SYNTHESIS AND REACTIONS OF 7-α-CYANOALKYLINDOLINES

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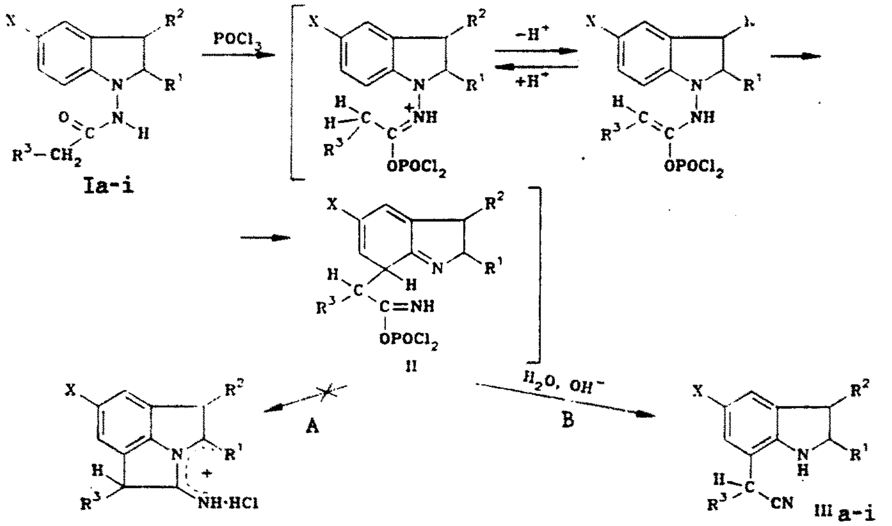
In the presence of phosphorus oxychloride N-acylaminoindolines rearrange to 7-α-cyanoalkyl(aralkyl)indolines. These have been converted to the corresponding amines, acids, and indoles.

It is known that β-arylhydrazides are heterocyclized to 2-aminoindoles in the presence of phosphorus halides (the Kost reaction) [1]. We have previously shown that phosphorus oxychloride reacts with N-acylaminotetrahydroquinolines to give the novel tricyclic 5-aminolilolidines [2]. In the present study we chose the N-acylaminoindolines Ia-i whose synthesis and structures have been reported in [3]. N-acylaminoindoles Ia-i react with phosphorus oxychloride in absolute dioxane to give the ortho-aminobenzylcyanides IIIa-i in 45-70% yields. Evidently compounds I react via the Kost mechanism but the expected tricyclic structure analogous to that obtained earlier for N-acylaminotetrahydroquinolines (route A) is not realized. The intermediate II instead yields the nitriles III (Table 1).



Compound*	R¹	R³	Compound*	R¹	R³	Compound*	R¹	R³
Ia, IIIa	H	CH_3	Id, IIId	H	Ph	Ig, IIIg	Ph	CH_3
Ib, IIIb	H	Ph	Ie, IIIe	CH_3	CH_3	Ih, IIIg	Ph	Ph
Ic, IIIc	H	$(CH_2)_5$	If, IIIf	CH_3	Ph	Ii, IIIg	CH_3	Ph

*I, IIIa-h $R^2 = H$, i $R^2 = CH_3$; a-c, e-i X = H, d X = Br; II $R^1 = R^2 = X = H$, $R^3 = CH_3$.

This conversion is a further convincing confirmation of the Kost rearrangement scheme proposed earlier by us [4]. The synthesized compounds III have an independent synthetic interest as starting materials for less readily available 7-substituted indoles.

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TABLE 1. Characteristics for Compounds IIIa-i

Compound	Empirical formula	mp, °C	IR spectrum, ν, cm^{-1}*1		PMR spectrum, δ, ppm (J, Hz)*2		
			CN	NH	R^1, 2-H	R^2, 3-H	R^3
IIIa	$C_{11}H_{12}N_2$	Oil	2240	3420	3,55 (2H, t, J=8,00)	3,15 (2H, t, J=8,00)	1,50 (3H, d J=6,00)
IIIb	$C_{16}H_{14}N_2$	Oil	2240	3400	3,55 (2H, t, J=8,00)	3,15 (2H, t, J=8,00)	6,50 . . . 7,50 (5H, m)
IIIc	$C_{15}H_{19}N_2$	83 . . . 84	2230	3415	3.55 (2H, t, J=8,00)	2,95 (2H, t, J=8,00)	1,30 . . . 2,40 (10H, m)
IIId	$C_{16}H_{13}BrN_2$	123 . . . 124	2235	3415	3.50 (2H, t, J=8,00)	2,95 (2H, t, J=8.00)	7.00 . . . 7,50 (5H, m)
IIIe	$C_{12}H_{16}N_2$	Oil	2235	3390	1,04 (d, J=6.54)*3; 1,06 (d, J=7,51): 3,80 (1H, m)	2,36 (1H, m); 2,91 (1H, m)	1,30 (d, J=7,14)*3; 1,33 (d, J=7.14)
IIIf	$C_{17}H_{16}N_2$	Oil	2250	3395	0,97 (t J=6,17)*3; 0,98 (d, J=6,12); 3,75 (1H, m)	2,37 (1H, d.d, J_{gem}==16,00; J_{23}=9,00); 2,90 (1H, d.d J_{gem}==15,70; J_{23}=8,75)	7,03 . . . 7,30 (5H, m)
IIIg	$C_{17}H_{16}N_2$	Oil	2240	3400	7,00 . . . 7,28 (5H, m); 4,80 (t, J==9,20)*4; 4,82 (t, J=9,20)	2.68 (1H, 2 d. d); 3,275 (1H, 2 d.d, J_{gem}=15,67; J_{25}=9,30)	1,385 (d J=7.17)*3; 1,390 (d, J=7,17)
IIIh	$C_{22}H_{18}N_2$	98 . . . 100	2240	3375	7,20 . . . 7,50 (5H, m); 4,96 (1H, t, J=9,50)	2,88 (1H, d.d J_{gem}==15,96; J_{23}=9,00); 3,49 (1H, d.d, J_{gem}==15,96; J_{25}−9,30)	7,20 . . . 7,50 (5H m)
IIIi	$C_{13}H_{18}N_2$	173 . . . 174	2220	3450	1,022 (d, J=6,61); 1,033 (d, J=6,63); 3,91 (1H, m)	1,12 (d, J=1,16)*3; 1,16 (d, J=7,16); 3,22 (1H, m)	7,31 . . . 7,44 (5H, m)

TABLE 1. (continued)

Compound	Empirical formula	mp, °C	IR spectrum, ν, cm^{-1}*1		PMR spectrum, δ, ppm (J, Hz)*2				Yield, %
			CN	NH	7'-CH	5-H	4-H, 6-H	NH (1H)	
IIIa	$C_{11}H_{12}N_2$	Oil	2240	3420	3,80 (1H, m)	6,60 . . . 7,30 (3H, m)		3,90 s	44
IIIb	$C_{16}H_{14}N_2$	Oil	2240	3400	5,20 (1H, s)	6,50 . . . 7,50 (3H, m)		3,95 s	56
IIIc	$C_{15}H_{19}N_2$	83 . . . 84	2230	3415	—	6,30 . . . 7,50 (3H, m)		4,30 s	70
IIId	$C_{16}H_{13}BrN_2$	123 . . . 124	2235	3415	5,00 (1H, s)	7,00 . . . 7,50 (3H, m)		5,30 s	56
IIIe	$C_{12}H_{16}N_2$	Oil	2235	3390	3,82 (1H, m)	6,41 (1H, t, J=7,40)	6,77 (1H, m, 4-H); 6,81 (1H, m, 6-H)	4,73 s	55
IIIf	$C_{17}H_{16}N_2$	Oil	2250	3395	5,22 (1H, s)	6,44 (1H, t, J=7,60)	6.80 (2H, d, J=7,51)	4,65 s	50
IIIg	$C_{17}H_{16}N_2$	Oil	2240	3400	3.95 (1H, m)	6.50 (1H, t J=7,56)	6.905 (1H, d.d, J_{45}=7,76, 4-H); 6,809 (1H, d.d, J_{56}=7,41, 6-H)	5,21 s	57
IIIh	$C_{22}H_{18}N_2$	98 . . . 100	2240	3375	5,56 (1H, s)	6,71 (1H, t, J=7,36)	7,037 (1H, d. J=7,12, 6-H); 7,025 (1H, d, J=7,12, 4-H)	5,25 s	71
IIIi	$C_{13}H_{18}N_2$	173 . . . 174	2220	3450	5,441 s*4; 5,467 s	6,699 (t, J=7,71)*4; 6,705 (t, J=7,60)	7,07 (1H, m, 4-H); 7,035 (1H, d.d J_{56}=7,36; J_{46}=1610, 6-H)	4,70d	47

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*In Vaseline mull.

**PMR spectra for IIIa-c in $CDCl_3$, IIId in CD_2Cl_2, IIIe-i in $(CD_3)_2CO$.

***Integrated intensity of 3H for the doubled set of signals.

****Integrated intensity of 1H for the doubled set of signals.

TABLE 2. ^{13}C NMR Spectra of IIIe-i

Compound	Chemical shift, ppm										
	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	$C_{(8)}$	$C_{(9)}$	2-CH_3	$C_{(7')}$	7'-CN	7'-CH_3
IIIe	55,538; 55,801	29,827	124,521	118,676	125,272; 125,154	117,659; 117,596	149,027; 149,157	129,984; 130,133	22,629; 22,484	38,235; 38,325	121,869	19,211; 19,095
IIIf	55,443; 55,837	29,825	124,970; 124,851	118,693	126,734; 126,649	116,394	149,380; 149,530	130,199; 130,454	22,615; 22,470	38,080; 38,190	119,896	—
IIIg	63,558; 63,774	29,807; 29,807	124,593; 124,548	119,320	125,731; 125,659	117,899; 117,147	149,330	129,473; 129,547	—	40,173	122,036	19,311; 19,233
IIIh	63,141	29,706	124,957; 124,877	119,197	126,863; 126,494	116,446	149,588	128,902	—	38,427	119,892	—
IIIi	58,989	29,808	124,150; 124,079	119,028; 119,062	126,895; 126,855	116,577; 116,501	148,829; 148,909	128,542	16,295	39,965; 39,991	120,063	—

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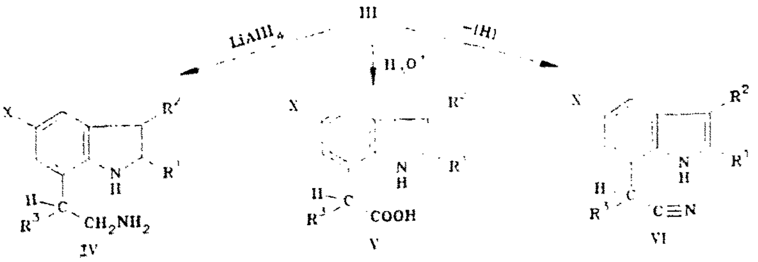
*13.616 and 13.863 ppm (3-CH_3).

The IR spectra of the ortho-aminobenzylcyanides show characteristic nitrile (2240) and amino group (3400 cm^{-1}) absorptions. The PMR spectra show the absence of the acyl residue signals of Ia-i and the presence of signals for the protons of the benzene 7-substituent. There is also a change in the appearance of the aromatic ring signals in line with the altered substitution of the ring. Examples of the Kost rearrangement are known in which not the ortho- but the para-aminobenzylcyanides are formed, i.e., the substituent occurs at position 5 in the benzene ring [5]. However, the high-resolution PMR signals for the aromatic protons of IIIe-i show that the 5 position is free. In particular, the 5-H proton is seen as a characteristic triplet at 6.4-6.7 ppm with an intensity of one proton.

The presence of a substituent in position 2 of the indole (IIIe-h) or in positions 2 and 3 (IIIi) means that 2 or 3 asymmetric centers are present in the molecule leading to a substantial mixture of diastereomers. Their high resolution PMR spectra show doubling of the signals (ratio 1:1) for some protons, e.g., the protons of 2-CH_3, 7-CH_3, and 7-CH and 2-H, 3-H, and 5-H in certain compounds. In the ortho-aminobenzylcyanides IIIe-i the 3-H^a and 3-H^b protons are diastereotopic and differ in their ^{13}C NMR spectra by about 0.5 ppm. The ^{13}C NMR spectra also show doubling of practically all of the carbon atom signals (see Table 2).

The ortho-aminobenzylcyanides are of interest not only as alternative Kost reaction products (which thus confirm the previously proposed scheme) but also as synthons for 7-aminoalkyl(aralkyl)indolines, 7-carboxyalkyl(aralkyl)indolines, and 7-α-cyanoalkyl(aralkyl)indoles. Preparation of these by other methods is almost impossible.



Reduction of III with lithium aluminum hydride to the corresponding 7-aminoalkyl(aralkyl)indolines IV goes in quantitative yield. Hydrolysis of the ortho-aminobenzylcyanides occurs in dilute hydrochloric acid in a sealed ampul to form the 7-carboxyalkyl(aralkyl)indolines V. The greatest interest is in the synthesis of the 7-α−cyanoalkyl(aralkyl)indoles VI which, in turn, can be used in the preparation of variously substituted indoles.

EXPERIMENTAL

Infra-red spectra were measured on a UR-20 instrument using Vaseline and hexachlorobutadiene mulls. ^{1}H and ^{13}C NMR spectra were measured on Tesla BS-467A (60 MHz) and VXR 300 (300 MHz) instruments with HMDS internal standards. Mass spectra were recorded on a Finnigan MAT 112 S instrument. The purity of the synthesized materials was monitored by TLC on Silufol UV-254 plates in the system hexane-ethyl acetate. The eluent ratio was selected individually for each substrate.

Elemental analytical data for C, H, and N agreed with that calculated. The structures of Va, b and VIe, i were also confirmed by mass spectrometry.

N-Propionylamino-2-phenyl-2,3-dihydroindole (Ig, $C_{17}H_{18}N_2O$) was obtained by the method described in [3] in 80% yield as white crystals with mp 143-144°C. IR spectrum: 1680 (CO), 3250 cm^{-1} (NH). PMR spectrum (in $CDCl_3$): 1.00 (3H, t, J = 8.5, CH_3); 2.03 (2H, q, J = 8.5, CH_2); 3.30 (2H, m, 3-H); 4.60 (1H, m, 2-H); 6.50-7.60 ppm (10H, m, arom + NH protons).

7-α-Cyanoalkyl(aralkyl)-2,3-dihydroindoles IIIa-i. Phosphorus oxychloride (2 mmoles) was added to a solution of the corresponding N-acylaminoindoline I (1 mmole) in absolute dioxane and heated for 2 h. After cooling, the solution was made alkaline with dilute NaOH (pH 8-9), extracted with benzene, and dried with Na_2SO_4. The oil remaining after distillation of solvent was purified by flash chromatography on a Silpearl grade silica gel column using hexane-ethyl acetate. Compounds IIIa, b, e remained as oils, unstable to storage and thus hindering measurement of elemental analytical data. They were therefore isolated as the acetyl derivatives III'a, b, e and were obtained by acylation of the corresponding ortho-aminobenzylcyanides with acetyl chloride in the presence of triethylamine. The melting points were 85-86, 115-116, and 152-153°C, respectively.

7-Aminoalkyl(aralkyl)-2,3-dihydroindoles (IVa, b) were obtained using a reported method [6] by reduction of IIIa, b with lithium aluminum hydride in benzene in the presence of triethylbenzylammonium chloride. **Amine IVa**

($C_{11}H_{16}N_2 \cdot 2HCl$) was isolated as the dihydrochloride from dry ether using an alcoholic solution of HCl [white crystals, mp 187-189°C (decomp.), quantitative yield]. IR spectrum: 2900 cm^{-1} (NH). PMR spectrum (in DMSO-D_6): 1.30 (3H, d, J = 8 Hz, 7'-CH_3); 3.30 (2H, t, J = 7.5 Hz, 3-H); 3.75 (2H, t, J = 7.5 Hz, 2-H); 4.60 (1H, br.q, 7'-CH); 7.32 (3H, m, arom. protons); 7.70 ppm (3H, br.s, NH). **Amine IVb ($C_{22}H_{24}N_2O_3$)** was obtained as the triacetyl derivative by acylation of the starting 7-aminoaralkylindoline with excess acetyl chloride in the presence of triethylamine (yield 80%, white crystals, mp 140°C, from benzene/pentane). IR spectrum: 1660, 1690, 1710 cm^{-1} (CO). PMR spectrum (in $CDCl_3$): 2.15 (9H, m, $COCH_3$); 2.90 (2H, t, J = 7 Hz, 3-H); 3.75 (2H, t, J = 7 Hz, 2-H); 4.45 (2H, d, J = 7 Hz, 7'-CH_2); 5.05 (1H, m, 7'-CH); 6.80-7.30 ppm (8H, m, arom. protons).

7-Carboxyalkyl(aralkyl)-2,3-dihydroindoles (Va, b) were obtained by heating the corresponding compound III for 2 h with dilute hydrochloric acid in a sealed ampul at 150°C. After evaporation of water the crystalline hydrochloride was washed with acetone to give Va ($C_{11}H_{13}NO_2 \cdot HCl$) in 42% yield as white crystals with mp 210-212°C (decomp.). IR spectrum: 1710 (COOH), 2900 cm^{-1} (NH). PMR spectrum (in D_2O): 1.00 (3H, d, J = 8 Hz, 7'-CH_3); 2.80 (2H, t, J = 7.5 Hz, 3-H); 3.50 (2H, t, J = 7.5 Hz, 2-H); 5.05 (1H, m, 7'-CH); 6.95 ppm (m. arom. protons). Mass spectrum: M^+: 192. Vb ($C_{16}H_{15}NO_2 \cdot HCl$) was obtained in 48% yield as white crystals with mp 225-227°C (decomp.). IR spectrum: 1720 (COOH), 3000 cm^{-1} (NH). PMR spectrum (in CD_3OD): 3.95 (2H, t, J = 8 Hz, 3-H); 4.35 (2H, t, J = 8 Hz, 2-H); 5.30 (1H, s, 7'-CH); 7.35 ppm (8H, m, arom. protons). Mass spectrum: $M^{+\cdot}$ 254.

7-α-Cyanoalkyl(aralkyl)indoles (VIa, e, i) were obtained by a known method [7] by refluxing the corresponding indolines in xylene with chloranil. Flash chromatography on a Silpearl silica gel column using hexane-ethyl acetate (3:1) gave indole VIa ($C_{11}H_{10}N_2$) in 52% yield as white crystals with mp 102-103°C. IR spectrum: 2240 (CN), 3380 cm^{-1} (NH). PMR spectrum (in $CDCl_3$): 1.60 (3H, d, J = 8 Hz, 7'-CH_3); 4.00 (1H, q, J = 8 Hz, 7'-CH); 6.15-7.45 (5H, m, arom. protons); 8.4 ppm (1H, br.s, NH). VIe ($C_{18}H_{16}N_2$) in 45% yield as a colorless oil. IR spectrum: 2240 (CN), 3380 cm^{-1} (NH). PMR spectrum (in $CDCl_3$): 1.55 (3H, d, J = 8 Hz, 7'-CH_3); 2.25 (3H, s, 2-CH_3); 4.00 (1H, q, J = 8 Hz, 7'-CH); 6.15-7.45 (4H, m, arom. protons); 8.40 ppm (1H, br.s, NH). Mass spectrum: $M^{+\cdot}$ 184. VIi ($C_{18}H_{16}N_2$) in 43% yield as a light yellow oil. IR spectrum: 2240 (CN), 3390 cm^{-1} (NH). PMR spectrum (in $CDCl_3$): 2.15 (6H, s, 2-CH_3, 3-CH_3); 4.95 (1H, s, 7'-CH); 6.75-7.15 (8H, m, arom. protons); 7.30 ppm (1H, br.s, NH). Mass spectrum $M^{+\cdot}$ 260.

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