Chemistry of Heterocyclic Compounds, Vol. 45, No. 6, 2009

HETEROCYCLIZATION OF 2-ACYL-3-INDOLYLACETIC ACIDS USING HYDRAZINE. SYNTHESIS OF 2,3-DIHYDRO-2-OXO-5-R[1]-1H-[1,2]DIAZEPINO[4,5-*b*]INDOLES

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The heterocyclization of 2-acetyl-3-indolylacetic acid hydrazones and its amides, in contrast to similar derivatives of phenylacetic acid, does not lead to 2,3-dihydro-2-oxo-5-R[1]-1H-[1,2]diazepino-[4,5-b]indoles but rather to 2-aminoindolo[2,3-c]pyridin-3(2H)-one or azines of 2-acetyl-3-indolyl-acetic acid. 2,3-Dihydro-2-oxo-5-R[1]-1H-[1,2]diazepino[4,5-b]indoles were obtained by the reaction of 1-alkylaminoacetylindolo[2,3-c]pyrilium perchlorates and of methyl esters of 2-acetyl- and 2-propionyl-3-indolylacetic acid with hydrazine hydrate.

Keywords: 2-aminoindolo[2,3-*c*]pyridin-3(2H)-one, hydrazine hydrate, hydrazones of 2-acetyl-3-indolylacetic acid, 2,3-dihydro-2-oxo-5-R[1]-1H-[1,2]diazepino[4,5-*b*]indoles.

Interest in derivatives of 2,3-benzodiazepines is related to the broad spectrum of their biological action on the central nervous system [1-7]. Some 2,3-benzodiazepines have been found to be tranquilizers and anticonvulsants [2-4]. The tranquilizer, *Tofizopam*, a 2,3-benzodiazepine, has found use in clinical practice [1]. Considerable attention has been given to the synthesis and study of the pharmacological properties of diazepines condensed with various heterocyclic systems [3, 4, 6].

A number of pathways have been reported for the synthesis of derivatives of 2,3-benzo-4-diazepinones based on the reaction of 2-aroyl-4,5-dimethoxyphenylacetic acids with hydrazine [2, 8-10]. 3H-[1,2]Diazepino[5,6-*b*]indoles were obtained by the cyclization of the ethyl esters of 2-formyl- and 2-acetyl-2-indolylacetic acids using hydrazine hydrate [11-13].

We have recently shown that the reaction of 2-acetylbenzo[*b*]furan-3-acetic acid as well as its ester and amide derivatives with hydrazine hydrate leads not to the corresponding benzofurodiazepines but rather to 2-aminobenzofuro[2,3-*c*]pyridin-3(2H)-ones or azines of 2-acetylbenzo[*b*]furan-3-acetic acid [14].

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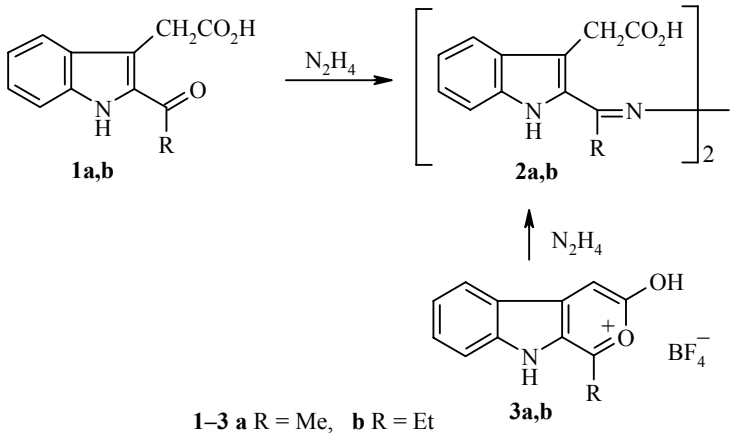
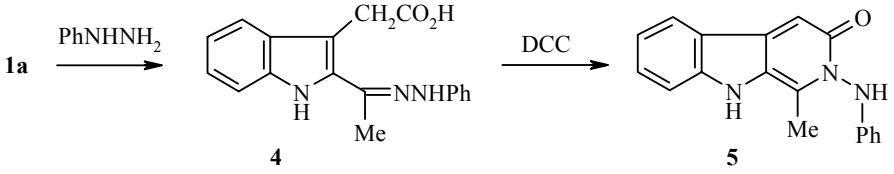
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 907-917, June, 2009. Original article submitted March 21, 2008.

In the present work, we studied pathways to the synthesis of diazepino[4,5-*b*]indoles by the reaction of 3-R^1,R^2-aminoindolo[2,3-*c*]pyrilium salts with hydrazine hydrate and the heterocyclization of derivatives of 2-acetyl-3-indolylacetic acid **1a** as well as ester and amide derivatives of **1a** with hydrazine hydrate.

Heating 2-acetyl-3-indolylacetic acid (**1a**) and 2-propionyl-3-indolylacetic acid (**1b**) with hydrazine hydrate in ethanol or heating their sodium salts in water with subsequent acidification by adding acetic acid lead to amines **2a** and **2b**, which are also obtained upon heating 1-methyl- and 1-ethyl-3-hydroxyindolo-[2,3-*c*]pyrilium borofluoride at reflux with hydrazine hydrate. In contrast to 2-acetylbenzo[*b*]furan-3-acetic acid, decarboxylation does not occur in formation of the azines.

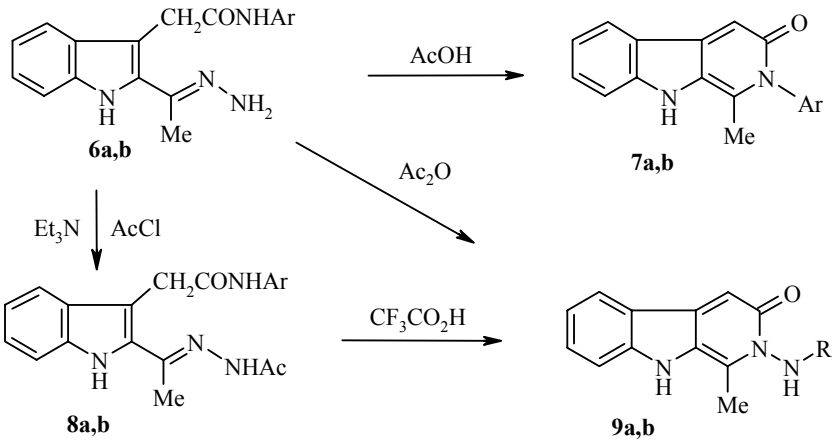


The reaction of keto acid **1a** with phenylhydrazine in ethanol leads to the phenylhydrazone of 2-acetyl-3-indolylacetic acid (**4**). Heterocyclization of phenylhydrazone **4** was carried out by the action of dicyclohexylcarbodiimide (DCC). The product isolated was 1-methyl-2-phenylaminoindolo[2,3-*c*]pyridin-3(2H)-one (**5**).



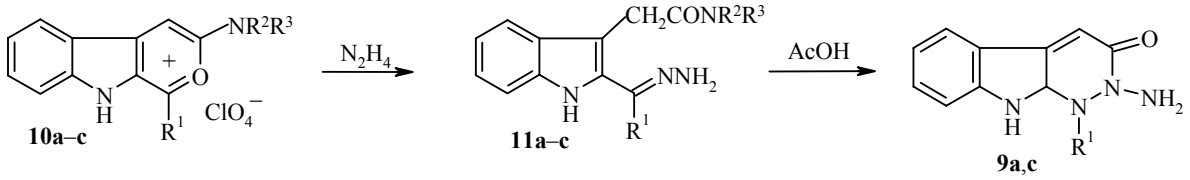
In previous work [15], we have shown that heating 3-arylamino-1-methylindolo[2,3-*c*]pyrilium perchlorates or arylamides of 2-acetyl-3-indolylacetic acids with hydrazine hydrate in ethanol gives exclusively hydrazones of the arylamides of 2-acetyl-3-indolylacetic acids **6**. Hydrazinolysis of the amides does not occur even upon prolonged heating of the reaction mixture at reflux [15]. We discovered that subsequent heterocyclization of hydrazones **6** proceeds only in acidic media. Heating hydrazones **6a** and **6b** in acetic acid at reflux gave 2-aryl-1-methylindolo[2,3-*c*]pyridin-3(2H)-ones **7a** and **7b**. This reaction is probably related to the hydrolysis of hydrazones **6a** and **6b** and subsequent acid-base catalysis, leading to 2-aryl derivatives **7a** and **7b** [15]. Hydrazones **6a** and **6b** are converted in trifluoroacetic acid into 2-amino-1-methylindolo[2,3-*c*]pyridin-3(2H)-ones **9**.

Acetylhydrazones **8a** and **8b** obtained by treating the corresponding hydrazones **6a** and **6b** with acetyl chloride in THF in the presence of triethylamine in acetic as well in trifluoroacetic acids cyclize to give 2-acetylamino-1-methylindolo[2,3-*c*]pyridin-3(2H)-one (**9b**), which was also obtained by heating hydrazones **6a** and **6b** directly with acetic anhydride.



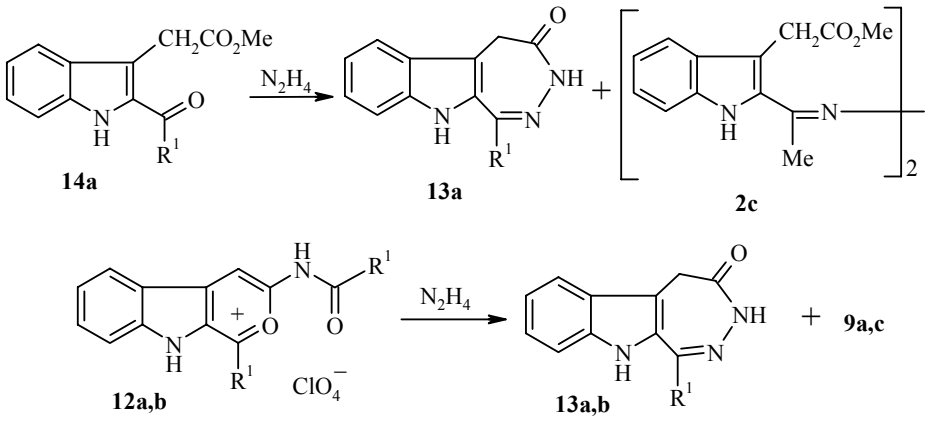
6–8 a Ar = 4-MeC_6H_4, **b** Ar = 4-$MeOC_6H_4$; **9 a** R = H, **b** R = Ac

2-Dimethylamino-1-methyl(ethyl)(morpholino)indolo[2,3-*c*]pyrilium perchlorates **10a-c** react with hydrazine hydrate in ethanol similarly to 3-arylaminoindolo[2,3-*c*]pyrilium salts, i.e., to give the hydrazones of the dimethylamide(morpholide) of 2-acetyl(propionyl)indolyl-3-acetic acid **11a-c**. The heterocyclization of hydrazones **11a-c** both in acetic acid and trifluoroacetic acid leads to already reported 2-amino-1-methylindolo-[2,3-*c*]pyridin-3(2H)-one (**9a**) and 2-amino-1-ethylindolo[2,3-*c*]pyridin-3(2H)-one (**9c**).



9 a R^1 = Me, **c** R^1 = Et; **10**, **11 a** $R^1 = R^2 = R^3$ = Me, **b** R^1 = Me, $R^2+R^3 = (CH_2CH_2O)_2$,
c R^1 = Et, $R^2+R^3 = (CH_2CH_2O)_2$

In contrast to 3-arylamino- and 3-dialkylaminopyrilium perchlorates **10-10c**, 3-acetylamino-1-methyl-indolo[2,3-*c*]pyrilium perchlorate (**12a**) and 3-acetylamino-1-ethylindolo[2,3-*c*]pyrilium perchlorate (**12b**) react with hydrazine hydrate to give 2,3-dihydro-2-oxo-5-R^1-1H-[1,2]diazepino[4,5-*b*]indoles **13a** and **13b** along with traces of 2-amino derivatives **9a** and **9c**. Diazepino[4,5-*b*]indole **13a** was also obtained by cyclization of the



12–14 a R^1 = Me, **b** R^1 = Et

methyl ester of 2-acetyl-3-indolylacetic acid **14a** with hydrazine hydrate. In this case, GC/MS analysis of the reaction mixture obtained in the conversion of ester **14a** showed the presence of the azine of the methyl ester of 2-acetyl-3-indolylacetic acid **2c**.

The ^{1}H NMR spectra of diazepines **13a** and **13b** display singlets for H-5 at 3.56 ppm and NHCO at 10.6 ppm, indicating that these compounds exist as lactams. We should note that, according to Monge et al. [13], isomeric 1-methyl-3H-[1,2]diazepino[5,6-*b*]indole exists in DMSO solution as a lactim.

The structure of 5-ethyl-2,3-dihydro-2-oxo-1H-[1,2]diazepino[4,5-*b*]indole (**13b**) was established by X-ray diffraction structural analysis (Fig. 1). The seven-membered heterocycle is in *boat* conformation. Atoms C(8), C(10), and N(3) deviate from the mean-square plane of the remaining ring atoms by 0.62, 0.57, and 0.64 Å, respectively. The angle between the C(7)–C(8)–C(10)–C(11) and C(8)–C(9)–N(2)–N(3) planes is 60.6°. The ethyl group is markedly twisted relative to the plane of the indole fragment; the N(1)–C(11)–C(10)–C(12) and C(11)–C(10)–C(12)–C(13) torsion angles are -27.9(1)° and -54.6(1)°, respectively.

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, % (method)
		C	H	Cl	N		
2a	$C_{24}H_{22}N_4O_4$	66.88 / 66.97	5.08 / 5.15	—	13.10 / 13.02	235-236	78
2b	$C_{26}H_{26}N_4O_4$	68.03 / 68.11	5.79 / 5.72	—	12.28 / 12.22	172-173	80
2c	$C_{26}H_{26}N_4O_4$	68.25 / 68.11	5.61 / 5.72	—	12.11 / 12.22	237-238 (decomp.)	32
4	$C_{18}H_{17}N_3O_2$	70.25 / 70.34	5.62 / 5.58	—	13.75 / 13.67	163-164	74
5	$C_{18}H_{15}N_3O$	74.63 / 74.72	5.29 / 5.23	—	14.65 / 14.52	246-247	67
6b	$C_{19}H_{20}N_4O_2$	67.98 / 67.84	5.81 / 5.99	—	16.76 / 16.65	185-186	93
8a	$C_{21}H_{22}N_4O_2$	69.71 / 69.59	6.23 / 6.12	—	15.36 / 15.46	265-266	89
8b	$C_{21}H_{22}N_4O_3$	66.58 / 66.65	5.75 / 5.86	—	14.91 / 14.80	256-257	89
9a	$C_{12}H_{11}N_3O$	67.42 / 67.59	5.39 / 5.20	—	19.54 / 19.71	282-283	92 (A), 83 (B)
9b	$C_{14}H_{13}N_3O_2$	65.97 / 65.87	5.10 / 5.13	—	16.55 / 16.46	264-265 (decomp.)	87
9c	$C_{13}H_{13}N_3O$	68.60 / 68.71	5.66 / 5.77	—	18.59 / 18.49	258-259 (decomp.)	90
10a	$C_{14}H_{15}ClN_2O_5$	51.55 / 51.46	4.53 / 4.63	10.80 / 10.85	8.71 / 8.57	>300	86
10b	$C_{16}H_{17}ClN_2O_6$	52.21 / 52.11	4.54 / 4.65	9.55 / 9.61	7.69 / 7.60	>300	90
10c	$C_{17}H_{19}ClN_2O_6$	53.45 / 53.34	5.08 / 5.00	9.19 / 9.26	7.44 / 7.32	292-293	78
11a	$C_{14}H_{18}N_4O$	64.98 / 65.09	7.12 / 7.02	—	21.75 / 21.69	204-205	73
11b	$C_{16}H_{20}N_4O_2$	64.06 / 63.98	6.63 / 6.71	—	18.75 / 18.65	230-231	76
11c	$C_{17}H_{22}N_4O_2$	64.79 / 64.95	7.29 / 7.05	—	17.69 / 17.82	224-225	80
12a	$C_{14}H_{13}BF_4N_2O_2$	51.13 / 51.26	4.10 / 3.99	—	8.66 / 8.54	211-212 (decomp.)	44
12b	$C_{16}H_{17}BF_4N_2O_2$	53.81 / 53.96	4.93 / 4.81	—	7.75 / 7.87	189-190 (decomp.)	40
13a	$C_{12}H_{11}N_3O$	67.70 / 67.59	5.11 / 5.20	—	19.79 / 19.71	270 (decomp.)	47 (A), 52 (B)
13b	$C_{13}H_{13}N_3O$	68.84 / 68.71	5.64 / 5.77	—	18.38 / 18.49	218-219	54 (A)

The configuration of the nitrogen atom of the amide fragment departs somewhat from planar. The sum of the bond angles centered at N(2) is 358°.

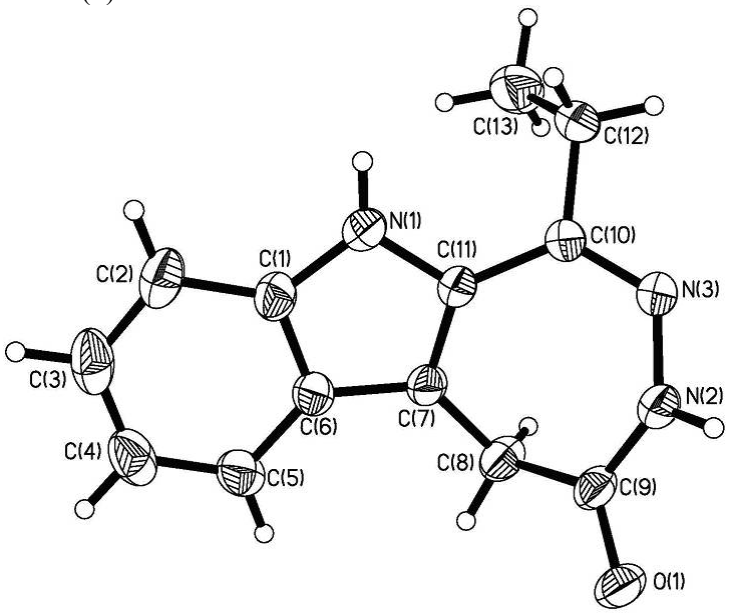


Fig. 1. Molecular structure of 5-ethyl-2,3-dihydro-2-oxo-1H-[1,2]diazepino-[4,5-*b*]indole (**13b**) from X-ray diffraction structural analysis data.

The molecules in crystalline **13** form centrosymmetric dimers by means of intermolecular hydrogen bonding N(2)–H(2A)···O(1)' (-*x*, 1-*y*, -*z*) (H···O, 2.11 Å; N-H···O, 178°). The dimers form chains along the 1 0 0 crystallographic axis due to intermolecular hydrogen bonding N(1)–H(1A)···O(1)' (*x*+1, *y*, *z*) (H···O, 1.99 Å, N–H···O angle 173°). Adjacent dimer chains are connected to each other by weak C–H···π bonds between the C(8)–H(8A) group and π-system of the benzene ring of the adjacent molecule (H(8A)···C(4) bond length is 2.76 Å, the sum of the van der Waals radii is 2.87 Å [16]).

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Gemini-200 spectrometer at 200 MHz and a Bruker DRX500 spectrometer at 500 MHz in DMSO-d_6 with TMS as the internal standard. The mass spectra were taken on a Finnigan MAT Incos-50 mass spectrometer; the ionizing electron energy was 70 eV. The LC/MS spectra were taken on an Agilent 1100 LC/MSD VL using atmospheric pressure chemical ionization (APCI). Chromatographic column parameters: 50 mm length, 4.6 mm diameter, ZORBAX SB-C18 stationary phase, 95:5 acetonitrile–water solvent, 0.1% trifluoroacetic acid, gradient elution, solvent inlet rate 3.0 ml/min. The preparative chromatography of the compounds was carried out on Merck 60 silica gel.

The characteristics of the products are given in Tables 1-3.

X-ray Diffraction Structural Analysis. Triclinic crystals of **13b** were grown from 3:1 chloroform–acetonitrile, $C_{13}H_{13}N_3O$. Unit cell parameters at 293 K: a = 7.4495(4), b = 7.8021(5), c = 10.30798(6) Å, α = 102.876(5), β = 94.570(5), γ = 100.536(5)°, V = 569.65(6) Å^3, M_r = 227.26, Z = 2, space group $P\bar{1}$, d_{calc} = 1.325 g/cm^3, μ(MoKα) = 0.087 mm^{-1}, F(000) = 240. The X-ray diffraction structural analysis of the compound **13b** was carried out at 20°C on an Xcalibur-3 diffractometer using MoKα radiation, CCD detector, graphite monochromator, ω-scanning, $2\theta_{max}$ = 60°. A total of 8233 reflections were measured, of which 3296 were independent (R_{int} = 0.021).

TABLE 2. ^{1}H NMR Spectra of Compounds Synthesized

Compound	Chemical shifts, δ, ppm (*J*, Hz)
2a	2.51 (3H, s, CH_3C=N); 4.09 (2H, s, CH_2); 7.07 (1H, t, *J* = 8.0, H-6); 7.17 (1H, t, *J* = 8.0, H-5); 7.44 (1H, d, *J* = 8.0, H-7); 7.58 (1H, d, *J* = 8.0, H-4); 11.28 (1H, s, NH); 12.12 (1H, s, COOH)
2b	1.15 (3H, t, *J* = 7.4, $C\underline{H}_3CH_2$); 3.08 (3H, q, *J* = 7.4, $CH_3C\underline{H}_2$); 4.09 (2H, s, CH_2); 7.02 (1H, t, *J* = 8.0, H-6); 7.16 (1H, t, *J* = 8.0, H-5); 7.43 (1H, d, *J* = 8.0, H-7); 7.55 (1H, d, *J* = 8.0, H-4); 11.21 (1H, s, NH); 12.03 (1H, s, COOH)
2c	2.53 (3H, s, CH_3C=N); 3.64 (1H, s, OCH_3); 4.15 (2H, s, CH_2); 7.07 (1H, t, *J* = 8.0, H-6); 7.20 (1H, t, *J* = 8.0, H-5); 7.43 (1H, d, *J* = 8.0, H-7); 7.61 (1H, d, *J* = 8.0, H-4); 11.24 (1H, s, NH)
4	2.37 (3H, s, CH_3C=N); 3.97 (2H, s, CH_2); 6.73 (1H, t, *J* = 6.0, H-4'); 6.95 (1H, t, *J* = 8.0, H-6); 7.06 (1H, t, *J* = 8.0, H-5); 7.18-7.29 (4H, m, H arom.); 7.36 (1H, d, *J* = 8.0, H-7); 7.46 (1H, d, *J* = 8.0, H-4); 9.13 (1H, s, NH); 10.84 (1H, s, 1-NH); 11.97 (1H, s, COOH)
5	2.68 (3H, s, 1-CH_3); 6.63 (2H, d, *J* = 7.6, H-2',6'); 6.87 (1H, t, *J* = 7.6, H-4'); 7.06 (1H, t, *J* = 8.0, H-7); 7.15 (2H, t, *J* = 7.6, H-3',5'); 7.33 (1H, d, *J* = 8.0, H-8); 7.45 (1H, t, *J* = 8.0, H-6); 7.97 (1H, d, *J* = 8.0, H-5); 9.03 (1H, s, NH); 10.75 (1H, s, 9-NH)
6b	2.26 (3H, s, CH_3C=N); 3.71 (3H, s, 4'-OCH_3); 3.78 (2H, s, CH_2); 6.72 (4H, d, *J* = 9.0, H-3',5'); 6.83 (2H, s, NH_2); 6.98 (1H, t, *J* = 7.6, H-6); 7.06 (1H, t, *J* = 7.6, H-5); 7.30 (1H, d, *J* = 7.6, H-7); 7.43 (2H, d, *J* = 9.0, H-2',6'); 7.62 (1H, d, *J* = 7.6, H-4); 10.48 (1H, s, CONH); 10.91 (1H, s, 1-NH)
8a	2.16 (6H, s, $COCH_3$ и 4'-CH_3); 2.40 (3H, s, CH_3C=N); 3.89 (2H, s, CH_2); 7.00 (2H, d, *J* = 8.6, H-3',5'); 7.08 (1H, t, *J* = 7.7, H-6); 7.15 (1H, t, *J* = 7.7, H-5); 7.39 (1H, d, *J* = 7.7, H-7); 7.44 (2H, d, *J* = 8.6, H-2',6'); 7.78 (1H, d, *J* = 7.7, H-4); 10.29 (1H, s, $CH_3CON\underline{H}$); 10.89 (1H, s, $CH_2CON\underline{H}$); 11.38 (1H, s, 1-NH)
8b	2.19 (3H, s, $COCH_3$); 2.41 (3H, s, CH_3C=N); 3.70 (3H, s, 4'-OCH_3); 3.91 (2H, s, CH_2); 6.68 (2H, d, *J* = 8.6, H-3',5'); 7.04 (1H, t, *J* = 7.4, H-6); 7.11 (1H, t, *J* = 7.4, H-5); 7.34 (1H, d, *J* = 7.4, H-7); 7.52 (2H, d, *J* = 8.6, H-2',6'); 7.84 (1H, d, *J* = 7.4, H-4); 10.15 (1H, s, $CH_3CON\underline{H}$); 10.70 (1H, s, $CH_2CON\underline{H}$); 11.07 (1H, s, 1-NH)
9a	2.67 (3H, s, 1-CH_3); 6.40 (2H, s, NH_2); 6.88 (1H, s, H-4); 7.03 (1H, t, *J* = 7.6, H-7); 7.31 (1H, d, *J* = 7.6, H-8); 7.43 (1H, t, *J* = 7.6, H-6); 7.97 (1H, d, *J* = 7.6, H-5); 10.68 (1H, s, 9-NH)
9b	2.08 (3H, s, $COCH_3$); 2.42 (3H, s, 1-CH_3); 6.88 (1H, s, H-4); 7.01 (1H, t, *J* = 8.0, H-7); 7.27 (1H, d, *J* = 8.0, H-8); 7.45 (1H, t, *J* = 8.0, H-6); 7.97 (1H, d, *J* = 8.0, H-5); 10.48 (1H, s, CONH); 10.79 (1H, s, 9-NH)
9c	1.32 (3H, t, *J* = 7.6, 1-$CH_2C\underline{H}_3$); 3.13 (3H, q, *J* = 7.6, 1-$C\underline{H}_2CH_3$); 5.97 (2H, s, NH_2); 6.71 (1H, s, H-4); 6.93 (1H, t, *J* = 8.2, H-7); 7.21 (1H, d, *J* = 8.2, H-8); 7.28 (1H, t, *J* = 8.2, H-6); 7.79 (1H, d, *J* = 8.2, H-5); 10.30 (1H, s, 9-NH)
10a	2.85 (3H, s, 1-CH_3); 3.37 (6H, s, $N(CH_3)_2$); 7.20 (1H, t, *J* = 8.0, H-7); 7.41 (1H, d, *J* = 8.0, H-8); 7.63 (1H, t, *J* = 8.0, H-6); 7.69 (1H, s, H-4); 8.21 (1H, d, *J* = 8.0, H-5); 11.43 (1H, s, 9-NH)
10b	2.83 (3H, s, 1-CH_3); 3.57–3.89 (8H, m, morpholine); 7.22 (1H, t, *J* = 8.0, H-7); 7.44 (1H, d, *J* = 8.0, H-8); 7.66 (1H, t, *J* = 8.0, H-6); 7.71 (1H, s, H-4); 8.22 (1H, d, *J* = 8.0, H-5); 11.52 (1H, s, 9-NH)
10c	1.33 (3H, t, *J* = 7.3, 1-$CH_2C\underline{H}_3$); 2.89 (3H, q, *J* = 7.3, 1-$C\underline{H}_2CH_3$); 3.30 (6H, s, $N(CH_3)_2$); 7.12 (1H, t, *J* = 8.0, H-7); 7.32 (1H, d, *J* = 8.0, H-8); 7.54 (1H, t, *J* = 8.0, H-6); 7.60 (1H, s, H-4); 8.09 (1H, d, *J* = 8.0, H-5); 11.28 (1H, s, 9-NH)
11a	2.11 (3H, s, CH_3C=N); 2.88 (3H, s, NCH_3); 3.04 (3H, s, NCH_3); 3.99 (2H, s, CH_2); 5.99 (2H, s, NH_2); 6.89 (1H, t, *J* = 8.0, H-6); 7.02 (1H, t, *J* = 8.0, H-5); 7.29 (1H, d, *J* = 8.0, H-7); 7.44 (1H, d, *J* = 8.0, H-4); 10.59 (1H, s, 1-NH)
11b	2.09 (3H, s, CH_3C=N); 3.36–3.53 (8H, m, morpholine); 4.01 (2H, s, CH_2); 6.28 (2H, s, NH_2); 6.91 (1H, t, *J* = 7.8, H-6); 7.02 (1H, t, *J* = 7.8, H-5); 7.30 (1H, d, *J* = 7.8, H-7); 7.47 (1H, d, *J* = 7.8, H-4); 10.81 (1H, s, 1-NH)
11c	1.05 (3H, t, *J* = 7.3, 1-$CH_2C\underline{H}_3$); 2.63 (3H, q, *J* = 7.3, 1-$C\underline{H}_2CH_3$); 3.32–3.51 (8H, m, morpholine); 4.01 (2H, s, CH_2); 6.48 (2H, s, NH_2); 6.89 (1H, t, *J* = 8.0, H-6); 7.00 (1H, t, *J* = 8.0, H-5); 7.28 (1H, d, *J* = 8.0, H-7); 7.47 (1H, d, *J* = 8.0, H-4); 10.78 (1H, s, 1-NH)
13a	2.44 (3H, s, 5-CH_3); 3.56 (2H, s, 1-CH_2); 7.13 (1H, t, *J* = 8.1, H-8); 7.26 (1H, t, *J* = 8.1, H-9); 7.44 (1H, d, *J* = 8.1, H-7); 7.71 (1H, d, *J* = 8.1, H-10); 10.64 (1H, s, CONH); 11.49 (1H, s, 6-NH)
13b	1.19 (3H, t, *J* = 7.3, 5-$CH_2C\underline{H}_3$); 2.85 (3H, q, *J* = 7.3, 5-$C\underline{H}_2CH_3$); 3.48 (2H, s, 1-CH_2); 7.05 (1H, t, *J* = 8.0, H-8); 7.17 (1H, t, *J* = 8.0, H-9); 7.38 (1H, d, *J* = 8.0, H-7); 7.59 (1H, d, *J* = 8.0, H-10); 10.23 (1H, s, CONH); 11.13 (1H, s, 6-NH)

TABLE 3. Mass Spectra of Compounds Synthesized

Compound	m/z (I_{rel}, %)*
2a	430 [M] (30), 342 (70), 171 (40), 155 (10), 129 (15), 63 (15), 44 (100)
2b	370 (20), 341 (15), 185 (40), 169 (17), 155 (15), 130 (13), 77 (9), 44 (100)
2c	459 $[M + 1]^+$ (100)
5	289 [M] (30), 197 (41), 169 (65), 127 (12), 101 (13), 93 (100), 77 (16), 65 (30), 51 (12), 42 (28)
9b	255 [M] (100), 238 (15), 213 (48), 197 (50), 184 (41), 169 (30), 154 (25), 127 (20), 115 (10), 101 (13), 77 (15), 51 (11), 43 (53)
13a	213 [M] (100), 197 (12), 184 (100), 169 (10), 154 (16), 128 (13)

*The strongest peaks are given. The mass spectrum for **2c** was obtained by HPLC/MSD method.

The structure was solved by the direct method and refined for F^2 by the full-matrix method of least squares anisotropically for the non-hydrogen atoms using the SHELXTL program package [17]. The positions of the hydrogen atoms were found in the electron density difference map and refined isotropically. The final divergence factors: $wR_2 = 0.095$ for 7900 reflections ($R_1 = 0.035$ for 2315 reflections with $F > 4\sigma(F)$, $S = 0.947$. The atomic coordinates, geometric parameters of the molecule, and crystallographic data are deposited at the Cambridge Crystallographic Data Center (CCDC deposit 673,503).

Samples of 2-acetyl-3-indolylacetic acid (**1a**), 2-propionyl-3-indolylacetic acid (**1b**), and their methyl esters **14a** and **14b** were obtained according to Plieninger et al. [18].

Preparation of Azines of 2-Acetyl-3-indolylacetic Acid (2a) and 2-Propionyl-3-indolylacetic acid (2b) (General Method). A. Hydrazine hydrate (2.5 g, 50 mmol) was added to a solution of **1a** or **1b** (10 mmol) in aqueous sodium bicarbonate, heated at reflux for 1 h, cooled, and made acidic by adding acetic acid to pH < 7. The precipitate formed was filtered off and washed with ethanol and water; compound **2a** was crystallized from aqueous DMSO, while compound **2b** was crystallized from methanol.

B. A mixture of corresponding 1-methyl- (**3a**) or 1-ethyl-3-hydroxyindolo[2,3-*c*]pyrilium borofluoride (**3b**) (10 mmol) [18] and hydrazine hydrate (2.5 g, 50 mmol) in methanol (30 ml) was heated at reflux for 1 h and cooled. Crystals of compounds **2a** or **2b** were filtered off and washed with ethanol and water.

Phenylhydrazone of 2-Acetyl-3-indolylacetic Acid (4). Phenylhydrazine (1.62 g, 15 mmol) was added to a solution of compound **1a** (2.3 g, 10 mmol) in 2-propanol and heated at reflux for 1 h. After cooling, the precipitate formed was filtered off, washed with cold 2-propanol, and crystallized from methanol.

1-Methyl-2-phenylaminoindolo[2,3-*c*]pyridin-3(2H)-one (5).) Dicyclohexylcarbodiimide (0.72 g, 3.5 mmol) was added to a solution of compound **4** (1 g, 3.1 mmol) in methylene chloride (20 ml) and stirred for 5 h. Dicyclohexylurea was filtered off and washed with methylene chloride. The filtrate was evaporated and the residue was crystallized from 2-propanol.

Hydrazone of 4-Methylphenylamide of 2-Acetyl-3-indolylacetic Acid (6a) was prepared from 1-methyl-3-(4-methylphenylamino)indolo[2,3-*c*]pyrilium perchlorate [15].

Hydrazone of 4-Methoxyphenylamide of 2-Acetyl-3-indolylacetic Acid (6b) was prepared from 1-methyl-3-(4-methoxyphenylamino)indolo[2,3-*c*]pyrilium perchlorate [15] analogously to compound **6a**. Hydrazone **6b** was crystallized from methanol.

2-(4-Methoxyphenylamino)-1-methylindolo[2,3-*c*]pyridin-3(2H)-one (7a) was prepared by heating hydrazone **6a** in glacial acetic acid at reflux for 2 h. This product was spectrally identical to previously prepared samples [15] and a mixed probe did not give a depressed melting point.

2-(4-Methoxyphenylamino)-1-methylindolo[2,3-*c*]pyridin-3(2H)-one (7b) was obtained by heating hydrazone **6b** in glacial acetic acid for 2 h. The product was spectrally identical to previously prepared samples [15] and a mixed probe did not give a depressed melting point.

N-Acetylhydrazone of 4-Methylphenylamide of 2-Acetyl-3-indolylacetic Acid (8a). Acetyl chloride (0.157 g, 2 mmol) was added with stirring and cooling solution of hydrazone **6a** (0.64 g, 2 mmol) and triethylamine (0.3 ml) in THF, stirred for 1 h, brought to reflux, cooled, and poured into water. The precipitate was filtered off and crystallized from DMSO.

N-Acetylhydrazone of 4-Methoxyphenylamide of 2-Acetylbenzo[*b*]furan-3-acetic Acid (8b) was obtained from hydrazone **6b** analogously to compound **8a**. This product was crystallized from DMSO.

2-Amino-1-methylindolo[2,3-*c*]pyridin-3(2H)-one (9a). A. A solution of 1 g hydrazones of aryl-amides of 2-acetyl-3-indolylacetic acid **6a** or **6b** was heated at reflux for 1 h in trifluoroacetic acid (20 ml). Then, trifluoroacetic acid was removed in vacuum and water (50 ml) was added. The remaining trifluoroacetic acid was neutralized by adding ammonium hydroxide to bring the pH to >7. The precipitate formed was filtered off, washed with water, and crystallized from ethanol.

B. Amino ketone **9a** was obtained by a procedure analogous to method A using hydrazones of alkylamides of 2-acetyl-3-indolylacetic acid **11a** or **11b** and acetic acid.

The samples of amino ketone **9a** obtained by methods A and B were spectrally identical and a mixed probe did not give a depressed melting point.

2-Acetylamino-1-methylindolo[2,3-*c*]pyridin-3(2H)-one (9b). A. Acetic anhydride (0.2 g, 4 mmol) was added to a solution of hydrazone **6a** (0.96 g, 3 mmol) in THF. The solution was brought to reflux, cooled, and poured into water. The precipitate formed was filtered off and crystallized from 2-propanol.

B. N-Acetylhydrazone of 4-methylphenylamide of 2-acetyl-3-indolylacetic acid (**8a**) (0.38 g, 1 mmol) was dissolved in acetic acid (20 ml) and heated at reflux for 1 h. The solution was cooled and 50 ml water was added. The acetic acid was neutralized by adding 10% ammonium hydroxide to bring the pH to >7. The precipitate formed was filtered off, washed with water, and crystallized from 2-propanol. Samples of compound **9b** obtained by methods A and B are spectrally identical and a mixed probe did not give a depressed melting point.

2-Amino-1-ethylindolo[2,3-*c*]pyridin-3(2H)-one (9c) was obtained from hydrazone **11c** analogous to compound **9a** (method B) and crystallized from 2-propanol.

3-Dimethylamino-1-methylindolo[2,3-*c*]pyrilium Perchlorate (10a) was obtained according to our reported method [19] by the cyclization of the dimethylamide of 2-acetyl-3-indolylacetic acid [18].

1-Methyl-3-morpholinoindolo[2,3-*c*]pyrilium Perchlorate (10b) was obtained according to our reported procedure [19] by the cyclization of the morpholide of 2-acetyl-3-indolylacetic acid [18].

1-Ethyl-3-morpholinoindolo[2,3-*c*]pyrilium Perchlorate (10c) was obtained according to our reported procedure [19] by the cyclization of the morpholide of 2-propionylindolyl-3-acetic acid [18].

Hydrazone of Dimethylamide of 2-Acetyl-3-indolylacetic Acid (11a). 60% Hydrazine hydrate (5 ml) was added to a suspension of pyrilium perchlorate **10a** (10 mmol) in 2-propanol (50 ml) and heated at reflux for 1.5 h. After cooling, 50 ml water was added. The precipitate was filtered off, washed with water, and crystallized from 2-propanol.

Hydrazone of Morpholide of 2-Acetyl-3-indolylacetic Acid (11b) was obtained from 1-methyl-3-morpho-linoindolo[2,3-*c*]pyrilium perchlorate (**10b**) analogously to hydrazone **11a** and crystallized from 2-propanol.

Hydrazone of Morpholide of 3-Propionyl-3-indolylacetic Acid (11c) was obtained from perchlorate **10c** analogously to hydrazone **11a** and crystallized from 2-propanol.

3-Acetylamino-1-methylindolo[2,3-*c*]pyrilium Perchlorate (12a) was obtained by the acylation of 3-indolylacetonitrile using acetic anhydride in the presence of boron trifluoride etherate according to a procedure analogous to the method of Dorofeenko et al. [20].

3-Acetylamino-1-ethylindolo[2,3-*c*]pyrilium Perchlorate (12b) was obtained by the acylation of 3-indolylacetonitrile using propionic anhydride in the presence of boron trifluoride etherate according to a procedure analogous to the method of Dorofeenko et al. [20].

2-Oxo-2,3-dihydro-5-R-1H-[1,2]diazepino[4,5-*b*]indoles 13a and 13b. A. 98% Hydrazine hydrate (5 ml) was added to a suspension of corresponding pyrilium perchlorate **12a** or **12b** (10 mmol) in 2-propanol (50 ml) and heated at reflux for 30 min. After cooling, 50 ml water was added and the excess hydrazine was neutralized by adding acetic acid to bring the pH to <7. The mixture was extracted with chloroform. The extract was washed with water and the solvent was removed. Indoles **13a** and **13b** were purified by preparative chromatography. Product **13a**, R_f 0.13, was eluted with 20:1 chloroform–methanol, while product **13b**, R_f 0.45, was eluted with 3:1 chloroform–acetonitrile.

B. 98% Hydrazine hydrate (0.75 ml)was added to a solution of keto acid methyl ester **14a** [18] (5 mmol) in 2-propanol (50 ml) and heated at reflux for 2 h. After cooling, water (30 ml) was added and excess hydrazine was neutralized by adding acetic acid to bring the pH to <7. The precipitate formed was filtered off and washed with water. Products **13a** and **2c** were separated by preparative chromatography using 20:1 chloroform–methanol as the eluent. Product **2c**, R_f 0.43, was crystallized from ethanol.

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