CYCLIZATION OF 1-(PENTAFLUOROPHENYL)-2-AMINOALKANOLS

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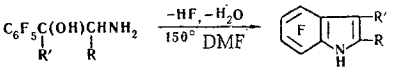
The nitro group in 1-(pentafluorophenyl)-2-nitroalkanols is reduced selectively to a hydroxylamino or amino group by controlled potential electrochemical reduction. The pentafluorophenylaminoalkanols cyclize readily on heating in dimethylformamide to give homologs of 4,5,6,7-tetrafluoroindole. It is shown that the intermediate in the cyclization of 1-pentafluorophenyl-2-aminoethanol is 3-hydroxy-4,5,6,7-tetrafluoroindoline. Cyclization of 1-pentafluorophenyl-2-hydroxyaminoethanol gave 1,3-dihydroxy-4,5,6,7-tetrafluoroindoline.

We have shown recently [1] that heating 1-pentafluorophenyl-2-aminoethanol (I) in dimethylformamide gives 4,5,6,7-tetrafluoroindole (II) in good yield. The reaction proceeds via the intramolecular nucleophilic displacement of the ortho fluorine atom [2], followed by dehydration. In order to demonstrate the general nature of this reaction, this paper describes the cyclization of other pentafluorophenylaminoalkanols, the mono and dimethyl derivatives of II being obtained in good yield.



$R' = H, CH_3, CH_3$; $R = CH_3, H, CH_3$.

The general nature of the reaction is confirmed by the formation of 2-hydroxymethyl-4,5,6,7-tetrafluoroindole [3] by cyclization of dl-erythro- or dl-threo-1-pentafluorophenyl-2-aminopropane-1,3-diol.

The literature method for the preparation of II, by cyclization of diethyl N-(2,3,4,5,6-pentafluorophenyl)aminofumarate, is of limited applicability by comparison with our method, and it gives lower yields of the reaction products.

In the cyclization of I, we have established that elimination of HF and H_2O takes place consecutively, and we have isolated the intermediate reaction product. In the presence of sodium bicarbonate, 3-hydroxy-4,5,6,7-tetrafluoroindoline (X) is formed smoothly. Compound X is stable in the free state or in alkaline solution, but it is readily dehydrated by concentrated hydrochloric acid with the formation of II. The formation of tetrafluoroindole and its homologs by boiling pentafluorophenylaminoalkanols in DMF is apparently explained by the catalytic effect of the hydrogen fluoride, liberated in the cyclization, on the dehydration of the intermediate 3-hydroxyindoline.

It was of interest to carry out the cyclization of 1-pentafluorophenyl-2-hydroxyaminoethanol (XI), since there are two possible routes for the nucleophilic substitution of the ortho fluorine atom, i.e., attack by the NH or by the OH groups. On heating in DMF with the addition of NaF, XI cyclized at the nitrogen to give 1,3-dihydroxy-4,5,6,7-tetrafluoroindoline. The latter readily breaks down on heating, and also on treatment with mineral acids, alkalis, or dehydrating agents ($POCl_3$), and it reduces ammoniacal $AgNO_3$ and $CuCl_2$ to the metallic state. It gives a dibenzoyl derivative, and it is reduced by zinc in acid solution to II.

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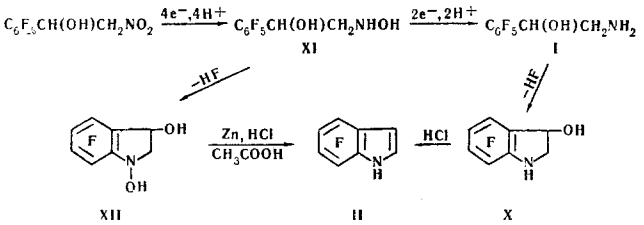

The amino alcohols used as starting materials were obtained by the controlled-potential electrochemical reduction of the nitro alcohols. Polarographic reduction of the nitroalkanols in a base of Robinson–Britton buffer solution in 50% aqueous ethanol showed that the reduction proceeded as far as the hydroxyamino alcohols, which were not further reduced at any pH between 1 and 8. Selective reduction of the intermediate hydroxyamino alcohols to amino alcohols without affecting the fluorine atoms was achieved by raising the potential of the mercury cathode above the hydrogen liberation potential (−1.8 V). The upper limit of the cathode potential, which was limited by attack on the fluorine atoms, was −2.1 V [5].

The electrochemical reduction of nitro alcohols has undoubted advantanges over chemical methods. For instance, English authors [6] failed to obtain I in the pure state by reduction of 1-pentafluorophenyl-2-nitroethanol with $LiAlH_4$.

Thanks to the accessibility of 1-pentafluorophenyl-2-nitroalkanols from the condensation of pentafluorophenylbenzaldehyde with nitroalkanes [1, 6], or by the nitration of ring-fluorinated tertiary alcohols [7], the cyclization of pentafluorophenylaminoalcohols is a convenient preparative route to II and its derivatives.

EXPERIMENTAL

The IR spectra were recorded on CCl_4 on a UR-10 instrument, and the UV spectra in ethanol on an SP.700C instrument. The PMR spectra (in CCl_4, relative to hexamethylsiloxane), and the ^{19}F NMR spectra (the solvent is given in the description, the shifts being relative to hexafluorobenzene) were taken on a Varian A56/60 instrument. The molecular weights were determined by mass spectrometry.

1-Pentafluorophenyl-2-nitropropanol (III) was obtained by condensation of pentafluorobenzaldehyde with nitroethanol by method [7]. Yield 77%, bp 153–154° C (12 mm), n_D^{20} 1.4632. Found, %: C 40.21, 40.52; H 2.15, 2.23; F 35.26. 35.28; N 5.17, 5.42. Calculated for $C_9H_6F_5NO_3$, %: C 39.90; H 2.21; F 35.04; N 5.17. IR spectrum, cm^{-1}: 1000 s (C-F), 1510 s and 1530 s (aromatic ring), 1365 m and 1570 s (NO_2), 2940 w and 2990 w (C–H and CH_3), 3540 broad (OH_{bonded}), and 3615 m (OH_{free}). UV spectrum, λ_{max}, nm (log ε): 204 (4.00) and 264 (3.15).

1-Pentafluorophenyl-2-aminopropanol (IV). A 13.55-g (0.05 mole) quantity of III in a mixture of 30 ml of acetic acid and 20 ml of 15% HCl was reduced using a potentiostat [8]. After electrolysis for 6 hr with a mercury cathode potential of −1.8 V relative to the saturated calomel electrode, the catholyte was diluted with 3 times its volume of water, and washed with ether to remove impurities. The aqueous layer was neutralized with an excess of aqueous ammonia, and extracted repeatedly with ether. The ether extracts were dried over $MgSO_4$, and evaporated in vacuo to give 9.9 g (82%) of IV, mp 109° C (decomp, from ether). Found, %: C 44.44, 44.43; H 3.24, 3.24; F 39.42, 39.15; N 5.99, 6.00. Calculated for $C_9H_8F_5NO$, %: C 44.81; H 3.32; F 39.44; N 5.82. UV spectrum, λ_{max}, nm (log ε): 202 (3.85) and 262 (2.63). Hydrochloride, mp 256–258° C. Found, %: C 38.75, 38.90; H 3.01, 3.12; Cl 12.82, 12.83. Calculated for $C_9H_8F_5NO \cdot HCl$, %: C 38.91; H 3.24; Cl 12.81.

2-Pentafluorophenyl-1-amino-2-propanol (V) was obtained by reduction of 13.55 g (0.05 mole) of 2-pentafluorophenyl-1-nitro-2-propanol [7] by the method given above, in a yield of 10.5 g (88%), mp 58–59° C (purified by reprecipitation of the hydrochloride). Found, %: C 44.90, 44.65; H 3.43, 3.36; F 39.52, 39.81; N 5.76, 6.00. Calculated for $C_9H_8F_5NO$, %: C 44.81; H 3.32; F 39.44; N 5.82. UV spectrum, λ_{max}, nm (log ε): 202 (3.81) and 262 (2.83). Hydrochloride, mp 182–183° C. Found, %: C 38.94, 38.96; H 3.67, 3.59; Cl 12.52, 12.55. Calculated for $C_9H_8F_5NO \cdot HCl$, %: C 38.91; H 3.21; Cl 12.81.

2-Pentafluorophenyl-3-amino-2-butanol hydrochloride (VI) was obtained by reduction of 5.7 g (0.02 mole) of 2-pentafluorophenyl-3-nitro-2-butanol [7], yield 3.5 g (61%), mp 112–114° C. Found, %: C 41.20, 41.31; H 3.78, 3.90; F 32.89, 33.06; N 5.15, 5.27; Cl 11.99, 11.80. Calculated for $C_{10}H_{10}F_5NO \cdot HCl$, %:

C 41.15; H 3.77; F 32.59; N 4.80; Cl 12.18. The free base was unstable at room temperature, losing HF and H_2O and cyclizing to give 2,3-dimethyl-4,5,6,7-tetrafluoroindole.

2-Methyl-4,5,6,7-tetrafluoroindole (VII). A solution of 1.2 g(5 mmole) of IV in 10 ml of dry dimethylformamide was boiled for 2 hr, diluted with three times its volume of water, and extracted with ether. The ether solution was dried over $MgSO_4$, evaporated in vacuo, and the crystalline residue was distilled in vacuo at 12 mm and 120° C to give 0.84 g (82%) of product, mp 140-141° C (from hexane). Found, %: C 53.13, 53.06; H 2.45, 2.45; F 37.63, 37.78; N 6.73, 6.93. Mol wt 203. Calculated for $C_9H_5F_4N$, %: C 53.25; H 2.42; F 37.43; N 6.90. Mol wt 203. IR spectrum, cm^{-1}: 996 strong (C-F), 1346 strong (C−N aromatic), 1500 strong and 1545 medium (aromatic ring), and 3485 strong (N−H). UV spectrum, λ_{max}, nm (log ε): 208 and 262 (4.51 and 3.77). ^{19}F NMR spectrum (in $CDCl_3$): 8.95, 6.33, 0.60, and −11.70 ppm.

3-Methyl-4,5,6,7-tetrafluoroindole (VIII) (4,5,6,7-tetrafluoroskatole) was obtained by cyclization of V in 84% yield, mp 96-97° C (from hexane). Found, %: C 52.97, 53.17; H 2.41, 2.38; F 37.39, 37.17; N 6.99, 6.56. Mol wt 203. Calculated for $C_9H_5F_4N$, %: C 53.25; H 2.42; F 37.43; N 6.90. Mol wt 203. IR spectrum, cm^{-1}: 1008 strong (C-F), 1335 strong (C−N aromatic), 1495 strong and 1535 strong (aromatic ring), and 3485 strong (N−H). UV spectrum, λ_{max}, nm (log ε): 212, 252, and 265 (4.50, 3.56, and 3.60). The PMR spectrum showed three singlets, at 2.32 (CH_3), 6.80 (α-H), and 7.84 ppm (broad, NH) with relative intensities 3 : 1 : 1. The ^{19}F NMR spectrum: 8.50, 3.90, 1.21, and −8.33 ppm.

2,3-Dimethyl-4,5,6,7-tetrafluoroindole (IX). A 1.46 g (5 mmole) quantity of VI was shaken with 3 ml of aqueous NH_4 and extracted repeatedly with ether. The ether extract was dried over $MgSO_4$, evaporated in vacuo, and the residue was cyclized by the method given above to give 90% of IX, mp 126-127° C (from hexane). Found, %: C 55.49, 55.75; H 3.13, 2.87; F 34.85, 35.20; N 6.75, 6.99. Mol wt 217. Calculated for $C_{10}H_7F_4N$, %: C 55.31; H 3.23; F 35.00; N 6.46. Mol wt 217. UV spectrum, λ_{max}, nm (log ε): 216 and 268 (4.36 and 3.66). IR spectrum, cm^{-1}: 1018 strong (C−F), 1335 strong (C−N aromatic), 1492 strong and 1542 strong (aromatic ring), and 3474 strong (NH). Two signals were seen in the PMR spectrum, at 2.22 (α- and β-CH_3) and 7.60 ppm (broad, NH), with relative intensities 6 : 1. ^{19}F NMR spectrum: 8.68, 5.37, 1.77, and −7.04 ppm.

3-Hydroxy-4,5,6,7-tetrafluoroindoline (X). Cyclization of the amino alcohol I was carried out by a similar method, but with the addition of 0.84 g (10 mmole) of $NaHCO_3$. Steam distillation of the reaction mixture gave 86% of X, mp 97-98° C (from water). Found, %: C 46.43, 46.30; H 2.47, 2.67; F 36.71, 36.70; N 6.84, 7.10. Calculated for $C_8H_5F_4NO$, %: C 46.40; H 2.41; F 36.70; N 6.76. UV spectrum, λ_{max}, nm (log ε): 198, 236, and 296 (4.34, 3.84, and 3.24). IR spectrum, cm^{-1}: 980 strong (C-F), 1510 strong and 1535 strong (aromatic ring), 3440 strong (N−H), 3620 strong (O-H). ^{19}F NMR spectrum: 10.9, 0.71, −5.06, and −18.6 ppm. A 0.21 g (1 mmole) quantity of X was dissolved in 2 ml of conc HCl, and after 5 min the precipitate of the indole II was filtered off, yield 95%. Identified by IR spectrum and mixed mp.

1-Pentafluorophenyl-2-hydroxyaminoethanol (XI) was obtained by reduction of 1-pentafluorophenyl-2-nitroethanol [1] by the method described above, at a cathode potential of −0.95 V, yield 94%, mp 116-117° C (from CCl_4). Found, %: C 39.32, 39.72; H 2.46, 2.26; F 38.85, 38.76; N 5.62, 5.79. Calculated for $C_8H_6F_5NO_2$, %: C 39.50; H 2.47; F 39.10; N 5.76. Hydrochloride, mp 160-161° C. Found, %: C 34.46, 34.71; H 2.47, 2.51; Cl 12.65, 12.92. Calculated for $C_8H_6F_5NO_2 \cdot HCl$, %: C 34.34; H 2.51; Cl 12.69. UV spectrum, λ_{max}, nm (log ε): 202 and 262 (3.88 and 2.72).

1,3-Dihydroxy-4,5,6,7-tetrafluoroindoline (XII). A solution of 2.41 g (0.01 mole) of XI in 25 ml of dimethylformamide containing 0.84 g (0.02 mole) of NaF was heated with stirring for 3 hr at 110° C. The mixture was diluted with water to a volume of 100 ml, saturated with sodium chloride, acidified carefully with dil HCl to pH 3, and extracted repeatedly with ether. The ether extract was washed with 0.1-N sodium bicarbonate, dried over $MgSO_4$, and evaporated in vacuo. The crystalline residue was washed with chloroform to give a yield of 63%, mp 135° C (decomp., from ether). Found, %: C 43.25, 43.47; H 2.46, 2.29; F 34.25, 33.90; N 6.45, 6.57. Calculated for $C_8H_5F_4NO_2$, %: C 43.02; H 2.24; F 34.10; N 6.28. UV spectrum, λ_{max}, nm (log ε): 199, 244, and 280 (4.32, 3.72, and 2.05). The ^{19}F NMR spectrum (in tetrahydrofuran) contained 4 multiplets of equal intensity at 2.27, −5.46, −5.73, and −17.40 ppm.

1,3-Dihydroxy-4,5,6,7-tetrafluoroindoline dibenzoate was obtained by reaction of benzoyl chloride with XII, in 5-N NaOH, yield 98%, mp 128-129° C (from hexane). Found, %: C 61.28, 60.92; H 2.88, 3.10; F 17.30, 17.52; N 3.21, 3.40. Calculated for $C_{22}H_{13}F_4NO_4$, %: C 61.28; H 3.02; F 17.63; N 3.25. IR spectrum, cm^{-1}: 1020 strong (C−F), 1260 strong C−O−C), 1510 strong and 1525 strong (aromatic ring), and 1730 strong and 1770 strong (C=O). UV spectrum, λ_{max}, nm (log ε): 200 and 232 (4.75 and 4.22).

To a solution of 0.22 g (1 mmole) of XII in 1 ml of glacial acetic acid and 2 ml of HCl was added with cooling 0.4 g of zinc dust, and the mixture was shaken for 1 hr. After dilution with 2 volumes of water, the mixture was neutralized with sodium carbonate solution and the product was isolated by ether extraction. Distillation at 100° C (12 mm) gave 0.14 g (72%) of II (identified by IR and mixed mp).

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