PREPARATION AND CYCLIZATION OF 2-HYDRAZINO-1-PENTAFLUOROPHENYLETHANOL

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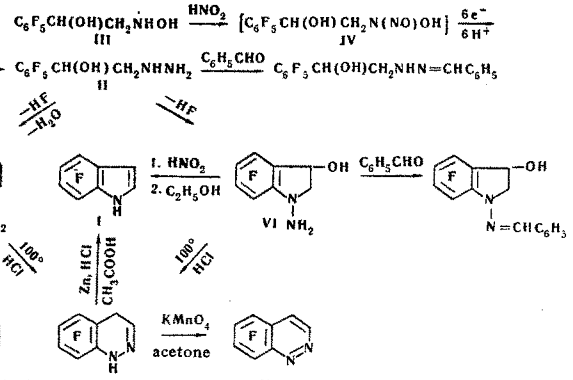
By potential-controlled electrochemical reduction, 2-hydroxyamino-1-pentafluorophenylethanol has been converted in the presence of nitrous acid into 1-hydrazino-2-pentafluorophenylethanol, which on heating in dimethylformamide forms 1-amino-4,5,6,7-tetrafluoroindole or 1-amino-4,5,6,7-tetrafluoro-3-hydroxyin hydroxyindoline, depending on the conditions. On being heated with hydrochloric acid, both cyclization products are converted into 5, 6, 7, 8-tetrafluoro-1, 4-dihydrocinnoline, which has been oxidized to 5, 6, 7, 8-tetrafluorocinnoline.

We have previously shown that the electrochemical reduction of 2-nitro-1-pentafluorophenylalkanols can give rise to polyfluorinated hydroxyamino alcohols or amino alcohols; these compounds have been used successfully for the synthesis of 4, 5, 6, 7-tetrafluoroindole (I) and its derivatives [1, 2].

The present paper describes a new method for obtaining 2-hydrazino-1-pentafluorophenylethanol (II) by the potential-controlled electrochemical reduction of 2-hydroxyamino-1-pentafluorophenylethanol (III) in the presence of nitrous acid. It is assumed that 2-(N-nitrosohydroxyamino)-1-pentafluorophenylethanol (IV) is an intermediate product of the reaction.

The methods given in the literature [3] for obtaining hydrazino alcohols may prove ineffectual for polyfluorinated derivatives, since under the conditions generally used for these purposes nucleophilic replacement of the fluorine atoms takes place.

It appeared of interest to study the cyclization of the hydrazino alcohol II, for which reactions involving both the primary and the secondary nitrogen atoms of the hydrazino group could be expected.



When the free base II was heated in dimethylformamide or in the presence of sodium bicarbonate, it cyclized at the secondary nitrogen atom with the formation of 1-amino-4, 5, 6, 7-tetrafluoroindole (V) and 1-amino-4, 5, 6, 7-tetrafluoro-3-hydroxyindoline (VI), respectively. The structures of V and VI were confirmed by their chemical reactions, their molecular weights, their spectra, and their elementary analyses.

The presence of an $H_2N—N <$ group in V and VI is shown by the formation of benzylidenehydrazones whose IR spectra lack the absorption band of the NH group. The PMR spectrum of V has three signals: a doublet at 6.95 ppm (H^2); a doublet of doublets at 6.25 ppm (H^3), and a multiplet at 4.98 ppm (NH_2) with a ratio of the intensities of 1 : 1 : 2; the spin-spin coupling constants ($J_{H^2H^3}$ = 3.2 Hz and $J_{H^3F^7}$ = 2.1 Hz) are close to the values obtained for some other N-substituted 4, 5, 6, 7-tetrafluoroindoles.

The indoline VI reduces an ammoniacal solution of silver nitrate with the formation of the metal, and on diazotization and subsequent heating with ethanol it forms the indole I. The IR spectrum of the benzylidene derivative of VI has the absorption band of an OH group and no band of an NH group.

Another confirmation of the structure of V is its rearrangement into 5, 6, 7, 8-tetrafluoro-1, 4-dihydrocinnoline (VII). It is known [4, 5] that in acid solution N-aminoindoles exist in equilibrium with 1, 4-dihydrocinnolines, and the latter can be oxidized to cinnolines or be reduced to indoles. In agreement with this, we obtained 5, 6, 7, 8-tetrafluorocinnoline (VIII) and the indole I from VII. The structures of VII and VIII were confirmed by their elementary analyses, molecular weights, and spectra. The IR spectrum of VII has bands at (cm^{-1}) 1510 (s) and 1535 (s) (aromatic ring), 2870 (w) and 2840 (w) (CH and CH_2), 1667 (m) (C═N) and 3428 (m) (NH); the PMR spectrum of VII contains three signals, a multiplet at 3.29 ppm (CH_2), a triplet at 6.70 ppm (CH), and a multiplet at 7.89 ppm (NH) with an intensity ratio of 2 : 1 : 1; it is similar to the PMR spectrum of the nonfluorinated analog (3 signals: doublet at 3.19 ppm (CH_2), multiplet at 6.4–7.1 ppm, and a singlet at 7.98 ppm (NH) [6]).

The spectra of VIII and its nonfluorinated analogs are similar; the IR spectrum of VIII has the characteristic band of the cinnolines [6] at 1571 cm^{-1}; the UV spectrum was somewhat simplified and shifted in the long-wave direction and it contains the absorption band of the N═N group at 394 nm (log ε 2.46) that is characteristic for the cinnolines [in the nonfluorinated analog it is at 390 nm (log ε 2.42) [6]] and, finally, the PMR spectrum has two doublets of equal intensity, at 8.00 ppm (CH), and 9.50 ppm (CH) (both with J = 6 Hz) [in the nonfluorinated analog there are three signals: a multiplet at 7.6–7.9 ppm, a multiplet at 8.3–8.5 ppm, and a doublet at 9.22 ppm (J = 6.0 Hz) [6]].

Compound VII was also obtained from the indole VI. Like the other 4, 5, 6, 7-tetrafluoro-3-hydroxyindolines [2], on being heated with hydrochloric acid VI undergoes dehydration, apparently to the indole V, which undergoes further rearrangement to form VII.

EXPERIMENTAL

The IR spectra were taken in CCl_4 on a UR-10 instrument, the UV spectra in ethanol on a SP 700s instrument, the PMR spectra (relative to hexamethyldisiloxane) and the ^{19}F NMR spectra (relative to C_6F_6) in CCl_4 on a Varian A 56/60A instrument. The molecular weights were determined from the mass spectra.

Hydrochloride of 2-hydrazino-1-pentafluorophenylethanol (II). A solution of 12.9 g (50 mM) of 2-nitro-1-pentafluorophenylethanol [1] in a mixture of 30 ml of ethanol and 20 ml of concentrated hydrochloric acid was reduced with the aid of a potentiostat [7] at a potential of the dropping mercury electrode of −0.95 V relative to the SCE. The resulting solution of the hydroxylamine III was slowly treated with a solution of 3.8 g (55 mM) of $NaNO_2$ in 10 ml of water and, with an increase in the potential of the cathode to −1.5 V, reduction was continued until the intensive evolution of hydrogen began. After electrolysis, which lasted for 8 hr, the catholyte was evaporated in vacuo at 50° C, and the crystalline residue was dissolved in 50 ml of water. The resulting solution was shaken for 1 hr with 5.5 ml (55 mM) of benzaldehyde and extracted with ether (3 × 50 ml). The ethereal extract was treated with 6.3 g (50 mM) of oxalic acid dihydrate, the ether was evaporated off, and the benzaldehyde was distilled off with steam. The crystals that deposited from the aqueous solution was filtered off, dried, washed with ether, and extracted with 15 ml of 20% sodium carbonate solution and 20 ml of ether. Extraction was carried out three times and then the ethereal solution was dried with $MgSO_4$ and II was precipitated with gaseous HC; yield 5.7 g (41%) of a substance decomposing at 180° C. Found, %: C 34.15, 34.26; H 2.85, 2.90; Cl 12.90, 13.00; F 34.56, 34.78; N 9.96, 9.66. Calculated for $C_8H_7F_5N_2O \cdot HCl$, %: C 34.49; H 2.87; Cl 12.75; F 34.10; N 10.04. Benzylidene derivative, mp 145–146° C (from aqueous methanol). Found, %: C 54.70, 54.97; H 3.44, 3.49; F 28.87, 29.00; N 8.56, 8.61. Calculated for $C_{15}H_{11}F_5N_2O$, %: C 54.58; H 3.32; F 28.79; N 8.47. IR spectrum, cm^{-1} (in KBr): 1100 s (C—F), 1510 s and 1535 s (aromatic ring); (in CCl_4, 0.05%): 3540 m (NH), 3612 m (OH). UV spectrum, λ_{max}, nm (log ε): 201, 221, 293 (4.14, 4.00, 4.13).

1-Amino-4, 5, 6, 7-tetrahydrofuroindole (V). 1.39 g (5 mM) of **II** was shaken with 2 ml of 20% sodium carbonate solution, and the free base was extracted with ether. The ethreal extract was mixed with 10 ml of dimethylformamide, the ether was distilled off, and the residual solution was boiled for 2 hr. The reaction product was distilled with steam and was purified by the precipitation of the hydrochloride from solution in CC_4; the yield of V with mp 95–97° C (from hexane) was 0.57 g (56%). Found, %: C 47.21, 47.31; H 1.78, 1.79; F 37.42, 37.66; N 13.92, 14.09. mol wt 204. Calculated for $C_8H_4F_4N_2$, %: C 47.02; H 1.96; F 37.21; N 13.71. mol wt 204. IR spectrum, cm^{-1}: 1003 s (C—F), 1310 s (C—N aromatic), 1495 s and 1550 (aromatic ring), 3380 m (NH_2). UR spectrum, λ_{max}, nm (log ε): 209, 245, 263, 280 (4.80, 3.51, 3.53, 3.44). The ^{19}F NMR spectrum contained four signals of equal intensity at: 7.80, 6.57, 3.45, and −11.32 ppm. Hydrochloride, mp 124° C (decomp). Found, %: C 39.68, 39.98; H 2.07, 1.99; Cl 14.68, 14.81; F 31.54, 31.49; N 11.65, 11.75. Calculated for $C_8H_4F_4N_2 \cdot HCl$, %: C 39.89; H 2.08; Cl 14.75; F 31.67; N 11.63. Benzylidene derivative, mp 136–137° C (from hexane). Found, %: C 62.04, 62.15; H 2.89, 2.92; F 26.08, 25.66; N 9.58, 9.69. Calculated for $C_{15}H_8F_4N_2$, %: C 61.60; H 2.74; F 26.08; N 9.59. IR spectrum, cm^{-1}: 1005 s (C—F), 1300 s (C—N, aromatic), 1490 s and 1555 s (aromatic ring). UV spectrum, λ_{max}, nm (log ε): 202, 224, 266, 332, 345 (4.37, 4.23, 4.04, 4.25, 4.22).

1-Amino-4, 5, 6, 7-tetrafluoro-3-hydroxyindoline (VI). A solution of 1.39 g (5 mM) of II in 10 ml of dimethylformamide was treated with 0.84 g (10 mM) of $NaHCO_3$, heated and stirred for 10 min, and then boiled for another hour. The reaction mixture was diluted twofold with water, the product was extracted with ether, the ethereal solution was dried with $MgSO_4$ and VI was precipitated in the form of the hydrochloride. The free base VI was sublimed in vacuo at 120° C (12 mm), yield 0.8 g (72%), mp 122–123° C (from $CHCl_3$). Found, %: C 43.32, 43.68; H 2.87, 3.00; F 33.94, 34.49; N 12.18, 12.29. Mol wt 222. Calculated for $C_8H_6F_4N_2O$, %: C 43.26; H 2.71; F 34.22; N 12.61. Mol wt 222. IR spectrum, cm^{-1} (in KBr): 1000 s and 1012 s (C—F); 1501 s and 1522 s (aromatic ring); (in CCl_4, 0.05%): 2860 m, 2930 m, and 2970 m (CH and CH_2), 3370 m (NH_2), 3612 s (OH). UV spectrum, λ_{max}, nm (log ε): 206, 242, 290 (4.13, 3.78, 3.44). The ^{19}F NMR spectrum has four multiplets equal in intensity (in tetrahydrofuran): at 6.63, 0.69, -5.65, and -15.70 ppm. Hydrochloride, mp 200–201° C. Found, %: Cl 13.75, 13.89. Calculated for $C_8H_6F_4N_2O \cdot HCl$, %: Cl 13.80. Benzylidene derivative, mp 166–167° C (from $CHCl_3$). Found, %: C 58.54, 58.30; H 3.32, 3.40; F 24.83, 24.88; N 9.04, 9.01. Calculated for $C_{15}H_{10}F_4N_2O$, %: C 58.08; H 3.23; F 24.50; N 9.04. IR spectrum, cm^{-1} (in KBr): 1495 s and 1528 s (aromatic ring); (in CCl_4, 0.05%): 2860 w, 2922 m, and 2990 w (CH and CH_2), 3025 w, 3065 w (C—H aromatic), 3611 s (OH). UV spectrum, λ_{max}, nm (log ε): 200, 228, 327 (4.29, 404, 4.41).

By heating 0.22 g (1 mM) of VI with conc HCl, using the method given below, 0.19 g (96%) of VII was obtained; it was identified by its IR spectrum and a mixed melting point test.

Compound VI, 0.11 g (0.5 mM), was diazotized with $NaNO_2$ in HCl solution at 0° C, then ethanol was added and the mixture was boiled for half an hour. Steam distillation yielded 0.08 g (83%) of the indole I.

5, 6, 7, 8-Tetrafluoro-1, 4-dihydrocinnoline (VII). A mixture of 0.2 g (1 mM) of V and 2 ml of conc HCl was heated at 90° C for 10 min; steam distillation yielded 0.19 g (96%) of VII, mp 81–82° C (from hexane). Found, %: C 47.58, 47.62; H 2.14, 1.89; F 37.13, 36.94; N 13.36, 13.29. Mol wt 204. Calculated for $C_8H_4F_4N_2$, %: C 47.02; H 1.96; F 37.21; N 13.71. Mol wt 204. UV spectrum, λ_{max}, nm (log ε): 209, 283 (3.94, 3.64). The ^{19}F NMR spectrum had four multiplets of equal intensity at 4.82, 1.33, -2.70, and -15.20 ppm.

When VII was reduced with zinc dust in glacial acetic acid with the addition of conc HCl, after the solution was cooled compound I was obtained with a yield of 75%.

5, 6, 7, 8-Tetrafluorocinnoline (VIII). A solution of 0.24 g (0.75 mM) of $KMnO_4$ in 10 ml of acetone was added to a solution of 0.2 g (1 mM) of VII in 1 ml of acetone, the mixture was shaken for 10 min, and the MnO_2 was filtered off. The filtrate was evaporated and the residue was dissolved in 2 ml of conc HCl. The solution was washed with ether, diluted with water, and neutralized with NH_4OH, and then ether extracted 0.13 g (64%) of VIII, mp 107–108° C (from hexane). Found, %: C 47.79, 48.01; H 0.97, 0.92; F 37.70, 37.35; N 13.77, 14.03. Mol wt 202. Calculated for $C_8H_2F_4N_2$, %: C 47.50; H 0.99; F 37.64; N 13.88. Mol wt 202. IR spectrum, cm^{-1}: 1500 s (aromatic ring), 1571 m (characteristic band of the cinnolines [8]). UR spectrum, λ_{max}, nm (log ε) (in cyclohexane): 230, 284, 294, 327, 394, (4.55, 3.27, 3.29, 3.29, 2.46). The ^{19}F NMR spectrum has two multiplets of equal intensity: one consists of two overlapping triplets (-10.12 and -10.58 ppm) and the second is the sum of two signals: a quartet of doublets and a doublet having the same chemical shift of -12.40 ppm.

REFERENCES

1. V. P. Petrov, V. A. Barkhash, G. S. Shchegoleva, T. D. Petrova, T. I. Savchenko, and G. G. Yakobson, DAN, **178**, 864, 1968.
2. V. P. Petrov and V. A. Barkhash, KhGS [Chemistry of Heterocyclic Compounds], **6**, 385, 1970.
3. G. Gever, J. Am. Chem. Soc., **76**, 1283, 1954.
4. H. Haddlesey, P. Mayor, and S. Szinai, J. Chem. Soc., 5262, 1964.
5. L. Besford and J. Bruce, J. Chem. Soc., 4037, 1964.
6. L. Besford, G. Allen, and J. Bruce, J. Chem. Soc., 2867, 1963.
7. G. G. Yakobson and V. P. Petrov, Izv. SO AN SSSR, ser. khim., **2**, 75, 1968.
8. A. Katritzky, ed., Physical Methods in Heterocyclic Chemistry [Russian translation], Khimiya, Moscow-

Leningrad, 603, 1966.

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