30 14.42	—	$C_{18}H_{17}N_3O$	291 $[M]^+$ (76), 289 $[M - H_2]^+$ (77), 260 $[M - H_2 - HCO]^+$ (79), 234 $[M - H_2 - CO - HCN]^+$ (100), 218 $[M - H_2 - HCO - HCN - Me]^+$ (71), 186 $[M - CO - C_6H_5]^+$ (34), 184 $[M - H_2 - CO - C_6H_5]^+$ (27)	3320	1661	—
19g	54***	290—291 (EtOH)	292	69.31 69.84	5.60 5.52	18.63 19.17	—	$C_{17}H_{16}N_4O$	292 $[M]^+$ (28), 290 $[M - H_2]^+$ (61), 261 $[M - H_2 - HCO]^+$ (100), 234 $[M - H_2 - HCO - HCN]^+$ (89), 170 $[M - H_2 - CO - C_6H_4NH_2]^+$ (8)	3473, 3390, 3318, 3160	1662	—
20	74	265—267 (MeOH)	305	70.82 70.81	4.98 4.95	14.23 13.76	—	$C_{18}H_{15}N_3O_2$	305 $[M]^+$ (51), 275 $[M - HCOH]^+$ (25), 261 $[M - HCOH - CH_2]^+$ (34), 219 $[M - CHO - CO\,CH_2NH]^+$ (100), 205 $[M - CHO - CO - CH_2NCH_2]^+$ (21)	3233	1646, 1679	—

* We were unable to prepare an analytical grade sample.
** For monohydrate.
*** Relative to crude product.

70 °C on a water bath, 4-nitrobenzonitrile (14.8 g, 100 mmol) was added in small portions, and the mixture was stirred on a boiling water bath for 1.5 h. The sludge was filtered off, 300 mL of water was added to it, and the mixture was brought to boiling. The hot mixture was filtered to remove the insoluble residue. The precipitate formed in the mother liquor was filtered off, washed with water, and dried to give 7.08 g (60%) of compound **2**, m.p. 84—86 °C (*cf.* Ref. 15: m.p. 85.5 °C).

1-Acetyl-3-[*N*-(4-cyanophenyl)amino]indole (3d). 4-Cyanoaniline **2d** (2.1 g, 18 mmol) was added to a solution of 1-acetylindoxyl (2.6 g, 15 mmol) in 10 mL of AcOH. The mixture was refluxed for 2 h and left for 48 h at 20 °C. The precipitate was filtered off and washed with AcOH and ether. This gave 3.1 g of a substance, which was then refluxed for 5—10 min with 20 mL of MeOH. The precipitate was filtered off from the hot solution and washed with hot MeOH and ether to give 2.6 g of compound **3d**.

1-Acetyl-3-[*N*-chloroacetyl-*N*-(4-ethoxyphenyl)amino]indole (4b) was prepared similarly to **4a** by a known method.[9] A mixture of 1-acetylindoxyl (1.75 g, 10 mmol), 1.5 mL of AcOH, and *p*-phenetidine **2b** (1.37 g, 10 mmol) was refluxed for 15 min and AcOH was evaporated to dryness. Chloroacetyl chloride (3 mL, 37.5 mmol) was added, the mixture was refluxed for 15 min, 4 mL of Pr^iOH was added dropwise, and the mixture was refluxed for additional 15 min and evaporated to dryness. The residue was triturated with MeOH with ice cooling. The precipitate was filtered off and washed with ether to give 2.2 g of compound **4b**.

1-Acetyl-3-[*N*-chloroacetyl-*N*-(4-cyanophenyl)amino]indole (4d) was prepared similarly to **4e** by a known method.[9] Chloroacetyl chloride (4 mL, 50 mmol) was added to compound **3d** (2.5 g, 10 mmol) and the mixture was stirred at reflux for 15 min. Chloroacetyl chloride was evaporated from the mixture to dryness, 5 mL of Pr^iOH was added, and the mixture was refluxed for additional 10 min. The precipitate formed on ice cooling was filtered off, washed with Pr^iOH, and dried to give 2.34 g of compound **4d**.

3-[*N*-Chloroacetyl-*N*-(4-ethoxyphenyl)amino]indole (5b) was prepared by a procedure described previously.[9] A mixture of diacyl derivative **4b** (2 g, 5.4 mmol), MeOH (20 mL), and Et_3N (1.5 mL, 10.8 mmol) was refluxed for 0.5 h and evaporated to dryness and the residue was triturated with petroleum ether (b.p. 70—100 °C). The precipitate was filtered off and washed with ether to give 1.6 g of compound **5b**.

3-[*N*-Chloroacetyl-*N*-(4-cyanophenyl)amino]indole (5d). Triethylamine (0.04 mL, 0.25 mmol) was added with stirring at 4—5 °C to a suspension of *N,N′*-diacyl derivative **4d** (0.35 g, 1 mmol) in 4 mL of MeOH, and the mixture was stirred at this temperature for 2 h and kept in a refrigerator (7 °C) for 16 h.

The precipitate was filtered off and washed with MeOH to give 0.19 g of compound **5d**.

3-[*N*-Chloroacetyl-*N*-(4-nitrophenyl)amino]indole (5e). Anhydrous Na_2CO_3 (0.23 g, 2.2 mmol) and chloroacetyl chloride (0.18 mL, 2.2 mmol) were added to a suspension of compound **6e** (0.5 g, 1.97 mmol) in 50 mL of toluene. The mixture was stirred at reflux for 6 h, left overnight at 20 °C (for 16 h), Na_2CO_3 and chloroacetyl chloride (each 2.2 mmol) were added, and refluxed for additional 7 h. The inorganic salts were filtered off, and the solution was clarified by adding activated carbon, concentrated to half its volume, and cooled. The precipitate was filtered off, washed with toluene and water, and dried to give 0.29 g of compound **5e**. ^{1}H NMR, δ: 4.24 (s, 2 H, $COCH_2Cl$); 7.01, 7.14 (both t, each 1 H, H(5), H(6), $J_{5,4} = J_{5,6} = J_{6,7} = 7.8$ Hz); 7.34, 7.42 (both d, each 1 H, H(4), H(7), $J_{4,5} = J_{7,6} = 7.8$ Hz); 7.60 and 8.15 (AA′XX′, 4 H, $C_6H_4NO_2$); 7.74 (d, 1 H, H(2), J = 2.8 Hz); 11.50 (br.s, 1 H, N(1)H).

When the charge was increased 10-fold, the reaction gave a mixture of mono- and bis(chloroacyl) derivatives **5e** and **12** whose ^{1}H NMR spectrum exhibited signals corresponding to pure compound **5e** (see above) and 3-[*N*-(4-nitrophenyl)-*N*-chloroacetylamino]-2-chloroacetylindole (**12**), δ: 4.25 (s, 2 H, *N*′-$COCH_2Cl$); 4.99 (s, 2 H, 2-$COCH_2Cl$); 7.18, 7.43 (both t, each 1 H, H(5), H(6), $J_{4,5} = J_{5,6} = J_{6,7} = 7.6$ Hz); 7.56, 8.17 (m, 6 H, H(4), H(7), $C_6H_4NO_2$); 12.50 (br.s, 1 H, N(1)H).

3-[*N*-(4-Cyanophenyl)amino]indole (6d). ***A.*** Triethylamine (2.7 mL, 19 mmol) was added to a suspension of 1-acetyl-3-[*N*-(4-cyanophenyl)amino]indole (**3d**) (4.8 g, 18 mmol) in 70 mL of MeOH and the mixture was refluxed for 1.5 h. Activated carbon (0.5 g) was added to the resulting solution and the mixture was refluxed for additional 10 min. The carbon was filtered off and the solution was cooled. The precipitate was filtered off and washed with MeOH to give 2.3 g of compound **6d**. The mother liquor was concentrated to a minimum volume and cooled. The precipitate was filtered off to give additionally 1.25 g of compound **6d**. Overall yield 3.55 g. ^{1}H NMR, δ: 6.78, 7.32—7.47 (both m, 7 H, H(2), H(4), H(7), C_6H_4CN); 6.99, 7.08 (both t, each 1 H, H(5), H(6), $J_{5,4} = J_{5,6} = J_{6,7} = 7.6$ Hz); 8.27 (br.s, 1 H, N′(3)H); 10.92 (br.s, 1 H, N(1)H).

B. Triethylamine (0.28 mL, 2 mmol) was added at 25—30 °C to a solution of *N,N*′-diacyl derivative **4d**, the resulting solution was kept for 3 days at 20—25 °C and concentrated to dryness, and the residue was triturated with MeOH. The precipitate was filtered off and washed with MeOH to give 0.08 g of compound **6d**. The melting point of a mixed sample consisting of compounds prepared by procedures ***A*** and ***B*** was undepressed. The IR spectra of these compounds were identical.

3-[*N*-Chloroacetyl-*N*-(4-R-phenyl)amino]-2-formylindoles (7a,c) were prepared by a known method[9] but with a ratio of compound **5a** or **5c** to the Vilsmeier complex equal to 1 : 1. This gave 80% of compound **7a**, m.p. 176—178 °C (*cf.* Ref. 9: m.p. 177—178 °C) and 65% of compound **7c**, m.p. 184—185 °C (*cf.* Ref. 9: m.p. 185—186 °C).

3-[*N*-Chloroacetyl-*N*-(4-ethoxyphenyl)amino]-2-formylindole (7b). A solution of *N*′-chloroacetyl derivative **5b** (1.4 g, 4.3 mmol) in 3.5 mL of DMF was added dropwise at 15—20 °C to the Vilsmeier complex prepared by a standard procedure from DMF (1.0 mL, 12 mmol) and $POCl_3$ (0.44 mL, 4.8 mmol). The mixture was kept for 16 h at 20 °C and ~40 mL of ice water was added. The precipitate was filtered off, washed with water, and transferred into a beaker. Isopropyl alcohol was added, and the mixture was heated to boiling. The suspension was cooled and the precipitate was filtered off and washed with Pr^iOH and ether to give 1.17 g of compound **7b**.

3-[*N*-Chloroacetyl-*N*-(4-cyanophenyl)amino]-2-formylindole (7d). ***A.*** Anhydrous Na_2CO_3 1.13 g (10.5 mmol) and chloroacetyl chloride (0.84 mL, 10.5 mmol) were added to a suspension of 2-formylindole **9a** (2.18 g, 8.4 mmol) in 200 mL of benzene, the mixture was stirred at reflux for 3 h. Activated carbon (0.5 g) was added, and the mixture was refluxed for 5—10 min. The carbon was filtered off. The solution was cooled and the precipitate was filtered off and washed with benzene. Then the precipitate was transferred into a beaker and covered with ~50 mL of water, and the mixture was stirred for 30 min. The precipitate was filtered off and washed with water and Pr^iOH on a filter to give 1.77 g of compound **7d**. ^{1}H NMR, δ: 4.27 (s, 2 H, $COCH_2Cl$); 7.20, 7.41 (both t, each 1 H, H(5), H(6), $J_{5,4} = J_{5,6} = J_{6,7} = 7.6$ Hz); 7.54—7.83 (m, 6 H, H(4), H(7), C_6H_4CN); 10.00 (s, 1 H, 2-CHO); 12.30 (br.s, 1 H, N(1)H).

B. A solution of chloroacyl derivative **5d** (0.48 g, 1.6 mmol) was added with stirring at 15—20 °C to the Vilsmeier complex prepared by the usual procedure from DMF (0.4 mL, 4.8 mmol) and $POCl_3$ (0.45 mL, 4.8 mmol). The solution was kept for 4 h at 25—30 °C, for 2 h at 45—50 °C, and for 16 h at 20—25 °C. The reaction solution was poured on ice water (~50 mL). The precipitate was filtered off, washed with water, and dried to give 0.46 g of compound **7d** containing 3-[*N*-chloroacetyl-*N*-(4-cyanophenyl)amino]-1,2-diformyl-indole **13b** and 3-[*N*-chloroacetyl-*N*-(4-cyanophenyl)amino]-1-formylindole **14** as impurities, the product ratio being 70 : 6 : 24 (according to ^{1}H NMR data). ^{1}H NMR (of the mixture), δ: 4.29 (s, 2 H, $COCH_2Cl$), 9.99 (s, 1 H, 2-CHO), 12.42 (br.s, 1 H, N(1)H) (**7d**); 4.43 (s, 2 H, $COCH_2Cl$), 8.43 (d, 1 H, H(7), $J_{7,6} = 8.2$ Hz), 9.98 (s, 1 H, 1-CHO), 10.29 (s, 1 H, 2-CHO) (**13b**); 4.39 (s, 2 H, $COCH_2Cl$), 8.24 (d, 1 H, H(7), $J_{7,6} = 7.6$ Hz), 8.29 (s, 1 H, H(2)), 9.40 (s, 1 H, 1-CHO) (**14**). All other signals of compounds **7d**, **13b**, and **14** formed a complex multiplet at about δ 7.00—8.00.

3-[*N*-Chloroacetyl-*N*-(4-nitrophenyl)amino]-2-formylindole (7e). Anhydrous Na_2CO_3 (2.07 g, 19.5 mmol) and chloroacetyl chloride (1.57 mL, 19.5 mmol) were added to a suspension of 2-formylindole **9b** (5 g, 17.8 mmol) in 500 mL of toluene. The mixture was refluxed for 3 h, portions (2.07 g) of sodium carbonate and chloroacetyl chloride (1.57 mL) being added every hour. Activated carbon (5 g) was added, the mixture was refluxed for 10 min, the carbon was filtered off, and the solution was cooled. The precipitate was filtered off, washed with toluene and water, and dried at 110 °C at a constant weight to give 6.2 g of compound **7e**. ^{1}H NMR, δ: 4.33 (s, 2 H, $COCH_2Cl$); 7.21, 7.42 (both t, each 1 H, H(5), H(6), $J_{5,4} = J_{5,6} = J_{6,7} = 8.2$ Hz); 7.55 (d, 1 H, H(4), $J_{4,5} = 8.2$ Hz); 7.67, 8.22 (both m, 5 H, H(7), $C_6H_4NO_2$); 10.00 (s, 1 H, 2-CHO); 12.50 (br.s, 1 H, N(1)H).

3-[*N*-Chloroacetyl-*N*-(4-nitrophenyl)amino]-2-formylindole diisopropyl acetal (16b). Activated carbon (0.1 g) was added to a solution of 2-formylindole **7e** (0.6 g, 1.7 mmol) in 40 mL of Pr^iOH, the mixture was refluxed for 10 min, filtered, cooled, and kept for 24 h in a refrigerator (7 °C). The precipitate was

filtered and washed with Pr^iOH to give 0.5 g of a mixture of **7e** and **16b** (according to TLC), which was separated by column chromatography (SiO_2, chloroform as the eluent) to give 0.3 g of acetal **16b**. ^1H NMR, δ: 1.03 (m, 12 H, $(OCH(C\underline{H}_3)_2)_2$); 3.85 (m, 2 H, $(OC\underline{H}(CH_3)_2)_2$); 4.44 (AB, 2 H, $COCH_2Cl$, J_{gem} = 14.9 Hz); 5.75 (s, 1 H, $C\underline{H}(OCH(CH_3)_2)_2$); 7.16 (m, 2 H, H(5), H(6)); 7.45, 7.50 (both d, each 1 H, H(4), H(7), $J_{4,5}$ = $J_{7,6}$ = 8.2 Hz); 7.63, 8.20 (AA´XX´, 4 H, $C_6H_4NO_2$); 11.65 (br.s, 1 H, N(1)H).

3-[*N*-Chloroacetyl-*N*-(4-nitrophenyl)amino]-2-formylindole diethyl acetal (16c). ***A.*** A mixture (0.54 g, 1.5 mmol) of 2-formylindole **7e**, 10 mL of anhydrous EtOH, and 1 drop of concentrated H_2SO_4 was refluxed for 30 min. The solution was cooled and the precipitate was filtered off, washed with EtOH and ether to give 0.57 g of compound **16c**. ^1H NMR, δ: 1.08 (br.t, 6 H, $CH(OCH_2C\underline{H}_3)_2$); 3.54 (br.q, 4 H, $CH(OC\underline{H}_2CH_3)_2$); 4.23 (AB, 2 H, $COC\underline{H}_2Cl$, J_{gem} = 14.9 Hz); 5.78 (s, 1 H, $C\underline{H}(OCH_2CH_3)_2$); 7.16 (m, 2 H, H(5), H(6)); 7.46 (m, 2 H, H(4), H(7)); 7.62 and 8.19 (AA´XX´, 4 H, $C_6H_4NO_2$); 11.63 (br.s, 1 H, N(1)H).

B. A mixture of diisopropyl acetal **16b** (0.15 g, 0.33 mmol), 10 mL of anhydrous EtOH, and *p*-toluenesulfonic acid (0.07 g, 0.42 mmol) was refluxed for 10 h. The solution was cooled and the precipitate was filtered off and washed with EtOH and ether to give 0.06 g of compound **16c**. The melting point of a mixed sample of compounds prepared by procedures ***A*** and ***B*** was undepressed. The IR spectra of these compounds were identical.

3-[*N*-(4-Cyanophenyl)amino]-2-dimethyliminomethylindole chloride (immonium salt, 8a). A solution of *N,N´*-deacylated indole **6d** (3.55 g, 15 mmol) in 10 mL DMF was added dropwise with stirring at 10—20 °C to the Vilsmeier complex prepared by the usual procedure from DMF (2 mL, 17 mmol) and $POCl_3$ (1.6 mL, 17 mmol), and the mixture was kept for 3.5 h at 20 °C. The resulting precipitate was filtered off, washed with DMF and $CHCl_3$, and dried to give 3.3 g (67%) of immonium salt **8a**, $C_{18}H_{17}N_4Cl$, m.p. > 230 °C (dec.).

3-[*N*-Chloroacetyl-*N*-(4-nitrophenyl)amino]-2-dimethyliminomethyl-2-formylindole chloride (immonium salt, 8b) was prepared similarly to immonium salt **8a** but taking a three-fold excess of the Vilsmeier complex (48 mL of DMF and 21.5 mL of $POCl_3$) relative to *N,N´*-deacylated indole **6e** (20.05 g, 79 mmol) [9] in 21 mL DMF. The reaction gave 18.3 g (67%) of immonium salt **8b**, $C_{17}H_{17}N_4O_2Cl$, m.p. > 200 °C (dec.).

3-[*N*-(4-Cyanophenyl)amino]-2-formylindole (9a). ***A.*** A suspension of immonium salt **8a** (3.3 g) in 150 mL of water was stirred at reflux for 0.5 h. The yellow precipitate was filtered hot and washed with water and Pr^iOH to give 2.18 g of compound **9a**. ^1H NMR, δ: 6.88, 7.31—7.56 (both m, 7 H, H(4), H(6), H(7), C_6H_4CN); 7.04 (t, 1 H, H(5), $J_{5,4}$ = $J_{5,6}$ = 7.6 Hz); 9.09 (br.s, N´(3)H); 9.92 (s, 1 H, 2-CHO); 11.68 (br.s, 1 H, N(1)H).

B. A mixture of 4-oxide **10d** (0.05 g, 0.16 mmol) and a solution of NaOH (0.048 g, 1.2 mmol) in 4 mL of water was heated on a boiling water bath for 1 h. The suspension was cooled, the precipitate was filtered off, washed with water, and dried to give 0.01 g of compound **9a**. The melting point of a mixed sample of compounds prepared by procedures ***A*** and ***B*** was undepressed. The IR spectra of these compounds were identical.

C. Formamidinosulfinic acid (**17**) (0.43 g, 4 mmol) in 11 mL of an aqueous solution of alkali prepared from NaOH (0.3 g, 7.5 mmol) and 25 mL of water was added to a suspension of 4-oxide **10d** (1 mmol) in 14 mL of the same alkali solution. The mixture was heated on a boiling water bath for 1 h and cooled. The precipitate was filtered off, washed with water, and dried to give 0.23 g of crude product, which was purified by column chromatography (SiO_2, AcOEt as the eluent) to gave 0.06 g of pure aldehyde **9a**. The melting point of a mixed sample of this compound and **9a** prepared by procedure ***A*** was undepressed.

3-[*N*-(4-Cyanophenyl)-*N*-formylamino]indole (15). The mother liquor (DMF) left after separation of the immonium salt **8a** was kept for 2 days, poured on ice water (~200 mL), and alkalized with 6 mL of 40% KOH (pH 10). The precipitate was filtered off, washed with water, and dried to give 1.48 g of *N´*-formylindole **15** containing (TLC data) traces of the starting compound **6d** and 2-formylindole **9a**. For identification, the product was purified by column chromatography (SiO_2, $CHCl_3$ as the eluent). The major fraction was concentrated, the residue was triturated with a minimum amount of acetone to give 0.36 g of compound **15**. ^1H NMR, δ: 7.10 (m, 3 H, H(7), H(5), H(6)); 7.49 (d, 1 H, H(4), $J_{6,7}$ = 8.2 Hz); 7.56, 7.79 (AA´XX´, 4 H, C_6H_4CN); 7.66 (br.s, 1 H, H(2)); 8.78 (br.s, 1 H, N´(3)CHO); 11.38 (br.s, 1 H, N(1)H).

Synthesis of 1-aryl-2-oxo-1,2,3,6-tetrahydro[1,4]diazepino[6,5-*b*]indole 4-oxides 10b,d,e (general procedure). ***A.*** The appropriate 2-formylindole **7b,d**,**e** (1 mmol) was dissolved in 30 mL of EtOH with heating, cooled to 25—30 °C, and hydroxylamine hydrochloride (0.08 g, 1.2 mmol) and fused AcONa (0.2 g, 2.4 mmol) were added. The mixture was stirred for 3 h at 20 °C and refluxed for 3 h. After 16 h, the precipitate was filtered off, washed with EtOH and water, and dried to give 0.21 g of compound **10b**, 0.19 g of **10d**, and 0.28 g of **10e**.

B. A mixture of 2-formylindole **7e** (1.07 g, 3 mmol), hydroxylamine hydrochloride (0.25 g, 3.6 mmol), fused AcONa (0.49 g, 6 mmol), and 15 mL of glacial AcOH was stirred at reflux for 1 h. The mixture was cooled, the precipitate was filtered off, washed with AcOH, water, and MeOH, and dried to give 0.38 g of compound **10e**. The mother liquor was diluted with a five-fold amount of water, the precipitate was filtered off, washed with water and MeOH, and dried to give additionally 0.31 g of compound **10e**. The precipitates were combined, washed with Me_2CO on the filter, and recrystallized from 60 mL of a 1 : 1 DMF—Me_2CO mixture. The yield of compound **10e** was 0.6 g.

C. Hydroxylamine hydrochloride (0.68 g, 9.7 mmol) and fused AcONa (1.33 g, 16.2 mmol) was added with stirring at 20 °C to a solution of compound **7e** (2.9 g, 8.1 mmol) in 15 mL of DMF. The mixture was heated on a boiling water bath for 1.5 h and cooled. The precipitate was filtered off, washed with DMF and water, and dried to give 1 g of compound **10e**. The mother liquor (DMF) was concentrated to dryness. The residue was triturated with water and the precipitate was filtered off and washed with water and Pr^iOH to give additionally 0.5 g of compound **10e**. Total yield 1.5 g. The melting points of mixed samples of **10e** prepared by procedures ***A*** and ***B*** or ***A*** and ***C*** were undepressed.

6-Methyl-2-oxo-1-phenyl-1,2,3,6-tetrahydro[1,4]diazepino[6,5-*b*]indole 4-oxide (10f). Compound **10a** (2.5 g,

8.6 mmol), TEBAC (1.95 g, 8.6 mmol), and methyl iodide (1.5 mL, 24 mmol) were added to a mixture of 2 *M* NaOH (21.5 mL) and 167 mL of CH_2Cl_2. The suspension was vigorously stirred for 8 h at 20 °C and left for 16 h. Water (70 mL) was added to the reaction mixture, and the organic layer was separated, washed with water (3×20 mL), dried with $CaCl_2$, and concentrated to dryness. The residue was triturated with 80 mL of water, and the precipitate was filtered off, washed with water and MeOH, and dried to give 1.77 g of compound **10f**.

2-Oxo-1-phenyl-1,2,3,4,5,6-hexahydro[1,4]diazepino[6,5-*b*]indole (19a). To a suspension of 4-oxide **10a** (0.3 g, 1 mmol) in 7 mL of DMF, Pd(10%)/C (0.03 g) was added. Hydrogenation was carried out at 20 °C for 3 h. The mixture was allowed to stand for 16 h. The catalyst was filtered off, the solution was evaporated to dryness, the residue was triturated with 8 mL of water, and the precipitate was filtered off, washed with water, MeOH, and dried to give 0.13 g (46%) of compound **19a**. The melting point of a mixed sample of the product with this compound prepared previously[8] was undepressed.

1-(4-Ethoxyphenyl)-2-oxo-1,2,3,4,5,6-hexahydro[1,4]diazepino[6,5-*b*]indole (19b). To a suspension of 4-oxide **10b** (0.34 g, 1 mmol) in 30 mL of EtOH, Pd(10%)/C (0.03 g) and 0.5 mL of concentrated HCl were added. Hydrogenation was carried out at 20 °C for 24 h. The precipitate was filtered off, ~20 mL of water was added to it, the mixture was heated to boiling, and the catalyst was filtered off. The aqueous mother liquor was cooled and alkalized with 2 *M* NaOH. The precipitate was filtered off, washed with water, and dried to give 0.15 g of compound **19b**.

1-(4-Chlorophenyl)-2-oxo-1,2,3,4,5,6-hexahydro[1,4]diazepino[6,5-*b*]indole (19c). To a suspension of 4-oxide **10c** (0.66 g, 2 mmol) in 60 mL of EtOH, Pd(10%)/C (0.06 g) and 0.6 mL of concentrated HCl were added. Hydrogenation was carried out at 20 °C for 6 days; after 24 h, an additional portion of the catalyst (0.06 g) was added. The precipitate was filtered off and washed with EtOH. Water (~20 mL) was added, the mixture was heated to boiling, and filtered hot to remove the catalyst. The precipitate of the hydrochloride of compound **19c** was filtered off, washed with water, transferred into a beaker, and dissolved in 15 mL of EtOH. Three drops of an ethanolic solution of KOH prepared from 3.7 g of KOH and 10 mL of EtOH were added to the resulting solution. The inorganic salts were filtered off, the mother liquor was evaporated to dryness, and the residue was triturated with 15 mL of water. The precipitate was filtered off, washed with water, and dried to give 0.04 g of compound **19c**. Four drops of 40% aqueous alkali were added to the aqueous mother liquor left after separation of hydrochloride **19c**. The precipitate was filtered off, washed with water, and dried to give additionally 0.08 g of compound **19c**. Total yield 0.12 g.

1-(4-Cyanophenyl)-2-oxo-1,2,3,4,5,6-hexahydro[1,4]diazepino[6,5-*b*]indole (19d) was prepared from 4-oxide **10d** (0.3 g, 0.41 mmol) similarly to compound **19c** but hydrogenation time was 72 h. This gave 0.01 g of compound **19d**.

1-(4-Aminophenyl)-2-oxo-1,2,3,4,5,6-hexahydro[1,4]diazepino[6,5-*b*]indole (19g) was prepared from 4-oxide **10e** (0.34 g, 1 mmol) similarly to compound **19d**. The catalyst was filtered off. The alcohol mother liquor was evaporated. The residue was dissolved in 20 mL of water. The solution was clarified using activated carbon and alkalized by ~0.5 mL of 2 *M* NaOH (pH = 8). The precipitate was filtered off, washed with water, and dried to give 0.13 g of compound **19g**.

Reduction of 4-oxides 10b,c,f with formamidinosulfinic acid. Acid **17** (0.43 g, 4 mmol) in 11 mL of an aqueous solution of alkali prepared from NaOH (0.3 g, 7.5 mmol) and 25 mL of water was added to a suspension of the corresponding 4-oxide **10b,c,f** (1 mmol) in 14 mL of the same alkali solution. The mixture was heated on a boiling water bath for 1 h. The suspension was cooled, and the precipitate was filtered off, washed with water, and dried to give 0.29 g of a mixture of **18b** and **19b** (60 : 40), 0.2 g of a mixture of tetrahydro (**18c**) and hexahydro[1,4]diazepinoindoles (**19c**) (30 : 70), and 0.2 g of compound **19f.**

Reduction of 4-oxide 10d with formamidinosulfinic acid was carried out under conditions similar to those used to reduce 4-oxides **10b,c,f** but the **10d** : **17** : NaOH ratio used was 1 : 4 : 4. This gave 0.09 g of a mixture of 4-oxide **10d** and tetrahydro (**18d**) and hexahydro derivatives (**19d**) (76 : 8 : 16).

Reduction of 4-oxide 10e with formamidinosulfinic acid was carried out under conditions similar to those used to reduce 4-oxides **10b,c,f** but taking 0.75 g (7 mmol) of reagent **17**, 0.59 g (13 mmol) of NaOH, and 44 mL of water per mmol of 4-oxide **10e**. The reaction gave 0.11 g of a mixture of **10g**, **18g**, and **19g** (3 : 85 : 12). The ^{1}H NMR spectra of the mixtures are presented in Table 2.

2-Oxo-1-phenyl-1,2,3,6-tetrahydro[1,4]diazepino[6,5-*b*]indole (18a). ***A.*** Pd(10%)/C (0.03 g) was added to a mixture of hexahydro derivative **19a** (0.3 g, 1 mmol) in 20 mL of MeOH. The mixture was refluxed for 64 h and cooled and the catalyst was filtered off. The mother liquor was concentrated to dryness and the residue was triturated with 5 mL of EtOH. The precipitate was filtered off, washed with EtOH, and dried to give 0.08 g (25%) of compound **18a**, m.p. 248—250 °C (*cf.* Ref. 8: m.p. 249—251 °C). The IR spectrum of the resulting compound was identical to the IR spectrum of the same compound prepared previously.[8]

B. Sodium bisulfite (0.63 g, 9 mmol) was added to a suspension of 4-oxide **10a** (0.3 g, 1 mmol) in 6 mL of DMSO and the mixture was kept for 25 min at 65 °C. The mixture was cooled and the inorganic precipitate was filtered off. The mother liquor was poured into a fifteen-fold excess of water and the solution was alkalized with 7 mL of 40% NaOH to pH 9. The precipitate was filtered off, washed with water and MeOH, and dried to give 0.18 g of compound **18a** (63%), m.p. 250—251 °C. The melting point of a mixed sample of compounds **18a** prepared by procedures ***A*** and ***B*** was undepressed.

1-(4-Ethoxyphenyl)-2-oxo-1,2,3,6-tetrahydro[1,4]diazepino[6,5-*b*]indole (18b). A mixture of compounds **18b** and **19b** (60 : 40) obtained by reduction of 4-oxide **10b** with reagent **17** (0.29 g) was mixed with 5 mL of acetone. The precipitate was filtered off and recrystallized from 5 mL of MeOH to give 0.06 g of pure compound **18b**.

4-Formyl-2-oxo-1-phenyl-1,2,3,4,5,6-hexahydro[1,4]diazepino[6,5-*b*]indole (20). A mixture of hexahydro derivative **19a** (0.3 g, 1 mmol) and 12 mL of ethyl formate was refluxed for 1.5 h. The suspension was cooled and the precipitate was filtered off, washed with ethyl formate, and dried to give 0.26 g of compound **20.**

References

1. M. D. Mashkovskii, *Lekarstvennye sredstva* [*Drugs*], Novaya Volna, Moscow, 2000, **1**, 72; 76; 95; 278 (in Russian).
2. M. D. Mashkovskii, *Lekarstva XX veka* [*XX Century Drugs*], Novaya Volna, Moscow, 1998, 320 pp. (in Russian).
3. V. G. Granik, *Lekarstva* [*Drugs*], Vuzovskaya kniga, Moscow, 2001, 146; 144; 191 (in Russian).
4. V. G. Granik, *Osnovy meditsinskoi khimii* [*Foundations of Medical Chemistry*], Vuzovskaya kniga, Moscow, 2001, 163; 322 (in Russian).
5. F. Gatta, V. Zaccari, J. P. Huidolbro-Toro, and S. Chiavarelli, *Farmaco, Ed. Sci.,* 1975, **10**, 8.
6. US Pat. 3,689,503; *Chem. Abstrs.,* 1972, **77**, 152241y.
7. US Pat. 3,641,030; *Chem. Abstrs.,* 1972, **76**, 140919s.
8. N. A. Lantsetti, S. Yu. Ryabova, L. M. Alekseeva, A. S. Shashkov, and V. G. Granik, *Izv. Akad. Nauk, Ser. Khim.*, 2002, 470 [*Russ. Chem. Bull.*, *Int. Ed.*, 2002, **51**, 506].
9. S. Yu. Ryabova, N. Z. Tugusheva, L. M. Alekseeva, and V. G. Granik, *Khim.-farm. zhurn.,* 1996, **30**, No. 7, 42 [*Pharm. Chem. J.*, 1996, **30**, No. 7, 472 (Engl. Transl.)].
10. J. F. K. Wilshire, *Austr. J. Chem.*, 1988, **41**, 995.
11. V. V. Budanov and S. V. Makarov, *Khimiya serosoderzhashchikh vosstanovitelei* [*Chemistry of Sulfur-Containing Reducing Agents*], Khimiya, Moscow, 1994, 140 pp. (in Russian).
12. L. M. Litvinenko, *Izv. Akad. Nauk SSSR*, *Ser. Khim.*, 1962, 1737 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1962 (Engl. Transl.)].
13. L. M. Litvinenko, R. S. Cheshko, and R. S. Popova, *Reaktsionnaya sposobnost' organicheskikh soedinenii* [*Reactivity of Organic Compounds*], 1964, **1**, No. 2, 20 (in Russian).
14. J. Ganboa and C. Palomo, *Synth. Commun.*, 1983, **13**, 219.
15. M.T. Bogert and L. E. Wise, *J. Am. Chem. Soc.*, 1910, **32**, 1495.

Received December 9, 2002;
in revised form January 28 , 2003