obtained 5.5 g (26%) of 3-bromoselenopheno[2,3-b]selenophene-5-carboxylic acid (II); mp 254-255°C (in a unit with preliminary heating). Methyl ester, mp 169-171°C (vacuum sublimation). PMR spectrum: 8.08 (3-H), 8.16 (5-H), 3.85 ppm (OCH_3). Found, %: Br 21.0; OCH_3 8.8. $C_8H_5BrO_2Se_2$. Calculated, %: Br 21.5; OCH_3 8.4.

3-Bromoselenopheno[2,3-b]selenophene (III). A mixture of 30 ml of freshly distilled quinoline, 1.8 g of the acid (II), and 0.5 g of powdered copper was boiled until the release of carbon dioxide had ceased. It was then cooled, acidified with 10% hydrochloric acid, and extracted with ether. The extract was washed with 10% hydrochloric acid, water, sodium chloride solution, and water and dried over sodium chloride. We obtained 1.1 g (70%) of compound (III); mp 66-67°C (from aqueous alcohol). PMR spectrum: 7.96 (2-H), 7.44 (4-H), 8.08 ppm (5-H), $J_{25} = 1.0$; $J_{45} = 5.9$; $J_{^{77}Se\text{-}5\text{-}H} = 48.0$; $J_{^{77}Se\text{-}2\text{-}H} = 45.2$ Hz. Found, %: Se 50.6. $C_6H_3BrSe_2$. Calculated, %: Se 50.5.

LITERATURE CITED

1. A. Bugge, Acta Chem. Scand., 23, 2704 (1969).
2. V. A. Briscoe, J. B. Pell, and P. L. Robinson, J. Chem. Soc., 2628 (1928).
3. S. Umezawa, Bull. Chem. Soc. Jpn., 14, 363 (1939).
4. B. Tamamushi, H. Akijama, and S. Umezawa, Bull. Chem. Soc. Jpn., 14, 318 (1939).
5. S. Gronowitz, T. Frejd, and A. B. Hörnfeldt, Chem. Scripta, 5, 236 (1974).
6. A. Villa, M. Nardelli, and C. Palmieri, Acta Crystallogr., 25, 1374 (1969).
7. B. Capron and C. Paulmier, Compt. Rend., C279, 447 (1974).
8. W. B. Wright, J. Heterocycl. Chem., 9, 879 (1972).
9. S. Gronowitz and B. Maltesson, Acta Chem. Scand., 26, 2982 (1972).
10. H. Tominaga, G. Hazato, and H. Oshima, J. Chem. Soc. Jpn., 63, 1291 (1943); Chem. Abs., 41, 3334 (1947).
11. Ya. L. Gol'dfarb, I. P. Konyaeva, and V. P. Litvinov, Izv. Akad. Nauk SSSR, Ser. Khim., No. 7, 1570 (1974).

CARBOLINES 10.*

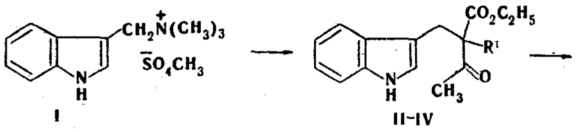
BASICITY CONSTANTS OF SOME 1H-PYRIDO[2,3-b]INDOLES (α-ISOCARBOLINES)

N. N. Pogodaeva, V. V. Kononova,
and A. A. Semenov

UDC 547.759.3.821:543.422.6

In connection with the fact that certain 2-chloro-α-isocarbolines possess fairly high cytotoxic activity [1], it seemed of interest to study their physicochemical characteristics for a subsequent structure—activity correlation in order to determine the factors which secure the maximum biological effect.

In the present work we studied the principal characteristics of a series of 2-chloro-α-isocarbolines containing alkyl substituents at positions 1 and 3.



---

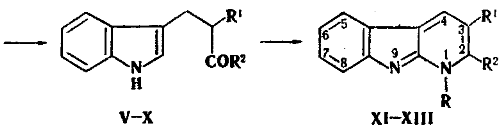
*For Communication 9, see [1].

Irkutsk Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR, Irkutsk 664033. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1074-1077, August, 1979. Original article submitted November 28, 1978.

0009-3122/79/1508-0879$07.50

TABLE 1. Basicity Constants of the α-Isocarbolines (XI-XVIII)

Compound	α-Isocarbolines			$pK_{bas}\pm\Delta x$	Mean-square error (s)	Number of degrees of freedom (f)
	R	R¹	R²			
XIV	CH_3	H	H	7,93±0,04	0,04	5
XV	CH_3	H	Cl	7,10±0,04	0,04	6
XVI	$C_6H_5CH_2$	H	Cl	6,53±0,04	0,07	14
XVII	C_3H_7	H	Cl	7,30±0,02	0,02	6
XVIII	C_4H_9	H	Cl	7,36±0,03	0,04	8
XI	CH_3	CH_3	Cl	7,69±0,02	0,03	7
XII	CH_3	C_2H_5	Cl	7,73±0,03	0,03	6
XIII	CH_3	C_3H_7	Cl	7,77±0,02	0,02	5



II $R^1=CH_3$; III $R^1=C_2H_5$; IV $R^1=C_3H_7$; V $R^1=CH_3$, $R^2=OH$; VI $R^1=C_2H_5$, $R^2=OH$; VII $R^1=C_3H_7$, $R^2=OH$; VIII $R^1=CH_3$, $R^2=NHCH_3$; IX $R^1=C_2H_5$, $R^2=NHCH_3$; X $R^1=C_3H_7$, $R^2=NHCH_3$; XI $R=R^1=CH_3$, $R^2=Cl$; XII $R=CH_3$, $R^1=C_2H_5$, $R^2=Cl$; XIII $R=CH_3$, $R^1=C_3H_7$, $R^2=Cl$

It is known that protonation of α-isocarbolines occurs at the pyrrole nitrogen atom [2]. However, systematic investigations into the basicity of these compounds have not been undertaken.

In order to study the basicity of α-isocarbolines we used a spectrophotometric method. The obtained constants are given in Table 1. As seen from the data in Table 1, among the investigated compounds 1-methyl-α-isocarboline has the highest basicity. The introduction of substituents which will reduce the electron density at the N_1 atom and, consequently, increase its —I effect into the 1-methyl-α-isocarboline molecule should lead to a decrease in basicity on account of the decrease in the stability of the conjugate acid of the base. In fact, the introduction of a chlorine atom, in which the —I effect predominates over the +M effect (σ_0 = 0.20) [3], into 1-methyl-α-isocarboline reduces the basicity by 0.83 pK unit. Substitution of methyl in 1-methyl-2-chloro-α-isocarboline by benzyl, which possesses a —I effect, leads to a further decrease of 0.57 pK unit in the basicity on account of the additional increase in the —I effect of the N_1 atom.

Conversely, a small increase in basicity compared with 1-methyl-2-chloro-α-isocarboline is observed in 1-propyl- and 1-butyl-2-chloro-α-isocarbolines, in which the +I effect of the alkyl substituents is somewhat higher than that of the methyl group.

Probably for the same reason the introduction of additional electron-donating alkyl substituents (CH_3, C_2H_5, C_3H_7) at position 3 of the 1-methyl-2-chloro-α-isocarboline molecule also leads to an increase in the pK value.

Thus, electron-withdrawing substituents at positions 1 and 2 of α-isocarboline lead to a decrease in basicity on account of an increase in the —I effect of the N_1 atom. Electron-donating substituents at positions 1 and 3, on the other hand, increase the basicity by reducing the —I effect of the N_1 atom.

EXPERIMENTAL

The method of synthesis and the physicochemical characteristics of compounds (XIV-XVIII) were given in [1, 4].

The synthesis of 1-substituted 2-chloro-α-isocarbolines was described in [1]. The 1,3-

TABLE 2. 1,3-Disubstituted 2-chloro-α-isocarbolines

Compound	R^1	mp, °C	λ_{max}, nm (lg ε)		Found, %				Molecular formula	Calculated, %				Yield, %
			in 0,1 N HCl	in 0,1 N KOH	C	H	N	Cl		C	H	N	Cl	
XI	CH_3	119—121	250 (4,20), 265 sh (4,02), 319 (4,16), 355 (3,91)	262 sh (4,20), 279 (4,27), 325 (4,17), 400 (3,63)	68,0	4,9	12,1	15,4	$C_{13}H_{11}N_2Cl$	67,7	4,8	12,1	15,4	60
XII	C_2H_5	203—205	250 (4,21), 265 sh (4,01), 320 (4,16), 355 (3,89)	260 sh (4,20), 280 (4,27), 317 sh (4,13), 400 (3,60)	59,9	5,3	9,7	25,1	$C_{14}H_{13}N_2Cl$	59,8	4,98	9,96	25,3	85
XIII	C_3H_7	189—191	250 (4,24), 265 sh (4,03), 318 (4,17), 355 (3,88)	260 sh (4,21), 280 (4,29), 325 (4,17), 400 (3,62)	60,7	5,4	9,5	24,0	$C_{15}H_{15}N_2Cl$	61,0	5,4	9,5	24,1	94

disubstituted derivatives were obtained by a scheme representing a combination of previously developed methods. The α-alkyl-β-indolylpropionic acids (V-VII) were obtained by acid cleavage of skatylacetoacetic esters (II-IV), which were synthesized by the reaction of the quaternary salt of gramine (I) with alkyl derivatives of acetoacetic ester [5]. The indole acids were converted into 2-chloro-α-isocarbolines (XI-XIII) by the method in [1], i.e., by treatment of their methylamides (VIII-X) with methylchlorophosphine in nitrobenzene.

2-Methyl-3-(3-indolyl)propionic Acid (V). Compound (V) was obtained by the method in [2]. To 10 g (57.5 mmole) of gramine in 76 ml of anhydrous alcohol, while cooling to 0°C, we added 7.24 g (57.5 mmole) of dimethyl sulfate. After 30 min we added 8.28 g (57.5 mmole) of 2-methylacetoacetic ester and then, over 20 min, a solution of 1.3 g (57.5 mmole) of sodium in 26 ml of anhydrous alcohol. The mixture was boiled in an atmosphere of nitrogen for 10 h until the release of trimethylamine had ceased. After cooling, the reaction mixture was filtered, the solvent was removed, 20-25 ml of water was added, and the mixture was extracted with chloroform. The organic layer was washed with dilute acetic acid, water, and sodium carbonate solution. The residue after distillation of the solvent was chromatographed on aluminum oxide in the 6:4 hexane—benzene system. We eluted 9 g (57%) of 3-skatyl-3-ethoxycarbonylbutanone (II) in the form of a viscous noncrystallizing liquid. A mixture of 3.2 g (11.7 mmole) of compound (II) and 8.2 ml of a 25% alcohol solution of potassium hydroxide was heated in an atmosphere of nitrogen at 80-90°C for 2 h 30 min. To the cooled mixture we added 32 ml of water. The mixture was extracted with ether, the aqueous layer was acidified with acetic acid, and the acid (V) was extracted with ethyl acetate. The ethyl acetate extracts were washed with water, dried, and evaporated. We obtained 1.7 g (71%) of an oil which crystallized on standing; mp 123-125°C (from water). Found, %: C 70.5; H 6.4; N 7.0. $C_{12}H_{13}NO_2$. Calculated, %: C 70.9; H 6.4; N 6.9. Methylamide (VIII), yield 79%, mp 93-95°C (from benzene). Found, %: C 72.2; H 7.4; N 12.9. $C_{13}H_{16}N_2O$. Calculated, %: C 72.2; H 7.4; N 12.96.

The following compounds were obtained similarly.

2-Ethyl-3-(3-indolyl)propionic Acid (VI). The compound was purified by chromatography on polyamide in the 95:5 benzene—methanol system. The yield was 57%; mp 103-105°C (from trichloroethylene). Found, %: C 71.5; H 6.8; N 6.9. $C_{13}H_{15}NO_2$. Calculated, %: C 71.9; H 6.9; N 6.5. Methylamide (IX), yield 72%, mp 97-98°C (from benzene). Found, %: C 73.4; H 8.2; N 12.2. $C_{14}H_{18}N_2O$. Calculated, %: C 73.0; H 7.8; N 12.2.

2-Propyl-3-(3-indolyl)propionic Acid (VII). Compound (VII) was isolated by chromatography on polyamide in the 95:5 benzene—methanol system in the form of a viscous liquid with a yield of 76%. Methylamide (X), yield 80%, mp 99-100°C (from benzene with hexane). Found, %: C 73.4; H 8.2; N 11.1. $C_{15}H_{20}N_2O$. Calculated, %: C 73.8; H 8.2; N 11.5. The methylamides (VIII-X) were obtained by the method in [6].

1H-1,3-Dimethyl-2-chloropyrido[2,3-b]indole (XI). A 0.35-g sample (1.62 mmole) of the amide (VIII) in nitrobenzene was rapidly added to a stirred suspension of 1 g (4.86 mmole) of phosphorus pentachloride in nitrobenzene, heated to 60-70°C. After 2 min the reaction mixture was cooled, the excess phosphorus pentachloride was decomposed with ice, and the

TABLE 3. Optical Densities and pH Values Used for Calculation of the Basicity Constants of 1-Methyl-2-chloro-3-propyl-α-isocarboline*

Density of solutions (form)			pH	pK
A_B	A_{HB}	A		
0,970	0,164	0,331	7,22	7,80
		0,413	7,44	7,79
		0,505	7,64	7,77
		0,642	7,92	7,76
		0,695	8,06	7,77
		0,840	8,48	7,76

---

*Mean pK_{bas} = 7.77 ± 0.02; s = 0.02; f = 5.

mixture was diluted with ether and extracted with dilute hydrochloric acid. After treatment with alkali the base (XI) was extracted with ether.

1H-1-Methyl-3-ethyl-2-chloropyrido[2,3-b]indole (XII) and 1H-1-methyl-3-propyl-2-chloropyrido[2,3-b]indole (XIII) were obtained similarly. On account of the difficulty in crystallization the bases were converted into the hydrochlorides. The physicochemical characteristics of compounds (XI-XIII) are given in Table 2.

The basicity constants were determined by the usual methods [7]. As seen from Table 2, the bases and the corresponding protonated forms differ in their spectral characteristics. The greatest difference in the absorption of the two forms is observed at 280 nm. This wavelength was selected as the analytical wavelength. In the case of 1-benzyl-2-chloro-α-isocarboline the additional wavelength of 360 nm was used. In order to obtain a series of solutions with various pH values and with constant ionic strength, we used 0.1 N solutions of hydrochloric acid and potassium hydroxide. In the case of 1-benzyl-2-chloro-α-isocarboline, on account of the poor solubility of the base, we used 0.1 N solutions of hydrochloric acid and potassium hydroxide in 20% aqueous ethanol. The concentration of the α-isocarbolines in the working solutions amounted to $5 \cdot 10^{-5}$ M.

The optical density measurements were made on an SF-4A spectrophotometer in a cylindrical 1-cm cuvette. The hydrogen ion concentration was measured on an LPU-01 pH meter with a system of glass and silver chloride electrodes, filled with a saturated solution of potassium chloride. The determinations were made at 25 ± 1°C. The constants were calculated by means of the formula in [7]. As an example, Table 3 gives the optical densities and pH values used to calculate the basicity constants of 1-methyl-2-chloro-3-propyl-α-isocarboline. The reliability of the obtained pK values was assessed by the mean-square error and by the confidence interval, calculated with 95% probability by the formulas in [8].

LITERATURE CITED

1. V. V. Kononova, A. L. Vereshchagin, V. M. Polyachenko, and A. A. Semenov, Zh. Fiz. Khim., No. 12, 30 (1978).
2. G. T. Tatevosyan, Anhydronium Basis of the Carboline Series [in Russian], Izd. Akad. Nauk ArmSSR, Erevan (1966), p. 78.
3. V. A. Pal'm, Fundamentals of the Quantitative Theory of Organic Reactions [in Russian], Khimiya, Moscow (1977), p. 300.
4. K. I. Kuchkova, E. P. Styngach, F. Sh. Rivilis, N. M. Frolova, and A. A. Semenov, Khim. Geterotsikl. Soedin., No. 3, 386 (1976).
5. A. A. Semenov and I. V. Terent'eva, Khim. Geterotsikl. Soedin., No. 2, 235 (1965).
6. D. C. Crosby, J. B. Boyd, and H. E. Johnson, J. Org. Chem., 25, 1826 (1960).
7. I. Ya. Bershtein and Yu. L. Kaminskii, Spectrophotometric Analysis in Organic Chemistry [in Russian], Khimiya, Moscow (1975), p. 143.
8. K. Doerfel, Statistics in Analytical Chemistry [Russian translation], Mir, Moscow (1969), pp. 29, 111.