N-ALKYLATED 4, 5, 6, 7-TETRAFLUOROINDOLES

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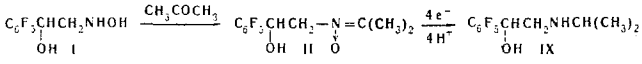
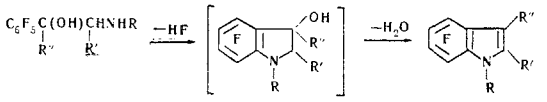
The electrochemical reduction of 2-nitro-1-pentafluorophenylalkanols in the presence of carbonyl compounds has given hydrochlorides of secondary amino alcohols which, in the form of the free bases, have been converted by heating in dimethylformamide into N-substituted derivatives of 4, 5, 6, 7-tetrafluoroindole and its homologs.

N-Alkylated indoles are generally obtained by the action on indole of dialkyl sulfates in liquid ammonia or with heating in aqueous alkali [1]. In the polyfluorinated series, under these conditions the reaction may be accompanied by nucleophilic replacement of the fluorine atoms. In this work we have studied the possibility of obtaining N-alkylated 4, 5, 6, 7-tetrafluoroindoles by the cyclization of secondary N-substituted 2-amino-1-pentafluorophenylalkanols. We have shown previously that when 2-amino-1-pentafluorophenylalkanols are heated in dimethylformamide they split out molecules of hydrogen fluoride and water and form 4, 5, 6, 7-tetrafluoroindole and its derivatives in good yields [2, 3].

The initial amino alcohols III–XI were obtained by the potential-controlled electrochemical reduction of 2-nitro-1-pentafluorophenylalkanols in the presence of a carbonyl compound, e.g., acetone, cyclohexanone, formaldehyde, acetaldehyde, propionaldehyde, or benzaldehyde. On the basis of literature information [4, 5], we may assume that nitrones are intermediate reaction products. This is confirmed by the formation of the amino alcohol IX in the electrochemical reduction of the nitrone II.



When the resulting amino alcohols were heated in dimethylformamide, N-substituted tetrafluoroindoles were formed. Under the same conditions, with the addition of sodium bicarbonate, the reaction can be stopped at the 3-hydroxyindoline stage. Thus, 2-(methylamino)-1-pentafluorophenylethanol yielded 4, 5, 6, 7-tetrafluoro-3-hydroxy-1-methylindoline which, on being heated with concentrated hydrochloric acid, was quantitatively dehydrated to form the indole XIII.



The secondary amino alcohols obtained possess a greater tendency to cyclization than the 2-amino-1-pentafluorophenylalkanols which have a primary NH_2 group. For example, the free bases IV and VI are converted into the corresponding indoles even at room temperature.

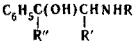
The structure of the indoles obtained was confirmed by their elementary analyses, molecular weights, and spectra (see Tables 2–4).

EXPERIMENTAL

The IR spectra (5% solutions in CCl_4) were recorded on a UR-10 instrument. The IR spectra of the indoles XIII–XXI have absorption bands for the C—F bond (935–1100 cm^{-1}), aromatic C—N (1320–1370 cm^{-1}), an aromatic ring (1495–1500 and 1513–1542 cm^{-1}) and aliphatic C—H (2820–3020 cm^{-1}). There is no absorption in the 3400–3800-cm^{-1} region.

The UV spectra were recorded in ethanol on an SP 700 C instrument. The PMR spectra (relative to hexamethyldisiloxane) and the ^{19}F NMR spectra (relative to hexafluorobenzene) were recorded in CCl_4 on a Varian A 56/60A instrument. The ^{19}F NMR spectra of XII–XXI each contained four multiplet signals of equal intensity.

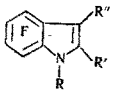
Table 1. Hydrochlorides of 2-Amino-1-pentafluorophenylalkanols



	R	R′	R″	Mp, °C	Empirical formula	Found, %					Calculated, %					Yield, %
						C	H	Cl	F	N	C	H	Cl	F	N	
III	CH_3	H	H	179—180	$C_9H_8F_5NO \cdot HCl$	38.92	3.40	12.78	34.23	5.11	38.91	3.21	12.81	34.21	5.05	60
IV	CH_3	H	CH_3	184—186	$C_{10}H_{10}F_5NO \cdot HCl$	41.45	3.47	12.16	32.10	4.87	41.15	3.77	12.18	32.59	4.80	66
V*	CH_3	CH_3	H	86 (decomp)	$C_{10}H_{10}F_5NO$	47.14	3.81	—	37.13	5.81	47.11	3.92	—	37.22	5.48	61
VI	CH_3	CH_3	CH_3	211—212	$C_{11}H_{12}F_5NO \cdot HCl$	43.15	4.18	11.54	31.13	4.60	43.17	4.25	11.60	31.18	4.57	42
VII	C_2H_5	H	H	176—177	$C_{10}H_{10}F_5NO \cdot HCl$	41.09	3.77	12.08	32.57	4.86	41.15	3.77	12.18	32.59	4.80	55
VIII	n-C_3H_7	H	H	172—173	$C_{11}H_{12}F_5NO \cdot HCl$	42.99	4.28	11.71	31.21	4.83	43.17	4.25	11.60	31.18	4.57	32
IX	i-C_3H_7	H	H	156—157	$C_{11}H_{12}F_5NO \cdot HCl$	43.01	4.06	11.67	31.14	5.05	43.17	4.25	11.60	31.18	4.57	61
X	$CH_2C_6H_5$	H	H	257—258	$C_{15}H_{12}F_5NO \cdot HCl$	51.01	3.62	10.23	26.95	4.06	50.88	3.68	10.14	26.84	3.96	59
XI	$CH(CH_2)_4CH_2$	H	H	195—196	$C_{14}H_{16}F_5NO \cdot HCl$	48.65	4.72	10.52	27.77	4.07	48.64	4.92	10.26	27.50	4.05	68

*Free base.

Table 2. 4, 5, 6, 7-Tetrafluoroindole Derivatives



	R	R′	R″	Mp, °C	Mol wt, from mass spectrum	Empirical formula	Найдено, %				Calculated, %				Yield, %
							C	H	F	N	C	H	F	N	
XIII	CH_3	H	H	100—101	203	$C_9H_5F_4N$	53.16	2.40	37.47	6.74	53.26	2.42	37.43	6.90	85
XIV	CH_3	H	CH_3	113—114	217	$C_{10}H_7F_4N$	55.39	3.23	35.22	6.45	55.35	3.22	35.00	6.44	79
XV	CH_3	CH_3	H	74—75	217	$C_{10}H_7F_4N$	55.04	3.27	34.96	6.75	55.35	3.22	35.00	6.44	84
XVI	CH_3	CH_3	CH_3	145—146	231	$C_{11}H_9F_4N$	56.98	3.98	32.83	6.42	57.15	3.89	32.90	6.06	55
XVII	C_2H_5	H	H	36—37	217	$C_{10}H_7F_4N$	54.88	3.18	34.87	6.72	55.35	3.22	35.00	6.44	75
XVIII	n-C_3H_7	H	H	—	231	$C_{11}H_9F_4N$	57.09	3.96	32.92	6.43	57.15	3.89	32.90	6.06	68
XIX	i-C_3H_7	H	H	62—63	231	$C_{11}H_9F_4N$	56.93	3.93	32.76	6.09	57.15	3.89	32.90	6.06	79
XX	$CH_2C_6H_5$	H	H	55—56	279	$C_{15}H_9F_4N$	64.78	3.21	26.88	4.89	64.54	3.22	27.22	5.02	78
XXI	$CH(CH_2)_4CH_2$	H	H	64—65	217	$C_{14}H_{13}F_4N$	62.23	4.75	28.03	5.54	62.00	4.78	28.08	5.16	85

*XIII and XIV were crystallized from hexane, XV-XVII and XIX-XXI from methanol; XVIII was purified by column chromatography (Al_2O_3), bp 119-120° C (16 mm); n_D^{20} 1.4953.

The molecular weights of compounds XIII–XXI, found from the mass spectra, were equal to the calculated figures.

Table 3. NMR Spectra of the 4, 5, 6, 7-Tetrafluoroindoles

Indole	PMR spectrum,* ppm				^{19}F NMR spectrum,** ppm			
	H^2	H^3	Substituents	Intensities	F^4	F^5	F^6	F^7
XIII	d 6,82	dd 6,35	s 2,36 (CH_3)	1:1:3	−13.0	+7.9	+4.9	+2.9
XIV	s 6,58	—	d 3,82 (CH_3^1), s 2,27 (CH_3^3)	1:3:3	−8.7	+9.2	+5.0	+2.4
XV		m 6,08	d 3,75 (CH_3^1), s 2,70 (CH_3^2)	1:3:3	−11.2	+8.8	+6.6	+4.6
XVI	—	—	d 3,76 (CH_3^1), s 2,24 (CH_3^2 and CH_3^3)	1:2	−6.7	+10.3	+6.9	+4.8
XVII	d 6,97	dd 6,45	q 4,28 (CH_2), t 1,48 (CH_3)	1:1:2:3	−12.3	+7.9	+4.5	+3.0
XVIII	d 6,93	dd 6,45	t 4,17 (α-CH_2), sx 1,85 (β-CH_2), t 0,90 (CH_3)	1:1:2:2:3	−12.2	+7.8	+4.4	+2.4
XIX	d 7,08	dd 6,53	m 4,86 (CH), d 1,49 $(CH_3)_2$	1:1:1:6	−12.6	+8.1	+4.5	+1.5
XX	d 6,93	dd 6,49	s 5,30 (CH_2), m 7,3—7,0 (C_6H_5)	1:1:2:5	−13.0	+7.3	+3.5	+1.5
XXI	d 7,07	dd 6,43	m 4,36 (CH), m 2,3—1,3 (C_6H_{10})	1:1:1:10	−12.6	+8.2	+4.7	+1.6

*Abbreviations: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; sx, sextet; m, multiplet.

**Compounds XIII and XIV were recorded in tetrahydrofuran.

The amino alcohols III and VII–XI were obtained from 2-nitro-1-pentafluorophenylethanol [2], and IV, V, and VI from 1-nitro-2-pentafluorophenylpropan-2-ol [6], 2-nitro-1-pentafluorophenylpropan-1-ol [3], and 3-nitro-2-pentafluorophenylbutan-2-ol, [6], respectively. Formalin (40%) and freshly distilled aldehydes and ketones were used as the carbonyl components.

Table 4. UV Spectra of the 4, 5, 6, 7-Tetrafluoroindoles

Indole	λ_{max}, nm	lg ε
XIII	207, 244, 261, 286	4,48; 3.59; 3.57; 3.46
XIV	215, 248, 269, 289	4,44; 3.46; 3.46; 3.53
XV	212, 250, 263	4,53; 3.69; 3.71
XVI	197, 217, 258, 273	4,49; 4.46; 3.62; 3.65
XVII	210, 246, 263, 278	4,32; 3.57; 3.60; 3.53
XVIII	209, 246, 262, 278	4,50; 3.53; 3.56; 3.48
XIX	209, 246, 263, 278	4,53; 3.57; 3.61; 3.54
XX	209, 244, 262, 276	4,54; 3.64; 3.68; 3.58
XXI	209, 246, 264, 280	4,54; 3.59; 3.62; 3.58

Reduction of the nitro alcohols. A mixture of 0.02 mole of a nitro alcohol and 0.06 mole of a carbonyl compound was reduced in 20 ml of methanol and 7 ml of conc HCl with the aid of a potentiostat [7] (the potential of the Hg cathode was −1.65 V relative to SCE). After electrolysis for 5 hr, the catholyte was evaporated in vacuo and the dry residue was dissolved in water. The aqueous solution was washed with ether and neutralized with 10% Na_2CO_3 solution, and the reaction product was filtered off (XI) or extracted with CCl_4 (III–X). The hydrochloride was obtained, and this was converted into the free base. To remove the primary amine, extraction with petroleum ether (40–60° C) was carried out. To avoid spontaneous cylization, the work with the free bases was performed rapidly and with cooling.

2-Isopropylideneamino-1-pentafluorophenylethanol N-oxide (II) was obtained by the evaporation of an acetone solution of 2-hydroxyamino-1-pentafluorophenylethanol [3]; yield 96%, mp 174–175° C (from dichloroethane). Found, %: C 46.70, 47.06; H 3.56, 3.56; F 33.31, 33.06; N 4.90, 5.05. Calculated for $C_{11}H_{10}F_5NO_2$, %: C 46.70; H 3.53; F 33.55; N 4.95. UV spectrum, λ_{max}, nm (log ε): 206, 238 (3.62, 3.99). IR spectrum, cm^{-1}: 1000 s (C—F), 1170 s (N → O), 1510 s and 1530 s (aromatic ring). The electrochemical reduction of II by the method described above, but without the addition of a carbonyl compound, gave IX, yield 55%.

4, 5, 6, 7-Tetrafluoro-3-hydroxy-1-methylindoline (XII). A solution of 1.39 g (5 mM) of III in 20 ml of dimethylformamide was treated with 1.26 g (15 mM) of $NaHCO_3$, and the mixture was stirred at 100° C for 10 min and boiled for about 2 hr. Then it was diluted fourfold with water, and the reaction product was extracted with ether, after which vacuum sublimation at 120° C (12 mm) yielded 0.9 g (82%) of XII, mp 99–100° C (from hexane). Found, %:

C 48.01. 49.21; H 3.12, 3.17; F 34.47, 34.39; N 6.57, 6.73. Calculated for $C_9H_7F_4NO$, %: C 48.90; H 3.16; F 34.39; N 6.33. UV spectrum, λ_{max}, nm (log ε): 204, 244, 300 (4.19, 3.92, 3.52). IR spectrum, cm^{-1}: 990 s (C—F), 1500 s and 1525 s (aromatic ring), 2805 m, 2840 m and 2960 m (CH and CH_2), 3610 s (OH). The ^{19}F NMR spectrum (in tetrahydrofuran) contained four multiplets of equal intensity at 9.44, 2.64, -6.07, and -17.70 ppm.

When XII was heated with concentrated hydrochloric acid, the indole XIII was obtained in a yield of 98%.

Cyclization of the amino alcohols. An amino alcohol hydrochloride, 5 mM, was shaken with 2 ml of concentrated ammonia, and the free base was extracted with ether. The ethereal extract was mixed with 20 ml of dimethylformamide, the ether was evaporated off with heating, and after 2 hr boiling the cyclization product was distilled off with steam.

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