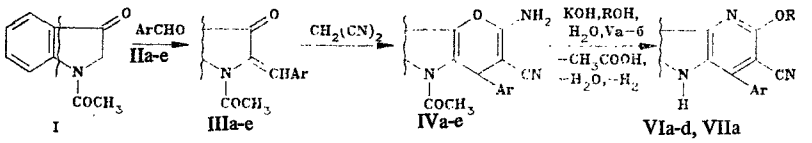
NEW METHOD OF SYNTHESIS OF δ-CARBOLINES FROM 3-INDOLINONE VIA PYRANO[3,2-b]INDOLES

V. S. Velzheva, K. V. Nevskii,
and N. N. Suvorov

UDC 547.756'828.07

2-Arylidene-1-acetylindolin-3-ones were obtained from 1-acetylindolin-3-ones and p-substituted benzaldehydes or 4-pyridinecarboxaldehyde, by the action of malonodinitrile, and were converted into 2-amino-4-aryl-5-acetyl-3-cyanopyrano[3,2-b]indoles. When heated with an aqueous-alcoholic solution of KOH, the latter compounds transform into 2-alkoxy-4-aryl-3-cyano-δ-carbolines. The possible paths of formation of δ-carbolines and pyrano[3,2-b]indoles are discussed.

There are very few known methods of synthesis of δ-carbolines, characterized by the formation of a pyridine ring at the concluding stage [1-5]. We have developed a new method for synthesizing δ-carbolines, starting from 1-acetylindolin-3-one (I), via 2-arylidene-1-acetylindolinones (IIIa-e) and pyrano[3,2-e]indoles (IVa-d).



III, IV, VI, VII a Ar = C_6H_5; III, IV, VI b Ar = p-Br-C_6H_4; c Ar = p-(i-C_3H_7)C_6H_4; d Ar = 4-pyridyl; III, IV e Ar = p-$NO_2C_6H_4$; Va, VIa–d R = CH_3; Vb, VIIa R = C_2H_5

The key stage of the method is the transformation of pyrans IVa-d into δ-carbolines VIa-d, VIIa, by the action of 5% KOH in primary alcohols Va,b. When pyrans IVa-d are heated with KOH or sodium ethylate only in water or in alcohol, then according to TLC data, 2-arylideneindolin-3-ones (indogenins) VIIIa-d are formed and not δ-carbolines. This process proceeds extremely slowly in alcohols. The same result is observed when the reaction is carried out in secondary alcohols, for example, in isopropanol, and not in primary ones. δ-Carbolines VIa-c, VIIa are formed in a yield of 30-60% from pyrans IVa-d with both electron-donor (i-C_3H_7) and electron-acceptor (Br) substituent in the benzene ring. Pyran IVe with p-nitrophenyl substituent, which does not transform into δ-carboline, is an exception.

δ-Carboline VIa was identified by the synthesis of the acetyl derivative IX. The characteristic feature of the PMR spectra of VIa-d, VIIa, like that of the previously synthesized δ-carbolines [3-5], is related to the presence of a doublet signal of 9-H in the 8.05-8.20 ppm region.

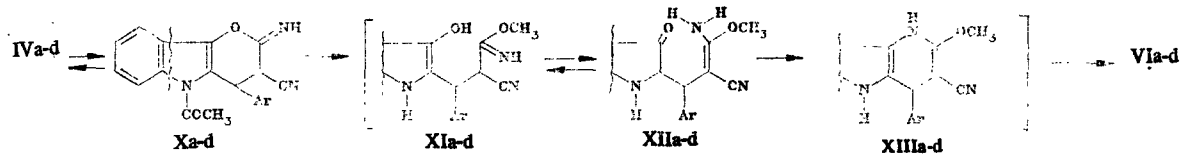
The formation of δ-carbolines VIa-d is explained by a reaction scheme including the stage of opening of the pyran ring, recyclization into dihydrocarbolines XIIIa-d, and dehydrogenation of the latter. The removal of the acetyl group can proceed in parallel with each of the above stages.

It is possible that the addition of alcoholate ions to pyrans IVa-d and subsequent ring opening are due to the existence of an enamine–imine equilibrium. It is quite understandable that iminopyrans Xa-d react with nucleophilic reagents similarly to α-pyrones [6,7], and not pyrans, for which an acid-catalyzed variant of ring opening is characteristic [8]. Whenever the addition of the alcoholate is hindered by the deprotonation process, as happens mainly in

D. I. Mendeleev Moscow Institute of Chemical Technology, Moscow 125047. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 230-235, February, 1985. Original article submitted February 15, 1984.

0009-3122/85/2102-0191$09.50

the case of "acidic" p-nitrophenylpyran IVe, δ-carboline is not formed

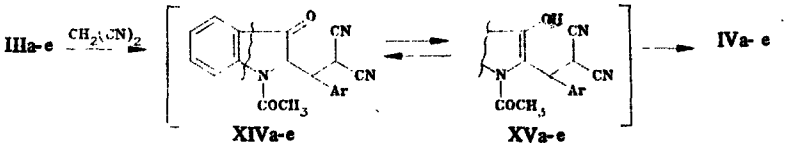


The enols formed after the addition of methanol to pyrans IVa-d isomerize into indolinones XIIa-d, which cyclodehydrate to form dihydrocarbolines XIIIa-d. The spontaneous dehydrogenation of the dihydropyridine ring was often noted in the course of the synthesis of δ-carbolines and quindolines [3-5, 9].

Diacetylindogenins IIIa-e, required for the synthesis of pyrans IVa-e, are readily formed for indolinone I and aldehydes IIa-e when benzene is heated in the presence of catalytic amounts of piperidine. The yields of compounds IIIa-e are 70-95%.

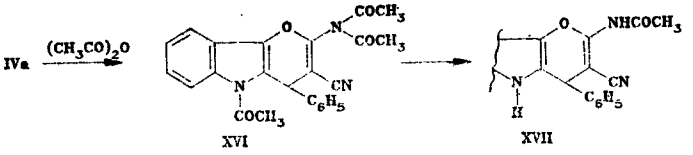
We obtained pyranoindoles IVa-e by a reaction carried out in one flask only from acetylindogenins IIIa-e and malonodinitrile in DMFA or in a mixture of alcohol with triethylamine. The yields of compounds IVa-e are 60-85%. In contrast to acetylindogenins IIIa-e, the deacetylated indogenins VIIIa-e do not enter the reaction under these conditions.

The most probable predecessors of pyrans IVa-e are dinitriles XIVa-e, whose analogs have already been obtained by the Michael reaction between NH and NCH_3 indogenins and malonodinitrile in alcohol in the presence of triethylamine [10]. In the case under consideration, the pyran ring is formed from anols XVa-e with the participation of the OH and CN groups.



It should be noted that formerly it was erroneously assumed that indogenins can, and indoxyl cannot, be used in the Knoevenagel condensation with CH acids [10]. As an example, the unsuccessful attempt has been cited to obtain a condensation product of malonodinitrile with indoxyl. It has so far been found that indogenins, regardless of the dependence on the character of the substituent at N(1) (H, alkyl, acyl), appear in this reaction as Michael acceptors, while indoxyl, certainly, in the form of a more stable N-acetyl derivative I, reacts with malonodinitrile and other CH acids via its carbonyl group [11, 12].

Pyran IVa was identified by the preparation of mono- and triacetyl derivatives (XVI, XVII).



Triacetate XVI is readily formed on short-term heating of pyran IVa with acetic anhydride in the presence of potassium acetate, without which the reaction proceeds slowly, but does not stop at the stage of the diacetate. Triacetate XVI deacetylates to monoacetate XVII by the action of 5% aqueous KOH in isopropanol at 20°C.

The PMR spectra of pyrans IVa-d and XVI, XVII are characterized by a singlet of the CH group in the 5.25-5.60 ppm range.

EXPERIMENTAL

The course of the reaction and the purity of the compounds obtained were controlled by the TLC method on Silufol UV-254. The IR spectra were run on a UR-10 spectrophotometer (in mineral oil); the UV spectra, on a Specord UV-VIs spectrophotometer (in alcohol); the PMR

TABLE 1. Characteristics of Components IIIa-e

Compound	mp,[a] deg C	IR spectrum, cm^{-1}		UV spectrum, λ_{max}, nm (log ε)	PMR spectrum, ppm			Found, %			M^+, mass-spectrometrically	Empirical formula	Calculated, %			Yield, %
		C=O	C=C		$COCH_3$[b] (s)	CH= (s)	CH, arom (m)	C	H	N			C	H	N	
IIIa	136—138	1710, 1690	1640	207 (4,54); 250 (4,41); 313 (4,35); 416 (3,53)	1,96	7,23	7,50—8,11	78,1	4,7	5,3	263	$C_{17}H_{13}NO_2$	77,6	4,9	5,3	85
IIIb	128—130	1730, 1690	1645	202 (4,45); 256 (4,23); 317 (4,20); 470 (3,70)	2,00	7,26	7,40—8,10	59,3	3,6	4,1	342	$C_{17}H_{12}BrNO_2$	59,6	3,5	4,1	88
IIIc[c]	87—90	1720, 1695	1640	204 (4,48); 253 (4,36); 325 (4,19); 400 (3,81)	1,97	7,40	7,30—8,57	78,9	6,5	4,8	305	$C_{20}H_{19}NO_2$	78,6	6,2	4,6	70
IIId	159—162	1720, 1705	1650	207 (4,53); 247 (4,18); 294 (4,27); 416 (3,53)	2,08	7,73	7,14—8,26	72,7	4,8	10,5	264	$C_{16}H_{12}N_2O_2$	72,7	4,6	10,6	96
IIIe	168—172	1720, 1690	1645	203 (4,41); 258 (4,16); 320 (4,27); 416 (3,53)	2,11	7,74	7,24—8,26	66,0	4,1	9,1	308	$C_{17}H_{12}N_2O_4$	66,2	3,9	9,1	80

[a]Compounds IIIa,d,e were crystallized from isopropanol; IIIb,c — from a benzene—petroleum ether mixture.
[b]Compounds IIIa,d — in DMSO-D_6; IIIb,c — in $CDCl_3$; IIIe — in acetone-D_6.
[c]PMR spectrum: 1.26 (d, CH_3); 3.25 ppm (q, CH).

TABLE 2. Characteristics of Compounds IVa-e

Compound	mp,[a] deg C	IR spectrum, cm^{-1}			UV spectrum, λ_{max}, nm (log ε)	PMR spectrum, ppm (in DMSO-D_6)				Found, %			M^+, mass-spectrometrically	Empirical formula	Calculated, %			Yield, %
		NH_2	C≡N	C=O		$COCH_3$ (s)	CH (s)	CH, arom. (m)	NH_2 (s)	C	H	N			C	H	N	
IVa	315	3215, 3380	2210	1700	206 (4,48); 241 (4,06)	2,48	5,24	6,70—7,40	6,78	73,1	4,9	11,5	329	$C_{20}H_{15}N_3O_2$	73,0	4,6	12,7	70
IVb	249—252	3210—3380	2210	1700	205 (4,53); 235 (4,36)	2,50	5,25	6,97—8,00	6,78	58,8	3,5	10,3	408	$C_{20}H_{14}BrN_3O_2$	58,8	3,4	10,3	76
IVc[b]	249	3190, 3450	2200	1700	204 (4,50); 238 (4,27)	2,72	5,45	7,17—8,31	6,86	74,3	5,7	11,2	371	$C_{23}H_{21}N_3O_2$	74,4	5,7	11,3	60
IVd	278	3180—3350	2200	1710	206 (4,47); 239 (4,35)	2,53	5,27	7,01—8,43	6,87	68,9	4,2	16,9	330	$C_{19}H_{14}N_4O_2$	69,1	4,2	17,0	85
IVe	252—254	3130, 3440	2200	1710	204 (4,47); 238 (4,31)	2,53	5,40	7,24—8,10	6,87	64,2	3,8	14,9	374	$C_{20}H_{14}N_4O_4$	64,2	3,7	15,0	87

[a]Compound IVa was crystallized from acetic acid, with decomposition; IVb — from dioxane, IVc,d — from isopropanol, IVe — from acetone.
[b]PMR spectrum: 3.20 (q, CH); 1.22 (d, CH_3).

TABLE 3. Characteristics of Compounds VIa-d and VIIa

Compound	mp,[a] deg C	IR spectrum, cm^{-1}		UV spectrum, λ_{max}, nm (log e)	PMR spectrum, ppm (in DMSO-D_6)			Found, %			M^+, mass-spectrometrically	Empirical formula	Calculated, %			Yield, %
		NH	C≡N		OCH_3 (s) or OC_2H_5 (q, t)	CH, arom. (m)	br.s	C	H	N			C	H	N	
VIa	307	3320	2235	208 (4,47); 3,26 (4,70); 339 (4,50); 396 (4,06)	4,14	7,20—8,16; 8,11 (d, 9-H)	11,10	76,2	4,3	14,0	299	$C_{19}H_{13}N_3O$	76,3	4,3	14,0	60
VIb	335	3360	2230	213 (3,86); 238 (3,94); 336 (3,74); 400 (3,24)	4,13	7,15—7,87; 8,11 (d, 9-H)	11,2	60,4	3,1	11,1	378	$C_{19}H_{12}BrN_3O$	60,3	3,2	11,1	50
VIc[b]	218	3270	2240	204 (4,47); 236 (4,58); 336 (4,40); 396 (3,88)	4,13	7,22—8,14; 8,11 (d, 9-H)	11,10	77,4	5,5	12,2	341	$C_{19}H_{22}N_3O$	77,4	5,6	12,3	25
VId	350	3330	2235	204 (4,00); 250 (4,06); 337 (3,67); 400 (3,40)	3,20	7,20—8,81; 8,11 (d, 9-H)	11,10	71,8	3,8	18,9	300	$C_{18}H_{12}N_4O$	72,0	4,0	18,7	35
VIIa	253—255	3360	2230	208 (4,48); 234 (4,60); 337 (4,38); 395 (3,85)	4,60; 1,46 $J_{CH_2CH_3}$ = =7,0 Hz	7,20—8,10; 8,10 (d, 9-H)	11,30	76,8	4,8	13,4	313	$C_{20}H_{15}N_3O$	76,7	4,8	13,4	60

[a]Compounds VIa and VIIa were crystallized from acetone, VIb — from acetone—DMFA mixture, VIc — from isopropanol, VId — from DMFA, with decomposition.

[b]PMR spectrum: 1.31 (d, CH_3); 3.05 ppm (q, CH).

spectra, on a CFT-20 spectrometer (working frequency 80 MHz, internal standard TMS). The mass spectra were run on an MKh-1303 mass spectrometer with direct introduction of the sample into the ionic source. Energy of ionizing electrons 50 eV, cathode emission current 1.25 mA.

General Method of Synthesis of N-acetylindogenins (IIIa-e). A mixture of 1.8 g (10 mmoles) of 1-acetylindolin-3-one (I), 12 mmoles of aldehydes IIa-e, and 5 drops of piperidine is boiled for 3.5 h with a Dean–Stark adapter. The solvent is evaporated, and the residue is crystallized after addition of ether. Indogenin IIIc is isolated by chromatography on silica gel (100 g), eluent — CCl_4 (Table 1).

2-Amino-4-aryl-5-acetyl-3-cyano-4H-pyrano[3,2-b]indoles (IVa-e). A. A mixture of 2 mmoles of acetylindogenin IIIa-e, 0.14 g (2.2 mmoles) of malonodinitrile, and 0.2 ml of triethylamine is boiled for 10 min (in the case of compound IIIb for 30 min, and of IIIc for 2.5 h) in 15 ml of isopropanol. The precipitate is filtered (Table 2).

B. Dry sodium ethylate, prepared from 0.3 g (13 mmoles) of sodium, is suspended in 90 ml of dry DMFA, and 0.9 g (13 mmoles) of malonodinitrile and 3.1 g (12 mmoles) of indogenin are added to the suspension. After 1 h the reaction mixture is neutralized with acetic acid. After 24 h, the precipitate is filtered and washed with water, the mother liquor is evaporated, the residue is washed with acetone, and the additional amount of the material isolated has the same melting point and IR spectrum as compound IVa obtained in experiment A. The overall yield of compound IVa is 2.8 g (70%).

5-Acetyl-2-diacetylamino-4-phenyl-3-cyano-4H-pyrano[3,2-b]indole (XVI). A mixture of 1 g (3 mmoles) of compound IVa, 25 ml of acetic anhydride, and 1 g (10 mmoles) of potassium acetate is boiled for 30 min, and the precipitate is filtered and washed with water. The mother liquor is evaporated, the residue is treated with water, and the precipitate is filtered and washed with alcohol. The overall yield of compound XVI is 1.1 g (85%), mp 203-205°C (from isopropanol). IR spectrum: 2230 (C≡N), 1750, 1725, 1830 cm^{-1} ($COCH_3$). PMR spectrum ($CDCl_3$): 2.42 (s, $2COCH_3$), 2.56 (s, $COCH_3$); 5.61 (s, CH); 7.25-9.20 ppm (m, CH, arom.). Found: C 70.1; H 5.0; N 10.1%. M^+ 413. $C_{24}H_{19}N_3O_4$. Calculated: C 69.7; H 4.6; N 10.2%; M 413.

2-Acetylamino-4-phenyl-3-cyano-4H-pyrano[3,2-b]indole (XVII). A mixture of 0.41 g (1 mmole) of triacetate XVI, 20 ml of isopropanol, and 5 ml of 5% KOH is stirred for 45 min at room temperature. The mixture is neutralized by 5% HCl, the solvent is evaporated, the residue is treated with water, and the precipitate is filtered. The yield of compound XVII is 0.31 g (95%), mp 253-255°C (from toluene). IR spectrum: 3240 (NH), 2230 (C≡N), 1710 cm^{-1} ($COCH_3$). UV spectrum, λ_{max} (log ε): 230 (4.73); 278 nm (4.15). PMR spectrum (acetone-D_6): 2.17 (s, $COCH_3$); 5.27 (s, CH, aliph.); 7.00-7.50 (m, CH, arom.); 9.40; 10.00 ppm (s, NH). Found: C 73.3; H 4.6; N 12.7%; M^+ 329. $C_{20}H_{15}N_3O_2$. Calculated: C 73.0; H 4.6; N 12.8%; M 329.

4-Aryl-2-methoxy-3-cyano-δ-carbolines (VIa-d) and 4-phenyl-3-cyano-2-ethoxy-δ-carboline (VIIa). A mixture of 0.5 g of compound IVa-d, 2 ml of 20% KOH, and 10 ml of methanol or ethanol is boiled for 3-5 h. The precipitate is filtered and washed with water (Table 3).

5-Acetyl-2-methoxy-4-phenyl-3-cyano-δ-carboline (IX). A mixture of 0.3 g (1 mmole) of compound VIa and 0.3 g (3 mmoles) of potassium acetate in 10 ml of acetic anhydride is boiled for 1 h. The solvent is evaporated, the residue is treated with water, and the precipitate is filtered. The yield of compound IX is 0.3 g (88%), mp 217-219 (from methanol). IR spectrum: 2230 (C≡N), 1720 cm^{-1} ($COCH_3$). UV spectrum, λ_{max} (log ε); 208 (4.03); 263 (3.77); 328 (3.83); 366 nm (3.56). PMR spectrum (DMSO-D_6): 1.83 (s, $COCH_3$); 4.18 (s, OCH_3); 7.40-8.20 (m, CH, arom.); 8.10 ppm (d, 8H). Found: C 74.0; H 4.1; N 12.3%; M^+ 341. $C_{21}H_{14}N_3O_2$. Calculated: C 73.9; H 4.1; N 12.3%; M 341.

LITERATURE CITED

1. O. N. Boyarintseva, G. N. Kurilo, O. S. Anisimova, and A. N. Grinev, Khim. Geterotsikl. Soedin., No. 1, 82 (1977).
2. G. N. Kurilo, O. N. Boyarintseva, and A. N. Grinev, Inventor's Certificate, No. 546616, Byull. Izobret., No. 6, 74 (1977).
3. V. S. Velezheva, A. V. Yarosh, T. A. Kozik, and N. N. Suvorov, Zh. Org. Khim., 14, 1712 (1978).
4. N. N. Surorov, V. A. Chernov, V. S. Velezheva, Yu. A. Ershova, S. V. Simakov, and V. P. Sevodin, Khim.-Farm. Zh., No. 9, 27 (1981).
5. V. P. Sevodin, V. S. Velezheva, and N. N. Suvorov, Khim. Geterotsikl. Soedin., No. 3, 368 (1981).

6. A. N. Kost and A. P. Terent'ev, Zh. Obshch. Khim., 26, 1992 (1956).
7. P. Waykole and R. N. Usgaonkar, Indian J. Chem., A21, 272 (1982).
8. R. Elderfield (ed.), Heterocyclic Compounds [Russian translation], Vol. 1, Inostr. Lit., Moscow (1953), p. 273.
9. V. P. Sevodin, V. S. Velezheva, and N. N. Suvorov, Khim. Geterotsikl. Soedin., No. 8, 1125 (1982).
10. R. W. Daisley and Z. A. Elagbar, J. Heterocycl. Chem., 19, 1013 (1982).
11. C. D. Nenitzescu and D. Raileanu, Chem. Ber., 91, 1141 (1958).
12. V. S. Velezheva, V. P. Sevodin, Yu. V. Erofeev, N. K. Genkina, T. A. Kozik, V. V. Vampilova, and N. N. Suvorov, Khim. Geterotsikl. Soedin., No. 3, 360 (1977).

INDOLOBENZOTHIOPHENES.

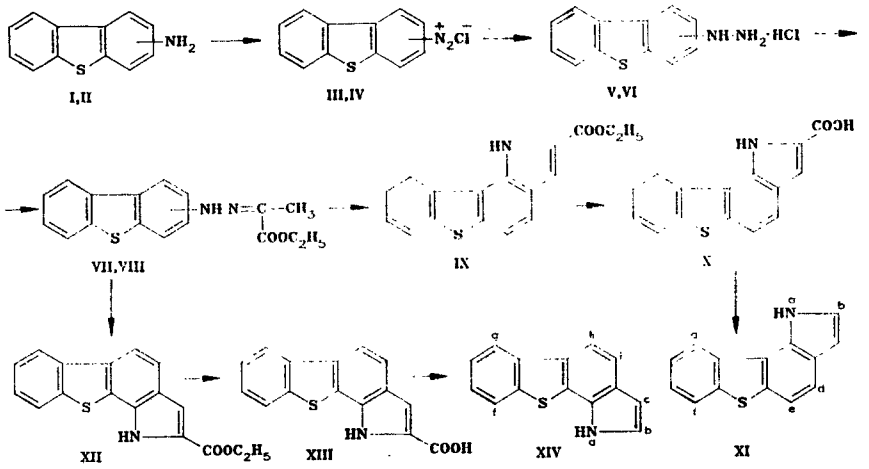
3.* SYNTHESIS AND PROPERTIES OF INDOLO[7,6-d]- AND INDOLO[6,7-d]BENZO[b]THIOPHENES

T. E. Khoshtariya, L. N. Kurkovskaya,
L. N. Kulesheva, and N. N. Suvorov

UDC 547.736'759.4.07:543.422

Precursors of a new heterocyclic system, indolo[7,6-d]- and indolo[6,7-d]benzo[b] thiophenes, have been synthesized using the Fischer reaction. Some physicochemical characteristics of the compounds are reported.

Continuing our research into tetracyclic compounds with a pyrrole ring system [1], we have synthesized some previously unreported isomeric indolobenzo[b]thiophenes using the Fischer reaction:



The 1- and 4-aminobenzothiophenes were used as starting compounds; 1-aminodibenzothiophene (I) was synthesized by the reduction of 1-nitrodibenzothiophene, obtained from 2-aminodibenzothiophene [2]. The reaction of the lithium derivative of dibenzothiophene with O-methylhydroxylamine [3] gave 4-aminodibenzothiophene (II). Compounds I and II were converted via the diazonium salts III and IV to the corresponding hydrazine hydrochlorides V, VI, which on treatment with ethyl pyruvate gave the hydrazones VII and VIII. Examination by TLC

*Communication 2, see [1].

I. G. Kutateladze Institute of Pharmaceutical Chemistry, Academy of Sciences of the Georgian SSR, Tbilisi.380059. D. I. Mendeleev Moscow Institute of Chemical Technology, Moscow 125047. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 236-240, February, 1985. Original article submitted January 2, 1984; revison submitted June 18, 1984.

 0009-3122/85/2102-0196$09.50