Synthesis and properties of pyrimido[4,5-*a*]- and pyrido[4,3-*a*]carbazole derivatives

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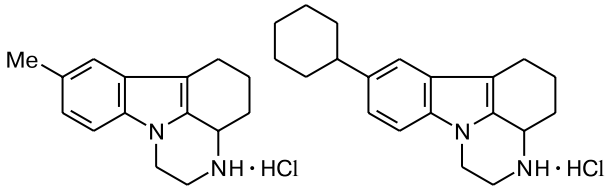
Methods for the synthesis of substituted pyrimido[4,5-*a*]- and pyrido[4,3-*a*]carbazoles were proposed. Condensation of 2-(dimethylaminomethylene)-6-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one with guanidine and thiourea afforded 2-amino-8-methyl-6,11-dihydro-5*H*-pyrimido[4,5-*a*]carbazole and 8-methyl-3,5,6,11-tetrahydro-2*H*-pyrimido[4,5-*a*]carbazole-2-thione, respectively. The reaction of cyano(6-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-ylidene)acetamide with dimethylformamide dimethyl acetal gave *N*-(dimethylaminomethylene)cyano(6-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-ylidene)acetamide. Cyclization of the latter yielded 1-cyano-8-methyl-3,5,6,11-tetrahydro-2*H*-pyrido[4,3-*a*]carbazol-2-one.

Key words: tetrahydrocarbazol-1-ones, pyrimido[4,5-*a*]carbazoles, pyrido[4,3-*a*]carbazoles, 2-substituted pyrimidines, acyl enamines, guanidine, thiourea, dimethylformamide dimethyl acetal.

Reversible inhibitors of monoamine oxidase (MAO), which belong to a new generation of antidepressants, are well known to play an important role among drugs used to treat various types of depression. They both suppress the activity of this enzyme and act like tricyclic antidepressants (*e.g.*, they inhibit neuronal re-uptake of monoamines). The latter process increases the concentrations of neurotransmitting amines (noradrenaline, dopamine, and serotonin) at the synaptic cleft but does not exclude their inactivation, *e.g.*, with monoamine oxidase. Such an approach seems to be quite physiological, for which reason tricyclic antidepressants hold a firm place in medical practice. Selectivity to the inhibition of neurotransmitter re-uptake is also important for the manifestation of various biological effects. For instance, inhibition of the neuronal re-uptake of noradrenaline is supposed to primarily enhance psychomotor activity, while an analogous process for serotonin results in a thymoleptic effect (elevated mood). A search for antidepressants in general and MAO-inhibiting ones in particular still remains of topical interest for health protection.[1—3]

The first and most important representative of preparations of this type is pyrazidole widely used in medical practice.[1—4] Another preparation of an analogous pharmacological effect is tetrindole belonging to the same chemical group of tetracyclic heterocycles.[1—4]



Pyrazidole Tetrindole

Both preparations are 1,9a,9-annelated derivatives combining the piperazine fragment with the carbazole tricycle.

The goal of the present work was to obtain tetracyclic compounds containing the carbazole fragment 1,2-fused with another azaheterocycle and to study some of their chemical and physicochemical properties. 2-(Dimethylaminomethylene)-6-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**1**) used as the starting compound was previously prepared by the reaction of 6-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**2**) with dimethylformamide dimethyl acetal (**3**) and employed for the synthesis of pyrazolo[3,4-*a*]carbazoles.[5]

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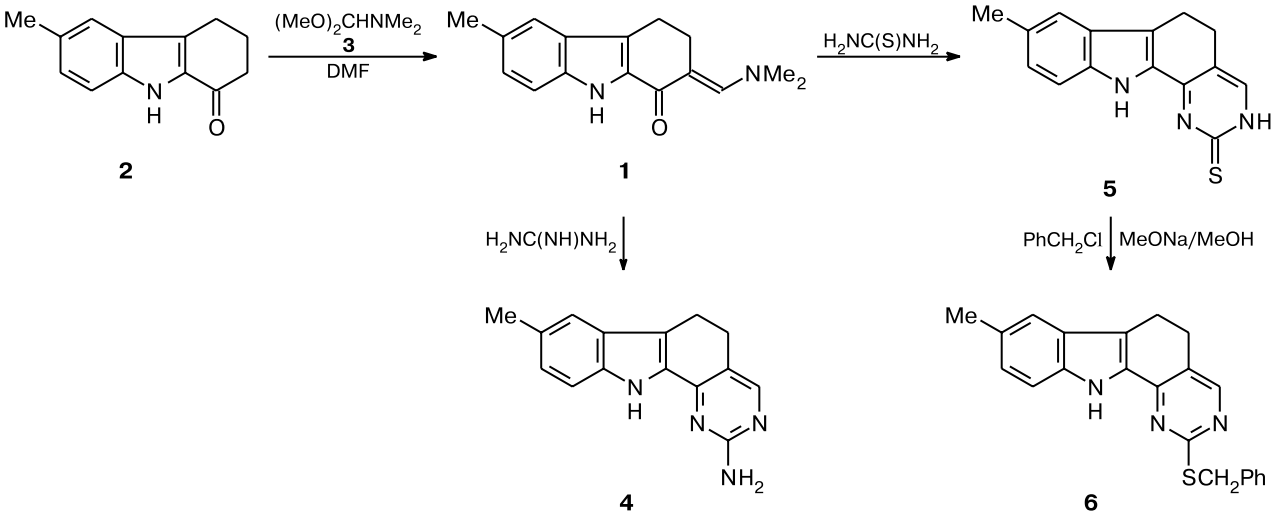
Scheme 1



The reaction of enamino ketone **1** with guanidine in ethanol in the presence of sodium ethoxide smoothly gave 2-amino-8-methyl-6,11-dihydro-5*H*-pyrimido[4,5-*a*]carbazole (**4**) (Scheme 1). Earlier,[6] such compounds were obtained in another way. The structure of compound **4** was confirmed by ^{1}H NMR data (δ: 6.04 (br.s, NH_2); 8.05 (s, C(4)H); 11.17 (br.s, N(11)H)). The reaction of enamino ketone **1** with thiourea under the same conditions yielded 8-methyl-3,5,6,11-tetrahydro-2*H*-pyrimido[4,5-*a*]carbazole-2-thione (**5**). Structure **5** was completely confirmed by ^{1}H NMR and MS data (Tables 1, 2). However, compound **5** was not isolated in the analytically pure state; for its unambiguous identification, it was *S*-benzylated to give 2-benzylthio-8-methyl-6,11-dihydro-5*H*-pyrimido[4,5-*a*]carbazole (**6**), which was purified without difficulties.

Another approach was used to obtain pyrido[4,3-*a*]carbazoles (Scheme 2). In this case, the initial condensation of ketone **2** with reactive methylene compounds (malononitrile and cyanoacetamide) gave substituted 1-methylenecarbazoles **7** and **8**, respectively, in high yields. We used amide **8** as a basic component for construction of a tetraheterocyclic system.

Compounds with a vinylene group bound to electron-withdrawing substituents can more or less easily be converted with amide acetals into the corresponding enamines.[7—10] At the same time, it is known[11] that amide acetals react with primary amides to give acylamidines. We

Table 1. ^{1}H NMR spectra of compounds **4—6** and **10—14**

Compound	δ								
	br.s, N(3)H	s, C(4)H	4 H, C(5)H_2C(6)H_2	C(7)H	s, C(8)Me	C(9)H[a]	d, C(10)H[a]	N(11)R	Other signals
4	—	8.05	2.87 m	7.32 br.s	2.38	7.00 dd	7.34	11.17 (br.s, 1 H)	6.04 (br.s, 2 H, 2-NH_2)
5	12.98	7.69	2.92 m	7.39 br.s	2.39	7.10 dd	7.34	11.69 (br.s, 1 H)	—
6	—	8.30	3.01 s	[b]	2.42	7.00 dd	[b]	11.43 (s, 1 H)	7.45 (dd[a], 2 H, C(2′)H, C(6′)H); 4.48 (s, 2 H, CH_2Ph)
10	10.59	7.47	2.83 m	7.34 br.s	2.42	7.08 dd	7.49	11.78 (br.s, 1 H)	—
11	—	8.33	2.97 s	7.32 s	2.42	7.06 dd	7.48	10.75 (s, 1 H)	—
12	—	8.16	2.91 s	7.34 s	2.42	7.05 dd	7.48	10.72 (s, 1 H)	4.00 (s, 3 H, C(2)OMe)
13	—	7.83	2.82 m	7.34 br.s	2.42	7.07 dd	7.48	10.71 (br.s, 1 H)	3.47 (s, 3 H, N(3)Me)
12[c]	—	8.14	2.93 s	7.34 br.s	2.42	7.05 br.d	7.48	10.63 (br.s, 1 H)	4.01 (s, 3 H, C(2)OMe)
14[c]	—	8.24	2.83 s	7.42 br.s	2.45	7.17 br.d	7.40	3.83 (s, 3 H, R = Me)	4.04 (s, 3 H, C(2)OMe)

[a] J_o = 8.2—8.4 Hz, J_m = 1.2—1.4 Hz.
[b] δ: 7.20—7.35 (m, 5 H, C(7)H, C(10)H, C(3′)H, C(4′)H, C(5′)H).
[c] A mixture of compounds **12** and **14**.

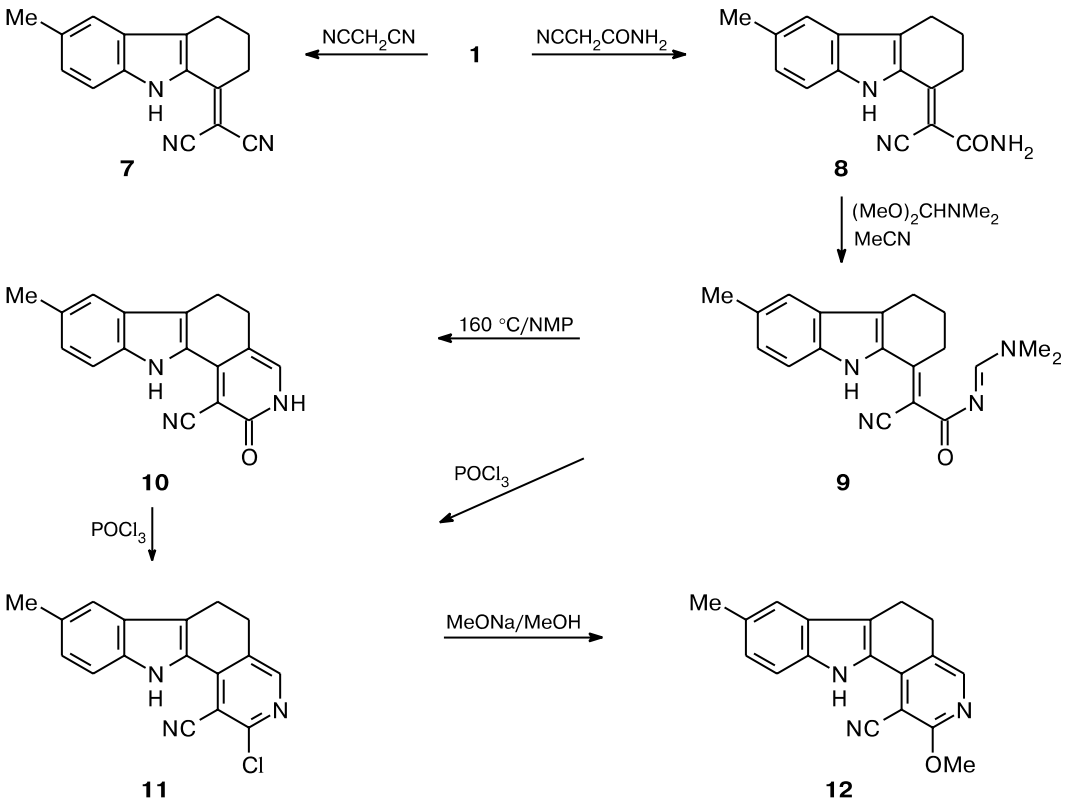
Table 2. Elemental analysis and MS data for the compounds obtained

Compound	Found / Calculated (%) C	H	N	Molecular formula	MS, m/z (I_{rel} (%))
4	72.16 / 71.98	6.01 / 5.64	22.44 / 22.38	$C_{15}H_{14}N_4$	250 $[M]^+$ (100), 234 $[M - NH_2]^+$ (4)
6	74.01 / 73.92	5.39 / 5.36	11.84 / 11.75	$C_{22}H_{19}N_3S$	357 $[M]^+$ (100), 324 $[M - SH]^+$ (56)
7	78.07 / 77.71	5.25 / 5.29	16.70 / 17.00	$C_{16}H_{13}N_3$	247 $[M]^+$ (95)
8	72.70 / 72.43	5.90 / 5.70	16.04 / 15.84	$C_{16}H_{15}N_3O$	265 $[M]^+$ (57), 247 $[M - H_2O]^+$ (100), 219 $[247 - CO]^+$ (53), 205 $[M - CONH_2 - CH_2]^+$ (19)
9	71.49 / 71.23	6.46 / 6.29	17.50 / 17.49	$C_{19}H_{20}N_4O$	320 $[M]^+$ (35), 275 $[M - HNMe_2]^+$ (32), 248 $[M - HNMe_2 - OH]^+$ (100), 219 $[248 - HCO]^+$ (88)
10	74.11 / 74.17	5.08 / 4.76	15.28 / 15.26	$C_{17}H_{13}N_3O$	274 $[M]^+$ (100)
11	69.85 / 69.50	4.23 / 4.12	14.47 / 14.30	$C_{17}H_{12}ClN_3$	293 $[M]^+$ (100)
12	75.13 / 74.72	5.68 / 5.23	14.68 / 14.52	$C_{18}H_{15}N_3O$	289 $[M]^+$ (100)
13	74.90 / 74.72	5.27 / 5.33	14.54 / 14.52	$C_{18}H_{15}N_3O$	289 $[M]^+$ (100), 274 $[M - Me]^+$ (18)

studied the direction of the reaction of amide **8** with dimethylformamide dimethyl acetal (**3**). Heating of a mixture of compounds **8** and **3** in acetonitrile afforded acylamidine **9**; its ^1H NMR spectrum shows the signals at δ 3.21, 3.28 (3 H each, NMe), and 8.63 (N=CH) for the dimethylformamidine fragment (complete spectrum is given in Table 3).

When heated in NMP, acylamidine **9** undergoes intramolecular cyclization with elimination of dimethylamine to give 1-cyano-8-methyl-3,5,6,11-tetrahydro-2*H*-

Scheme 2



NMP is *N*-methyl-2-pyrrolidone

Table 3. ^{1}H NMR spectra of compounds **7**—**9**

Compound	δ (*J*/Hz)								
	C(2)H$_2$	C(4)H$_2$	q, 2 H, C(3)H$_2$, *J* = 6.0	br.s, C(5)H	C(7)H[a]	d, C(8)H[a]	s, C(6)Me	br.s, N(9)H	Other signals
7	2.93 (t, *J* = 6.0)	[b]	2.01	7.43	7.23 br.d	7.53	2.39	10.61	—
8	2.89 (m, 4 H)		1.99	7.36	7.12 dd	7.38	2.36	11.71	8.00 (br.s, 2 H, CONH$_2$)
9	2.92 (t, *J* = 6.0)	3.04 (t, *J* = 6.0)	2.07	7.34	7.10 dd	7.29	2.41	12.91	8.63 (s, 1 H, N=CH); 3.21 and 3.28 (both m, 3 H each, NMe$_2$)

[a] J_o = 8.2—8.4 Hz, J_m = 1.2—1.4 Hz.
[b] The signal coalesces with the signal for water in DMSO-d$_6$ (δ 3.23).

pyrido[4,3-*a*]carbazol-2-one (**10**). This cyclization requires a high temperature; extensive studies of its kinetics with a number of simpler examples revealed that the entropy of activation of such processes has a high negative value (sterically strained transition state).[12]

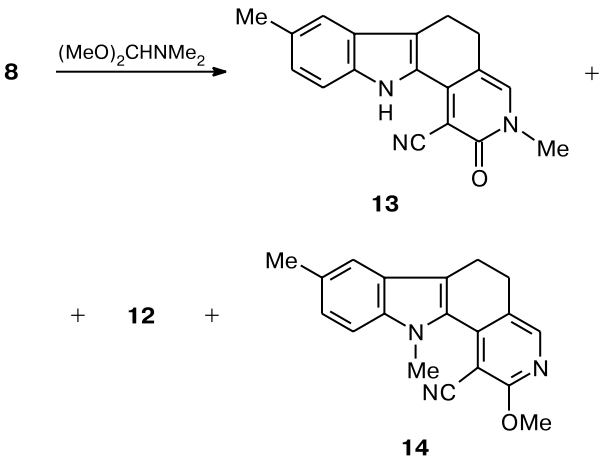
On heating in POCl$_3$, the oxo group in compound **10** is replaced by a Cl atom to give 2-chloro derivative **11**. The Cl atom in tetracycle **11** proved to be very labile. The reaction of compound **11** with sodium methoxide in methanol smoothly gave 1-cyano-2-methoxy-8-methyl-6,11-dihydro-5*H*-pyrido[4,3-*a*]carbazole (**12**) in high yield. Its ^{1}H NMR spectrum shows the signals at δ 4.01 (3 H, OMe), 8.13 (1 H, C$_4$H), and 10.66 (1 H, NH, indole) (for complete spectrum, see Table 1).

Attempted synthesis of compound **11** directly from acylamidine **9** by heating in POCl$_3$, which would allow avoiding the isolation and purification of pyridone derivative **10**, gave the target product in very low yield under these conditions and the two-step procedure described above is preferred in a preparative respect.

Thus, the key step in the synthesis of pyridocarbazole is condensation of dimethylformamide dimethyl acetal (**3**) with the amide NH$_2$ group of compound **8**. As shown above, this reaction smoothly proceeds under mild conditions (heating in acetonitrile) to give acylamidine **9**.

Finally, we carried out the reaction of compound **8** with acetal **3** under significantly more drastic conditions (heating in acetal **3** used as both the reagent and solvent). It turned out that the pyridine ring closure under these conditions is accompanied by *N*- and *O*-alkylation generally characteristic of amido acetals,[13] but probably not observed earlier in such a combination (Scheme 3). *N*-Methyl derivative **13** was isolated in high yield; its ^{1}H NMR spectrum shows the signals at δ 3.47 (3 H, N(3)Me), 7.83 (1 H, C(4)H), and 10.71 (1 H, NH, indole) (for complete spectrum, see Table 1). In addition, an inseparable mixture of two products was obtained. According to the ^{1}H NMR data, the mixture consists of compounds **14** and **12**.

Scheme 3



The ^{1}H NMR spectrum of compound **14** shows the signals at δ 3.83 (3 H, N(11)Me), 4.04 (3 H, C(2)OMe), and 8.14 (1 H, C(4)H) (for complete spectrum, see Table 1). The alkylation of the indole NH group with amide acetal is of particular interest.

Thus, we developed the methods for the synthesis of carbazoles fused with azaheterocycles and proposed the rational route to tetracyclic heterocycles.

Experimental

Mass spectra were recorded on a Finnigan SSQ-710 mass spectrometer (direct inlet probe). ^{1}H NMR spectra were recorded on a Bruker AC-200 spectrometer in DMSO-d$_6$. The course of the reactions was monitored and the purity of the compounds was checked by TLC on Silufol UV-254 plates in chloroform—methanol (10 : 1) for compounds **1**, **2**, **4**, **6**, **7**, **9**, and **12**—**14**, benzene—methanol (9 : 1) for compounds **5**, **8**, and **10**, and benzene for compound **11**. The ^{1}H NMR spectra of compounds **4**—**6** and **10**—**14** are given in Table 1 and those of compounds **7**—**9** are presented in Table 3. Elemental analysis and MS data for compounds **4** and **6**—**13** are given in Table 2.

2-(Dimethylaminomethylene)-6-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (1) was prepared according to a known procedure[5] from 6-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**2**)[4] and dimethylformamide dimethyl acetal (**3**).

2-Amino-8-methyl-6,11-dihydro-5*H*-pyrimido[4,5-*a*]carbazole (4). A solution of EtONa prepared from metallic Na (0.83 g, 36 mmol) and anhydrous EtOH (30 mL) was added to a suspension of guanidine hydrochloride (2.86 g, 30 mmol) in 5 mL of anhydrous EtOH. The precipitate of NaCl that formed was filtered off. The filtrate was added to a suspension of enamino ketone **1** (1.60 g, 6.3 mmol) in 15 mL of anhydrous EtOH. The stirred reaction mixture was refluxed for 8 h, cooled, and neutralized with AcOH. The precipitate was filtered off, washed with water, dried *in vacuo*, and recrystallized from chloroform (1.33 g from 110 mL) to give pure aminopyrimidine **4** (0.80 g, 50%), m.p. 248—251 °C.

8-Methyl-3,5,6,11-tetrahydro-2*H*-pyrimido[4,5-*a*]carbazole-2-thione (5). A solution of EtONa prepared from Na metal (1.38 g, 60 mmol) and anhydrous EtOH (40 mL) was added to a mixture of enamino ketone **1** (5 g, 19.6 mmol) and thiourea (4.5 g, 59.2 mmol) in 50 mL of anhydrous EtOH. The stirred reaction mixture was refluxed for 2 h and worked up as described for compound **4** to give pyrimidinethione **5** (4.5 g, 78%), m.p. 318—322 °C (decomp.). Compound **5** was not purified because of its low solubility and thermal instability. MS, m/z (I_{rel} (%)): 267 $[M]^+$ (14), 240 $[M - HCN]^+$ (12).

2-Benzylthio-8-methyl-6,11-dihydro-5*H*-pyrimido[4,5-*a*]carbazole (6). A solution of MeONa prepared from Na metal (0.09 g, 4 mmol) and MeOH (3 mL) was added to a suspension of pyrimidinethione **5** (1.06 g, 3.9 mmol) in 15 mL of MeOH. The reaction mixture was stirred at 50 °C and benzyl chloride (0.6 g, 4.7 mmol) was added. The mixture was kept at 50 °C for 3 h and cooled. The precipitate that formed was filtered off, washed with water, and dried *in vacuo* to give a crude product (1.14 g, 80%). Recrystallization from chloroform (9 mL) gave benzylthiopyrimidine **6** (0.73 g, 52%), m.p. 154—157 °C.

1-(Dicyanomethylene)-6-methyl-2,3,4,9-tetrahydro-1*H*-carbazole (7). A mixture of ketone **2** (5.97 g, 30 mmol), malononitrile (2 g, 30 mmol), ammonium acetate (2.5 g, 32.5 mmol), and AcOH (5.94 g, 99 mmol) in 50 mL of toluene was stirred at 105 °C for 5 h. On cooling, the precipitate that formed was filtered off, washed with hexane (40 mL), and dried at 100 °C to give a crude product (6.7 g). Double recrystallization from dichloroethane gave compound **7** (4.5 g, 61%), m.p. 251—255 °C.

Cyano(6-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-ylidene)acetamide (8). A mixture of ketone **2** (30 g, 0.15 mol), cyanoacetamide (37.8 g, 0.45 mol), ammonium acetate (38.5 g, 0.5 mol), and AcOH (30 g, 0.5 mol) in 120 mL of toluene was stirred at 60 °C for 5 h. On cooling, the precipitate that formed was filtered off and routinely treated to give crude product **8** (37.3 g, 90%). Recrystallization from DMF (95 mL) gave compound **8** (23.5 g, 59%), m.p. 212—216 °C (decomp.).

***N*-(Dimethylaminomethylene)cyano(6-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-ylidene)acetamide (9).** A suspension of compound **8** (10 g, 37.7 mmol) and dimethylformamide dimethyl acetal (**3**) (8.8 g, 74 mmol) in 160 mL of MeCN was stirred at 35 °C for 1 h. The reaction mixture was cooled to 15 °C and the precipitate that formed was filtered off, washed with MeCN, and dried in a desiccator to give crude product **9** (9.96 g, 83%). Recrystallization from MeCN (160 mL) gave acylamidine **9** (5.6 g, 46%), m.p. 173—175 °C.

1-Cyano-8-methyl-3,5,6,11-tetrahydro-2*H*-pyrido[4,3-*a*]carbazol-2-one (10). A solution of compound **9** (3.5 g, 11 mmol) in 5 mL of *N*-methylpyrrolidone (NMP) was stirred at 155 to 160 °C for 1 h. The resulting suspension was cooled to 10 °C, diluted with MeCN (20 mL), and stirred for 10 min. The precipitate that formed was filtered off to give compound **10** (1.49 g, 49%). An analytically pure sample was obtained by recrystallization from chloroform, m.p. 372—374 °C (decomp.).

2-Chloro-1-cyano-8-methyl-6,11-dihydro-5*H*-pyrido[4,3-*a*]carbazole (11). ***A.*** A mixture of compound **10** (1 g, 3.6 mmol), triethylamine hydrochloride (0.66 g, 5.4 mmol), and $POCl_3$ (7 mL) was refluxed for 5 h. The reaction mixture was cooled and poured into ice. The precipitate was filtered off and dried. The product was extracted with boiling benzene and the extract was cooled, passed through a layer of L40/100 silica gel (7×3.5 cm), and concentrated to a minimum volume. The crystals that formed were filtered off to give compound **11** (0.64 g, 61%), m.p. 269—271 °C (decomp.).

B. A mixture of compound **9** (1 g, 3.1 mmol), triethylamine hydrochloride (0.56 g, 4.6 mmol), and $POCl_3$ (7 mL) was refluxed for 1 h. The reaction mixture was worked up as described in procedure ***A***. The yield of compound **11** was 0.1 g (11%), m.p. 269—271 °C (decomp.).

1-Cyano-2-methoxy-8-methyl-6,11-dihydro-5*H*-pyrido[4,3-*a*]carbazole (12). A solution of MeONa prepared from metallic Na (0.6 g, 26 mmol) and MeOH (11 mL) was added to a suspension of compound **11** (0.4 g, 1.3 mmol) in 4 mL of MeOH. The resulting suspension was refluxed for 6 h and then cooled to 15 °C. The precipitate that formed was filtered off, washed with water, dried, and recrystallized from benzene (7.5 mL) to give compound **12** (0.2 g, 54%), m.p. 218—220 °C.

1-Cyano-3,8-dimethyl-3,5,6,11-tetrahydro-2*H*-pyrido[4,3-*a*]carbazol-2-one (13). A mixture of compound **8** (1 g, 3.7 mmol) and dimethylformamide dimethyl acetal (10 mL) was refluxed for 6 h and then cooled to 15 °C. The precipitate that formed was filtered off, washed with MeCN (2 mL), and dried to give a crude product (0.85 g). Recrystallization from dichloroethane (70 mL) gave compound **13** (0.54 g, 46%), m.p. 304—307 °C.

The filtrate containing an excess acetal, MeCN, and other reaction products was evaporated to dryness *in vacuo*. The residue (0.3 g) was dissolved in benzene (30 mL) and the resulting solution was passed through a layer of L40/100 silica gel (1×3.5 cm). The solvent was removed in a rotary evaporator to give a mixture (0.12 g, 11%) of compound **12** and 1-cyano-2-methoxy-8,11-dimethyl-6,11-dihydro-5*H*-pyrido[4,3-*a*]carbazole (**14**) in the 55 : 45 ratio (^{1}H NMR data). MS, m/z (I_{rel} (%)): 303 $[M_1]^+$ (100), 289 $[M_2]^+$ (51).

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