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INDOLOPYRIDINES WITH A HETERO ATOM AT A POSITION OF FUSION. 7.* ELECTROPHILIC SUBSTITUTION IN 5,6-DIHYDROINDOLO-[2,1-a]ISOQUINOLINE

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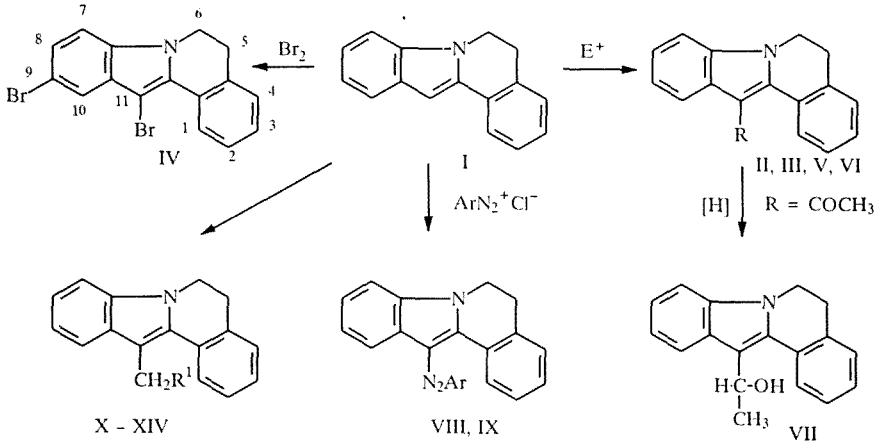
Halogenation, acylation, azo coupling, and alkylaminomethylation of 5,6-dihydroindolo[2,1-a]isoquinoline were carried out at the $C_{(11)}$ position (pyrrole fragment). In dibromination, the second bromine atom was introduced into the $C_{(9)}$ position (indole part of the molecule).

5,6-Dihydroindolo[2,1-a]isoquinoline (I) is a model of 1,2-disubstituted indole having one free β position in the pyrrole ring, the functionalization of which can result in the synthesis of potentially biologically active compounds. It is obvious, above all, that electrophilic monosubstitution reactions should occur at this position with formation of $C_{(11)}$-substituted compounds of interest for the comparative study of the reactivity of two benzene rings fused in one molecule with a π-excess pyrrole ring (one of them is coplanar with pyrrole, and the other is partially removed from bonding with it).

All the electrophilic monosubstitution reactions, i.e., halogenation, acylation, azo coupling, and alkylaminomethylation, were carried out by the methods described previously for completely aromatic indolo[2,1-a]isoquinoline [1]. In iodination by a KI_3 complex and bromination by bromine water, 11-iodo- (II), 11-bromo- (III), and 9,11-dibromo-5,6-dihydroindolo[2,1-a]isoquinoline (IV) were obtained.



II R = I; III R = Br; V R = CHO; VI R = $COCH_3$; VIII Ar = Ph; IX Ar = $C_6H_4NO_2$-p; X R^1 = $(NMe)_2$; XI R^1 = $N(Et)_2$; XII R^1 = piperidyl; XIII R^1 = morpholinyl; XIV R^1 = $^+NH(Et)_2Cl^-$

*For Communication 6, see [1].

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TABLE 1. Characteristics of Compounds II-XIV*

Compound	Empirical formula	mp, °C	R_f (heptane : ether)	Mass spectrum, m/z, %	IR spectrum, ν, cm^{-1}	Yield, %
II	$C_{16}H_{12}IN$	78...80	0,52 (3 : 1)	M^+ 345 (7), $[M-Ph]^+$ 268 (35), $[M-C_7H_7]^+$ 254 (95), 219 (98), 128 (100), 127(97)	–	38
III	$C_{16}H_{12}BrN$	101...103	0,63 (3 : 1)	M^+ 299 (67), 297 (78), 219 (86), 218 (55), 217 (100), 108,5 (13)	–	15
IV	$C_{16}H_{11}Br_2N$	125...127	0,31 (2 : 1)	M^+ 377 (4), 270 (25), 228 (68), 211 (23), 162 (42), 160 (90), 158 (42), 102 (83), 82 (100), 81 (40), 80 (99), 79 (40)	–	77
V	$C_{17}H_{13}NO$	120...123	0,2 (1 : 1)	M^+ 247	1739, 1722 we, 1641, 1629 (br.d, s)	72
VI	$C_{18}H_{15}NO$	108...110	0,27 (1 : 1)	M^+ 261	1646 (v.s), 1533 (s), 1413 (s)	98
VII	$C_{18}H_{17}NO$	163...165	0,3 (1 : 1)	M^+ 263	3480 (v.wide), 1453 (v.s.), 1363 (s)	75
VIII	$C_{22}H_{17}N_3$	99...101	0,29 (1 : 1)	M^+ 323	1600 (br.s) 1530...1510 (doub. v.s), 1420 (we.),1345, 1320 (br. v.s), 1110 (me.)	72
IX	$C_{22}H_{16}N_4O_2$	118...120	0,28 (1 : 1)	M^+ 368	1610 (wide s), 1526 (s), 1455 (me.), 1430 (me.), 1375 (br. v.s)	70
X	$C_{19}H_{20}N_2$	93...95	0,46 (1 : 1)	M^+ 276(23), $[M-N(CH_3)_2]^+$ 232 (100), 219 (6), 218(3), 217(8)	–	54
XI	$C_{21}H_{24}N_2$	100...102	0,31 (1 : 1)	M^+ 304(73), $[M-C_2H_5]^{+\cdot}$ 275(7), $[M-2\times C_2H_5]^+$ 246(5), $[M-N(C_2H_5)_2]^+$ 232 (51) 218(34), 271(100), 108,5(13)	–	63
XII	$C_{22}H_{24}N_2$	165...168	–	M^+ 316 (25), $[M-C_5H_9]^+$ 247 (40), $[M-C_5H_{10}N]^+$ 232 (100), 218 (23), 217 (34)	–	59
XIII	$C_{21}H_{22}N_2O$	124...126	–	M^+ 318	–	94
XIV	$C_{21}H_{25}ClN_2$	196...198	–	–	–	44

*we) weak, br.d) broadened doublet, s) strong, v.s) very strong, v.wide) very wide, br.s) broadened strong, doub.v.s) doublet very strong, br.v.s) broadened very strong, me) medium, wide s) wide strong.

TABLE 2. Parameters of PMR Spectra of Compounds II-VI, VIII-IX, and XIV ($CDCl_3$)

Compound	Chemical shift, δ, ppm (multiplet nature, spin-spin coupling constant, J, Hz)					
	1-H	5-H**	6-H	7-H	10-H	Other protons
II	8,76 (d, 5, 6 and 2)	3,17	4,25	7,6 (m)	7,5 (m)	7,05...7,45 (m,5H)
III	8,62 (ddd, 6, 6; 2 and 1, 5)	3,13	4,18	7,62 (m)	7,38 (m)	7,1 ...7,35 (m,5H)
IV*	8,55 (m)	3,18	4,33	7,8 (d, 6, 5)	7,33 (d, 1, 6)	7,15...7,5 (m,4H)
V	8,46 (m)	3,18	4,24	7,95 (m)	—	7,3...7,5 (m,6H); 10,51 (s, CHO)
VI	8,04 (m)	3,13	4,18	8,04 (m)	—	7,14...7,5 (m,6H); 2,66 (s, CH_3)
VIII	8,75 (m)	3,27	4,29	7,92 (dd, 7,0, 1, 4)	—	7,65...7,12 (m,11H)
IX	8,69 (m)	3,3	4,35	8,3 (m	8,30 (m)	8,0 (d, 8,1 Hz, 3,5-H); 7,59 (d, 8,1 Hz, 2,6-H); 7,5...7,2 (m,5H)
X	8,26 (dd, 7 and 1, 5)	3,1	4,22	7,74 (m)	—	7,0...7,5 (m,6H); 3,7 (s, 2H, C_{11}—CH_2); 2,35 (s, 6H, 2 × CH_3
XI	8,53 (br.d, 7)	3,08	4,2	7,75 (m)	—	7,0...7,5 (m 6H); 3,9 (s, 2H, C_{11}—CH_2); 2,65 (q, 4H, 2 × CH_2—CH_3); 1,1 (t, 6H, 2 × CH_2—CH_3)
XIV	7,23...8,00 (9H, m, H_{arom}); 3,37...4,63 (6H, m, 5-, 6-H_2, CH_2N)					2,9 (br.q, 4H, 2 × CH_2—CH_3); 1,21 (t, 6H, 2 × CH_2—CH_3)

*In DMSO-D_6.

**The 5- and 6-H protons were manifested as triplets with J = 6.0-7.0 Hz.

***d) doublet, m) multiplet, ddd) double double doublet, s) singlet, dd) doublet doublet, br.d) broadened doublet, q) quartet, t) triplet, br.q) broadened quartet.

Interpretation of the PMR spectra of monohalo derivatives II and III is not difficult. Firstly, they contained no 1-H proton peak at 6.86 ppm [2]. Secondly, just as in the case of unhydrogenated indolo[2,1-a]isoquinoline I, the 1-H proton peak was found to be very sensitive to the anisotropic effect of the substituent introduced into the $C_{(11)}$ position. Here the 1-H proton resonated in an almost 1-ppm weaker field unlike in the case of the remaining protons, whose chemical shifts did not undergo significant shift (see Table 2).

The fact that the PMR spectrum of compound IV contained a peak of one proton of system ABCD with chemical shift (at 8.55 ppm) and multiplet nature analogous to those for the 1-H proton of the starting I and monosubstituted II and III indicates the presence of a second bromine atom in the indole fragment. In its turn, its position at $C_{(9)}$ was indicated by the doublet proton peak manifested in its characteristic region at 7.8 ppm with $J_{7,8}$ = 6.5 Hz (in monosubstituted compounds II and III, it resonated as a multiplet). The doublet with J = 1.6 Hz at 7.3 ppm can be assigned to the 1-H proton peak. These data indirectly confirm the orientation of the electrophilic attack of the second bromine atom of the $C_{(9)}$ position of the isoquinoline fragment of completely aromatic indolo[2,1-a]isoquinoline [1].

11-Formyl- (V) and 11-acetyl-5,6-dihydroindoloisoquinoline (VI) were also obtained by the methods described in [1]. Unlike its aromatic precursor, dihydroindoloisoquinoline I was not acetylated by acetyl chloride in aqueous alkali, and, in the presence of acetic anhydride in CH_3COOH [3, 4], acetylation occurred quantitatively. Acetyl derivative VI was reduced by $NaBH_4$ to alcohol VII.

Azo coupling of indoloisoquinoline I with phenyl- and 4-nitrophenyldiazonium salts gave derivatives at the $C_{(11)}$ atom of the pyrrole ring (compounds VIII and IX) in good yields.

Unlike indolo[2,1-a]isoquinoline I, 5,6-dihydroindolo[2,1-a]isoquinoline facilely entered into Mannich alkylaminomethylation. Here we obtained 11-(dimethylaminomethyl)- (X), 11-(diethylaminomethyl)- (XI), 11-(1-piperidinylmethyl)- (XII), and

11-(4-morpholinylmethyl)-5,6-dihydroindolo[2,1-a]isoquinoline (XIII) and also the diethylaminomethyl hydrochloride derivative (XIV). The PMR spectrum of compounds X and XI contained no single-proton singlet peaks from the 11-H proton but did contain two-proton singlet peaks of the methylene group at $C_{(11)}$ (in the region of 3.7 and 3.9 ppm) and corresponding peaks of methyl and ethyl groups (Table 2). The mass spectra of amines X-XIII contained peaks of molecular ions of varying intensity (25-73%), which facilely abstracted dialkylamino groups and gave characteristic peaks of $[M-NR^2]^{+\cdot}$ ions of medium (compound XI) or maximum intensity (amines X and XII).

EXPERIMENTAL

The methods for synthesis, recovery, and purification of compounds II-XIV and the methods and instruments for analysis and establishment of their structure are presented in a previous communication [1]. The characteristics and PMR spectra of the synthesized compounds are given in Tables 1 and 2.

The data of elemental analysis corresponded to the calculated data.

11-(Dimethylaminomethyl)- (X), 11-(Diethylaminomethyl)- (XI), 11-(Piperidin-1-ylmethyl)- (XII), and 11-(Morpholin-1-ylmethyl)-5,6-dihydroindolo[2,1-a]isoquinoline (XIII). To a mixture, cooled to 5°C, consisting of 4 ml of a 33% dimethylamine solution, 2 ml of a 40% formaldehyde solution, and 2.4 ml of CH_3COOH, was added dropwise, with stirring, 0.22 g (1 mmole) of indoloisoquinoline I, and then the mixture was heated for 1.5 h at 70°C and held for 10 h at 20°C. The mixture was poured into a 12% KOH solution (30 ml) and cooled for 3 h at 0°C. The precipitate was separated, washed with water, and dried. We obtained 0.15 g of light-yellow crystals of compound X.

Amine XI. It was obtained similarly from 0.3 g (1.4 mmoles) of the starting I and 4 ml of a 33% diethylamine solution (0.27 g). Its hydrochloride XIV (0.34 g of dark-green crystals) was obtained by the method presented in [1] from 0.5 g (2.3 mmoles) of I.

Amine XII. It was obtained similarly from 0.3 g of the starting I and 4 ml of a 33% piperidine solution (0.26 g).

Amine XIII. It was obtained from 0.3 g of I and 4 ml of a 33% morpholine solution (0.42 g).

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