3-INDOLYLPHENYLACETONITRILES

N. A. Kogan

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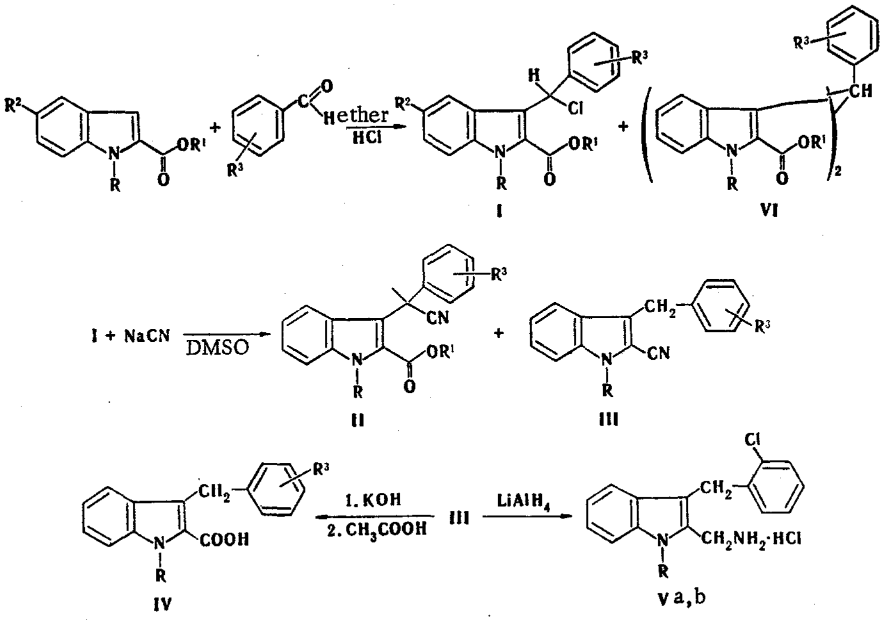
The reaction of 2-carbethoxyindole with aromatic aldehydes in ether saturated with HCl gave 2-carbethoxy-3-(α-chlorobenzyl)indoles. Reaction of the latter with sodium cyanide in dimethyl sulfoxide gave 3-indolylphenylacetonitriles in 47-85% yields. If the indole NH group is substituted, rearrangment to give 1-methyl-2-cyano-3-benzylindoles occurs simultaneously. The latter were reduced with $LiAlH_4$ to aminomethyl derivatives and were hydrolyzed with KOH in ethylene glycol to 1-methyl-3-benzylindole-2-carboxylic acids. The structures were proved by the UV, IR, and PMR spectra.

3-Indolylphenylacetonitriles are starting compounds for the preparation of phenyl-substituted heteroauxins [1], tryptamines, and β-carbolines [2]. However, the known methods for their synthesis are multistep processes [3] and require severe conditions [2]. Our goal was to develop a method for the preparation of 3-indolylphenylacetonitriles (II) via the scheme



V a $R=CH_3$; b $R=CH_2C_6H_5$

We have previously shown [4] that aromatic aldehyde smoothly add N-alkylindole-2-carboxylic acids to the C=O bond in the presence of HCl to give 1-alkyl-3-(α-chlorobenzyl)indole-2-carboxylic acids (Ie, f, Table 1). Nitrogen-unsubstituted indole-2-carboxylic acid esters also form the corresponding 2-carbethoxy-3-(α-chlorobenzyl)indoles (Ia-d, Table 1) in high yields. When this reaction is carried out in a refluxing mixture of hydrochloric acid and ethanol, it leads exclusively to the formation of bis(2-carbethoxy-3-indolyl-phenylmethanes (VI) [5], which are formed only as impurities in 5-15% yields in the preparation of Ia-d in ether saturated with HCl at 0-5°C. The action of NaCN in dimethyl sulfoxide (DMSO) on I converted them to 3-indolylphenylacetonitriles II (Ie → IId, If → IIg, and Ia → IIe). Compounds IIa-c were obtained by the same method from the corresponding "chlorides" described in [4]. The IR spectra of IIa-g contain bands of stretching vibrations of C=O (1675-1690 cm^{-1}) and C≡N (2250-2270 cm^{-1}) groups.

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TABLE 1. 3-(α-Chlorobenzyl)indole-2-carboxylic Acid Derivatives (Ia-f)

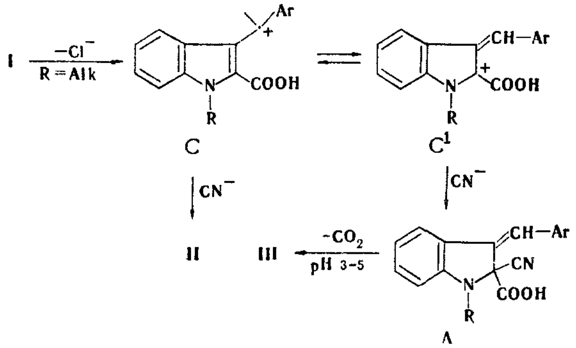
Compound	R	R^1	R^2	R^3	mp, °C	Found, %		Empirical formula	Calc. %		Yield, %
						Cl	N		Cl	N	
Ia	H	C_2H_5	H	o-Cl	148—149	19,8	3,9	$C_{18}H_{15}Cl_2NO_2$	20,2	4,0	80
Ib	H	C_2H_5	Cl	o-Cl	156—157	26,9	3,4	$C_{18}H_{14}Cl_3NO_2$	27,0	3,7	75
Ic	H	C_2H_5	Cl	p-NO_2	170—171	17,6	7,3	$C_{18}H_{14}Cl_2N_2O_4$	18,0	7,2	85
Id	H	C_2H_5	OCH_3	o-Cl	145—147	18.8	3,4	$C_{19}H_{17}Cl_2NO_3$	18,6	3,7	90
Ie	CH_3	H	H	p-NO_2	146—148	9.7	7,7	$C_{17}H_{13}ClN_2O_4$	10,3	8,1	90
If	$C_6H_5CH_2$	H	H	o-Cl	138—139	16,8	4,6	$C_{23}H_{17}Cl_2NO_2$	17,3	3,4	89

The ester group in IIe is readily saponified by alcoholic alkali to give carboxylic acid IIf. Signals of aromatic protons (7.3 ppm, 8H), an NCH_3 group (s, 3.93 ppm, 3H), and a lone benzyl proton (s, 6.85 ppm, 1H) are observed in the PMR spectrum of IIb in $(CD_3)_2SO$. The position of λ_{max} and the molar extinction [λ_{max} 295-297 nm (log ε 4.20-4.35)] that are characteristic for 1-methylindole-2-carboxylic acid [λ_{max} 296 nm (log ε 4.16)] are retained in the UV spectrum of IIa-d. The simplicity of the experimental method and the yields (45-85%) make this method a convenient one for the synthesis of 3-indolylphenylacetonitriles.

In the preparation of IIa-d, g compounds with neutral character, for which a 1-alkyl-2-cyano-3-benzylindole structure (IIIa-e, Table 3) was proposed on the basis of their chemical properties, UV, IR, and PMR spectra and the identical character of one of them (IIIb) and the previously described [6] 1-methyl-2-cyano-3-(o-chlorobenzyl)indole, were isolated from the reaction mixtures in 10-50% yields.

The PMR spectrum of IIIe contains NCH_2 (s, 5.68 ppm, 2H), CH_2 (s, 4.50 ppm, 2H), and aromatic proton (7.2-7.4 ppm, 13H) signals. An intense band of a C≡N group bonded to an aromatic ring [8] is observed in the IR spectra of IIIa-d; carbonyl absorption is not observed. A bathochromic shift of the absorption maximum as compared with the UV spectrum of 1-methyl-2-cyanoindole [λ_{max} 284 nm (log ε 4.504)] is observed in the UV spectrum of 2-cyano-3-benzylindoles (III, Table 3) because of inclusion of an electron-donor substituent (a benzyl group) in the indole ring.

Compounds III are formed at the same time as II, since the conversion of II to III was not observed in special experiments that reproduce the conditions of the reaction of "chlorides" I with NaCN. The formation of nitriles II and III proceeds with the participation of carbonium ion C. Migration of the charge to the α position of indole (C^1), which is similar to allylic rearrangement, makes this position sensitive to nucleophilic reagents.



Attack on the benzyl carbon atom by the cyanide ion leads to the formation of normal substitution product II, whereas attack on the α-carbon atom of indole leads to rearrangement product III (after decarboxylation). The cyclic derivative (A) of cyanoacetic acid is stable in aqueous solution when R = $CH_2C_6H_5$ at pH 9-10 and undergoes decarboxylation only on acidification, in contrast to the N-methyl derivatives, which are extracted by chloroform and ether from alkaline solutions. A rearrangement product was not detected in the preparation of IIe from Ia, probably because of the low stability of cation C^1 when R = H.

We have previously described [6] the preparation of IIIb in 85% yield from 1-methyl-2-carbomethoxy-3-(α-acetoxy-o-chlorobenzyl)indole by the action of NaCN in aqueous ethanol. Such a high yield as compared with the replacement of chlorine (15% yield) in 1-methyl-2-carboxy-3-(α-chloro-o-chlorobenzyl)indole by a cyano group under the same conditions is due

TABLE 2. 3-Indolylphenylacetonitriles (IIa-g)

Compound	R	R^1	R^3	mp, °C	Spectra		Found, %		Empirical formula	Calc. %		Yield, %
					IR, cm^{-1}	UV, λ_{max}, nm (lg ε)	Cl	N		Cl	N	
IIa	CH_3	H	H	245—247	1685 2250	295 (4,20)	—	9,6	$C_{18}H_{14}N_2O_2$	—	9,6	70
IIb	CH_3	H	o-Cl	212—214	1675 2250	295 (4,30)	10,8	8,5	$C_{18}H_{13}ClN_2O_2$	11,0	8,6	58
IIc	CH_3	H	p-NO_2	197—198	1680 2260	297 (4,35)	—	12,3	$C_{18}H_{13}N_3O_4$	—	12,5	45
IId	CH_3	H	m-NO_2	205—207	1675 2270	297 (4,20)	—	12,4	$C_{18}H_{13}N_3O_4$	—	12,5	47
IIe	H	C_2H_5	o-Cl	166—168	1690 2250	—	10,1	8,2	$C_{19}H_{15}ClN_2O_2$	10,5	8,3	85
IIf	H	H	o-Cl	235—238	—	—	11,3	8,9	$C_{17}H_{11}ClN_2O_2$	11,5	9,0	87
IIg	$C_6H_5CH_2$	CH_3	o-Cl	145—148	—	—	8,8	6,8	$C_{24}H_{17}ClN_2O_2$	8,9	7,0	69

to the higher lability of the leaving acetoxy group as compared with the chloride ion. The use of DMSO as the solvent in our research enabled us to obtain normal substitution products (II), which are not formed when alcohol is used as the solvent [6, 7].

1-Alkyl-2-cyano-3-benzylindoles IIIa-e were saponified by KOH in refluxing ethylene glycol to the corresponding acids (IVa-e, Table 4), one of which (IVb) has a considerable antiphlogistic effect [9], and IIIb, e were reduced by $LiAlH_4$ to the corresponding 2-aminomethyl derivatives Va, b, which are intermediates in the synthesis of benzo-1,4-diazepines [10].

EXPERIMENTAL

The PMR spectra of the compounds were recorded with a Varian spectrometer (60 MHz). The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-22 spectrometer. The UV spectra of ethanol solutions of the compounds were obtained with an SF-16 spectrophotometer. The individuality of all of the synthesized compounds was monitored by thin-layer chromatography (TLC) on Silufol in a cyclohexane–ethyl acetate system (3:1).

2-Carbethoxy-3-(α-chloro-o-chlorobenzyl)indole (Ia). A total of 10 ml of ether saturated with HCl was added with stirring at 0°C to a mixture of 1.5 g (8 mmole) of ethyl indole-2-carboxylate and 1.3 g (9 mmole) of o-chlorobenzaldehyde. The solid dissolved rapidly, and after 5-7 min, Ia began to precipitate. After 1 h, the precipitate was removed by filtration, washed with heptane, and air dried to give 2.22 g (80%) of Ia. The product was crystallized from heptane for analysis. The insoluble portion [0.14 g (5%)], with mp 253-255°C, was identified as bis(2-carbethoxy-3-indolyl)-o-chlorophenylmethane. Found: N 5.4; Cl 6.8%. $C_{29}H_{25}ClN_2O_4$. Calculated: N 5.6; Cl 7.1%.

Compounds Ib-f (Table 1) were obtained similarly; however, for the isolation of Ib-d an equal volume of heptane was added to the reaction mixture, and the liberated oil began to crystallize upon trituration. During an attempt to crystallize Id from acetonitrile it was converted to bis(2-carbethoxy-5-methoxy-3-indolyl)-o-chlorophenylmethane (VIb) with mp 280-282°C. Found: Cl 6.2; N 4.8%. $C_{31}H_{29}ClN_2O_6$. Calculated: Cl 6.4; N 5.0%. According to the results of TLC and elementary analysis, the percentage of VIb (R_f 0.2) in a sample of Id (R_f 0.35) isolated from the reaction mixture was 15%, which was reduced to not more than 3% after crystallization from heptane. An experiment to obtain Ie in CH_3COOH–CH_3COCl (1:1) led to the formation of exclusively bis(1-methyl-2-carboxy-3-indolyl)-m-nitrophenylmethane (VIc) with mp 231-233°C. Found: N 8.1%. $C_{27}H_{21}N_3O_8$. Calculated: N 8.5%.

Reaction of 1-Methyl-2-carboxy-3-(α-chlorobenzyl)indole with Sodium Cyanide. A 3.6-g (12 mmole) sample of 1-methyl-2-carboxy-3-(α-chlorobenzyl)indole [4] was added at 100°C to a solution of 1.2 g (24 mmole) of NaCN in 30 ml of DMSO, and the mixture was stirred for 1 h. Water (60 ml) was added to the cooled solution, and IIIa was extracted with ether. The ether extracts were washed with 50 ml of water and dried with anhydrous Na_2SO_4, and the ether was removed by evaporation to give crystals of IIIa (Table 3). The solution from which IIIa was extracted was acidified to pH 5-6 with acetic acid, and the precipitated IIa (Table 2) was removed by filtration and crystallized from ethanol.

TABLE 3. 1-Alkyl-2-cyano-3-benzylindoles (IIIa-e)

Compound	R	R³	mp, °C	Spectra		Found, %			Empirical formula	Calc., %			Yield, %
				UV, λ_{max}, nm (lg ε)	IR, cm⁻¹ (C≡N)	C	H	N		C	H	N	
IIIa	CH_3	H	101—103	290 (4.28)	2240	82,0	5,5	11,1	$C_{17}H_{14}N_2$	83,0	5,7	11,3	12
IIIb	CH_3	*o*-Cl	108—109	290 (4.28)	2250	73.0	4,2	10,0	$C_{17}H_{13}ClN_2$[a]	73,0	4,6	10,0	26
IIIc	CH_3	*m*-NO_2	130—132	291 (4.35)	2220	69,2	4,5	14,1	$C_{17}H_{13}N_3O_2$	70,0	5,5	14,5	12
IIId	CH_3	*p*-NO_2	172—174	290 (4,48)	2230	69,9	4,1	14,1	$C_{17}H_{13}N_3O_2$	70,0	4,5	14,5	11
IIIe	$CH_2C_6H_5$	*o*-Cl	112—114	—	—	78,0	5,1	7,4	$C_{23}H_{17}ClN_2$[b]	77,6	4,8	7,9	50

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a) Found: Cl 12.3%. Calculated: Cl 12.6%. b) Found: Cl 9.4%. Calculated: Cl 10.0%.

TABLE 4. 1-Alkyl-3-benzyl-2-carboxylic Acids (IVa-e)

Compound	R	R³	mp, °C	Found, %	Empirical formula	Calc., %	Yield, %
				N		N	
IVa	CH_3	H	195—196	5,2	$C_{17}H_{15}NO_2$	5,3	65
IVb	CH_3	*o*-Cl	220—221	4,7	$C_{17}H_{14}ClNO_2$	4,7	85
IVc	CH_3	*m*-NO_2	165—168	8,8	$C_{17}H_{14}N_2O_4$	9,0	70
IVd	CH_3	*p*-NO_2	300—303	8,6	$C_{17}H_{14}N_2O_4$	9,0	30
IVe	$CH_2C_6H_5$	*o*-Cl	189—190	3,3	$C_{23}H_{18}ClNO_2$[a]	3,7	65

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a) Found: Cl 9.2%. Calculated: Cl 9.5%.

Compounds IIb-d and IIIb-d were isolated similarly.

In the reaction with "chloride" If (Table 1) the reaction mixture was diluted with water, and the aqueous mixture was acidified to pH 3-5 with CH_3COOH (to bring about decarboxylation of cyanoacetic acid derivative A). The mixture was then made alkaline to pH 9-10, and nitrile IIIe was extracted with ether. The aqueous layer was again acidified with acetic acid, and IIg was extracted with chloroform.

In the preparation of IIe the reaction mixture was diluted with water, and the aqueous mixture was acidified with acetic acid. The precipitated IIe was removed by filtration and crystallized from ethanol (TLC of the product gave one spot with R_f 0.66).

Compound IIf was obtained by heating 0.5 g of IIe in 10 ml of 5% alcoholic alkali until all the solid dissolved, after which the mixture was diluted to twice its original volume with water and acidified to pH 5-6 with acetic acid. The precipitated IIf [0.4 g (87%)] was removed by filtration and dried.

1-Methyl-2-carboxy-3-benzylindole (IVa, Table 4). This compound, with mp 195-196°C (mp 194-194.5°C [10]), was obtained from nitrile IIIa by the method in [6] by refluxing in ethylene glycol containing KOH until ammonia evolution ceased. Acids IVb-e were obtained by the same method from the corresponding nitriles IIIb-e (Table 4).

1-Benzyl-2-aminomethyl-3-(o-chlorobenzyl)indole (Vb). This compound was obtained by reduction of 0.35 g (1 mmole) of nitrile IIIe with 0.2 g of $LiAlH_4$ in 20 ml of ether. After decomposition of the excess $LiAlH_4$ with water, the ether layer was filtered, dried with Na_2SO_4, treated with a few drops of ether saturated with HCl, and allowed to stand in a refrigerator. After 2 days, the precipitated Vb was removed by filtration to give 0.23 g (60%) of a product with mp 228-230°C. Found: Cl 17.9; N 6.9%. $C_{23}H_{21}ClN_2 \cdot HCl$. Calculated: Cl 18.3; N 7.2%. Compound Va was described in [6].

LITERATURE CITED

1. V. N. Rusinova, Yu. I. Smushkevich, O. V. Telenkova, M. V. Vasin, and N. N. Suvorov, Khim. Geterotsikl. Soedin., No. 2, 211 (1974).
2. E. P. Styngach and A. A. Semenov, Khim. Geterotsikl. Soedin., No. 5, 621 (1971).

3. V. N. Borisova, E. N. Gordeev, and N. N. Suvorov, Khim. Geterotsikl. Soedin., No. 3, 357 (1977).
4. N. A. Kogan, Khim. Geterotsikl. Soedin., No. 4, 504 (1975).
5. C. Granacher, A. Mahal, and M. Herb, Helv. Chim. Acta, 7, 579 (1924).
6. N. A. Kogan, Khim. Geterotsikl. Soedin., No. 6, 801 (1976).
7. N. A. Kogan, Khim. Geterotsikl. Soedin., No. 6, 857 (1975).
8. E. N. Zil'berman, Reactions of Nitriles [in Russian], Moscow (1972), p. 13.
9. N. A. Kogan, É. G. Gromova, R. N. Zozulya, and M. I. Vlasova, Khim.-Farm. Zh., No. 7, 41 (1976).
10. V. I. Shvedov, G. N. Kurilo, and A. N. Grinev, Khim.-Farm. Zh., No. 7, 10 (1969).

BEHAVIOR OF SEMICARBAZONES UNDER THE CONDITIONS OF THE FISCHER REACTION

M. F. Marshalkin and L. N. Yakhontov

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Cyclohexanone semicarbazone and phenylsemicarbazone form 1,2,3,4-tetrahydro- and 1,2,3,4,5,6,7,8-octahydrocarbazoles under the conditions of the Fischer reaction. The reaction proceeds through a cyclohexanone azine intermediate. The product of oxidation of the azine is oxidized by air oxygen to 1,2,3,4-tetrahydrocarbazole. The investigated semicarbazones are stable with respect to the action of sodium ethoxide at up to 300°C.

In addition to the extensively studied Fischer indolization of arylhydrazones, various transformations of N-acylated hydrazines and hydrazones have been described in the literature: the cyclization of N-acyl-N'-arylhydrazines to hydroxyindoles by the Brunner method [1], the thermal cleavage of benzaldehyde benzoylhydrazone to benzamide and benzonitrile with cuprous chloride [2], and the cationotropic rearrangement of N-acyl-N'-arylhydrazines to 2-aminoindoles [3]. The behavior of semicarbazones, which are N-acylated hydrazones in which the acylating group is a carbamide residue, under the conditions of the Fischer reaction has not been previously investigated.

We have studied the behavior of cyclohexanone phenylsemicarbazone (I) under the conditions of the Fischer reaction. 1,2,3,4-Tetrahydrocarbazole (II), which was identical to the substance formed in the Fischer cyclization of cyclohexanone phenylhydrazone [4], was obtained in 10% yield when I was heated with zinc chloride to 240-250°C and the mixture was chromatographed on aluminum oxide. A subsequent study of the reaction products enabled us to isolate aniline (IV) in 47% yield and 1,2,3,4,5,6,7,8-octahydrocarbazole (III) in 24% yield. Analysis of the reaction mixture by gas—liquid chromatography (GLC) showed that the percentages of II, III, and IV prior to separation are 15, 35, and 50%, respectively. These results constitute evidence that the principal transformation of semicarbazone I is not indolization of the Fischer type but rather cleavage of the N—N bond with the subsequent formation of aniline and an intermediate containing two cyclohexane residues that is capable of undergoing cyclization to octahydrocarbazole III. Experiments with pure octahydrocarbazole III showed that III is capable upon heating of undergoing oxidation by air oxygen to tetrahydrocarbazole II; this oxidation process is virtually quantitative at 240°C after 6 h. Thus the formation of tetrahydrocarbazole II to a considerable extent may be due to secondary oxidation of octahydrocarbazole III. (See scheme at top of next page.)

In order to determine the role of the phenyl residue in the formation of the tetrahydrocarbazole system we carried out a similar reaction with cyclohexanone semicarbazone (V), which does not contain a phenyl group. The reaction was carried out under the same conditions as in the reaction with semicarbazone I and led to the formation of octahydrocarbazole III in ~90% yield and tetrahydrocarbazole II in ~3% yield (according to GLC data). We were

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