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SYNTHESIS AND TRANSFORMATIONS OF 4-HYDROXY-5-METHYL-2-TRIFLUOROMETHYLPYRIDINE

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4-Hydroxy-5-methyl-2-trifluoromethylpyridine was synthesized from 3-hydroxy-3-methyl-6-trifluoromethyl-2,3-dihydro-4H-pyran-4-one. Its methylation leads to the formation of a mixture of N- and O-alkylation products, which were isolated chromatographically in the pure state. Convenient methods of their preparation are proposed.

Fluorinated heterocyclic compounds are becoming increasingly important [1-3]. Thus, perfluoroalkylated derivatives of pyridines and pyridinones have found applications in agriculture and medicine [4-8]. The principal approaches to the synthesis of the corresponding 4(1H)-pyridin-4-ones are based on reactions of acyclic fluorinated precursors, which usually lead to compounds unsubstituted at the nitrogen atom [7-12]. An appreciable biological activity is manifested by N-alkylated 4(1H)-pyridin-4-ones containing perfluoroalkyl substituents, which include the commercial herbicide fluridone [13].

Using previously prepared 3-hydroxy-3-methyl-6-trifluoromethyl-2,3-dihydro-4H-pyran-4-one (I) [14], we synthesized 4-hydroxy-5-methyl-2-trifluoromethylpyridine (II) and studied its transformations, including the reaction of methylation in various solvents. Dehydration of hydroxypyranone I in the presence of a small excess of thionyl chloride in pyridine formed 5-methyl-2-trifluoromethyl-4H-pyran-4-one (III), which is a suitable intermediate in the synthesis of hydroxypyridine II and its analogs. As was shown by data of PMR spectroscopy and TLC, the raw product of dehydration, containing an admixture of 3-methyl-6-trifluoromethyl-3-chloro-2,3-dihydro-4H-pyran-4-one (IV) (not more than 10%), was isolated in the pure state by means of column chromatography and was converted to the target pyranone III by boiling in triethylamine. However, dehydrochlorination of compound IV by pyridine takes place very slowly even with prolonged boiling, and therefore, pyranone

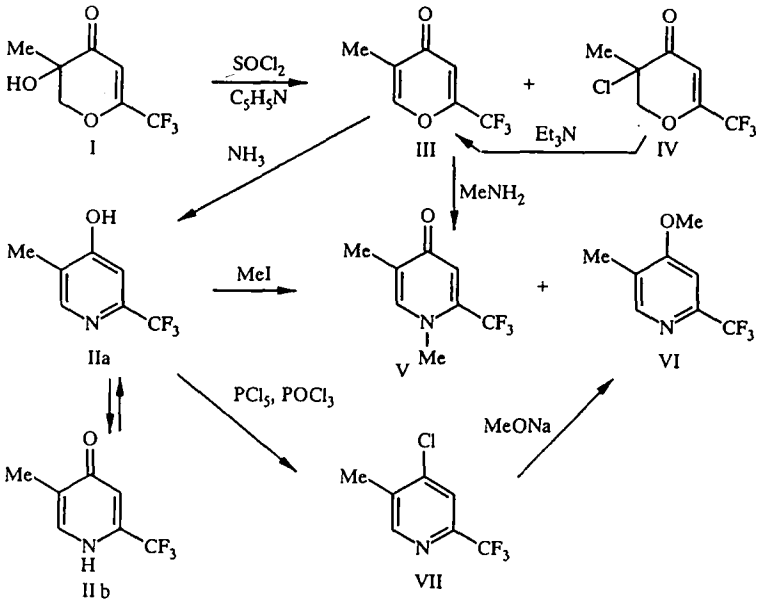

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TABLE 1. Properties of Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, % C	Found, % / Calculated, % H	mp, °C [T_b, °C (gPa)]*	M+	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm (J, Hz)	Yield, %
II	$C_7H_5F_3O_2$	47,34 / 47,20	3,01 / 2,83	15 [69...70 (19)]	178	1680, 1650	7,76 (1H, q, J = 1,3, 6-H), 6,53 (1H, s, 3-H), 1,83 (3H, d, J = 1,3, CH_3)	71
III	$C_7H_6ClF_3O$	39,25 / 39,18	2,89 / 2,82	[65...67 (15)]	214 (216)	1710, 1650	5,95 (1H, s, 5-H), 4,72, 4,44 (2H, d. d, J = 13, CH_2), 1,70 (3H, s, CH_3)	10
IV	$C_7H_6F_3NO$	47,61 / 47,47	3,58 / 3,41	143...144	177	1637 weak, 1600	11,82 (1H, s, OH), 8,19 (1H, s, 6-H), 7,28 (1H, s, 3-H), 2,29 (3H, s, CH_3)	94
V	$C_8H_8F_3NO$	50,12 / 50,27	4,37 / 4,22	124...125	191	1650, 1600, 1575	7,28 (1H, s, 6-H), 6,69 (1H, s, 3-H), 3,65 (3H, q, J = 1,3, NCH_3), 1,96 (3H, s, CH_3)	92†
VI	$C_8H_8F_3NO$	50,35 / 50,27	4,40 / 4,22	[77 (15)]	191	1607, 1585	8,53 (1H, s, 6-H), 7,11 (1H, s, 3-H), 3,97 (3H, s, OCH_3), 2,25 (3H, s, CH_3)	85‡
VII	$C_7H_5ClF_3N$	43,18 / 42,99	2,75 / 2,58	[74...75 (27)]	—	1595, 1585, 1560	8,56 (1H, s, 6-H), 7,69 (1H, s, 3-H), 2,48 (3H, s, CH_3)	80

*nD^{20}: II) 1.4401; III) 1.4379; VI) 1.4532; VII) 1.4570.

†Yield from pyranone II.

‡Yield from chloropyridine VII.

III free from impurities was obtained with a total yield of 71% by treating the unpurified dehydration product with triethylamine.

The reaction of pyranone III with ammonia in methanol formed hydroxypyridine II in almost quantitative yield. As expected [9], its methylation with iodomethane in boiling acetone in the presence of potassium carbonate led to a mixture of N- and O-alkylation products: 1,5-dimethyl-2-trifluoromethyl-4(1H)-pyridin-4-one (V) and 5-methyl-4-methoxy-2-trifluoromethylpyridine (VI) in a ratio of 3:2 (according to data of PMR spectroscopy). These compounds were isolated in the pure state by means of column chromatography with yields of 55% and 41%, respectively. The low solubility of pyridinone V in carbon tetrachloride makes it possible to isolate it in the same yield by crystallizing the reaction mass from the indicated solvent, but the yield of methoxypyridine VI remaining in the mother liquor as a result of distillation did not exceed 28%. To study the influence of the solvent on the ratio of the reaction products, the methylation of pyridinone V with iodomethane was also carried out in N,N-dimethylformamide under similar conditions (potassium carbonate, external heating to 60-70°C). To facilitate the monitoring of the ratio of the reaction products by means of PMR spectroscopy, DMFA-D_7 was used. It was found that in that case, compounds V and VI present in the reaction mixture were in a ratio of 2:5, i.e., the O-methylation product predominated, consistent with reported data for alkylation of analogous systems [15].

To confirm the structure of compounds V and VI, we carried out their synthesis by alternative schemes. Pyridinone V, like compound II, was obtained with a 92% yield by reacting pyranone III with methylamine in methanol. Methoxypyridine VI was synthesized with a total yield of 68% by methanolysis of 5-methyl-2-trifluoromethyl-4-chloropyridine (VII), formed by treating compound II with phosphorus pentachloride in boiling $POCl_3$.

The composition and structure of compounds II-VII obtained were confirmed by elemental analysis and spectroscopic data. In particular, the assignment of the signals in the PMR spectrum of pyranone III was based on the observed allylic splitting of the signals of the methyl group and 6-H proton, which appear as a doublet and a quartet at 1.83 ppm and 7.76 ppm, respectively, with an SSCC of 1.3 Hz. The PMR spectra of hydroxypyridine II and pyridinone V are similar to the spectrum of the initial pyranone III, but in this case the signals of the methyl group and 6-H proton are observed as singlets. An interesting feature of the spectrum of pyridinone V is the splitting of the N-methyl group signal as a result of the spin-spin interaction with the fluorine atoms of the trifluoromethyl group, this being characteristic of analogous compounds [9]. One should note the very weak intensity of the absorption band in the IR spectrum of hydroxypyridine II in the 1640 cm^{-1} region ($\nu_{C=O}$), indicating the existence of this compound almost exclusively in the hydroxy form IIa and a minor content of the pyridine form IIb [11].

EXPERIMENTAL

The PMR spectra were recorded on the spectrometers Bruker AC-200 (solvent, $CDCl_3$; internal standard, TMS) and Tesla BS-467A, with a working frequency of 60 MHz (for the solutions of compounds III in CCl_4 and II in $CDCl_3$, the internal standard was HMDS). The IR spectra were recorded on a Specord IR-75 spectrometer in CCl_4 or $CHCl_3$ (compounds II, V). The mass spectra were obtained on a Shimadzu QP-5000 instrument (ionizing electron energy, 70 eV). The course of the reaction and purity of the compounds obtained were checked by the TLC method on Silufol UV-254 plates, and the development was carried out with iodine vapor or an aqueous solution of potassium permanganate.

The properties and spectral data of the new compounds are listed in Table 1.

3-Hydroxy-3-methyl-6-trifluoromethyl-2,3-dihydro-4H-pyran-4-one (I) was obtained by condensation of 2-acetyl-2-methyloxirane with ethyl trifluoroacetate in the presence of sodium isopropylate [14].

5-Methyl-2-trifluoromethyl-4H-pyran-4-one (III). To a solution of 13.8 g (0.07 mole) of hydroxypyranone I in 20 ml (0.25 mole) of pyridine is added dropwise for 20 min, with stirring and cooling to −15°C, 7.1 ml (0.10 mole) of $SOCl_2$. After 8 h of stirring at 0-5°C, the reaction mass is decomposed by carefully adding 30 g of ice and extracting with ether (5 × 25 ml). The combined ether extracts are dried with anhydrous sodium sulfate, the residue after removal of ether is dissolved in 15.0 ml (0.11 mole) of triethylamine, and boiling is carried out for 4 h. The amine is evaporated at reduced pressure, and the residue is diluted with 10 ml of water and extracted with ether (5 × 20 ml). The extract is washed with 10% HCl, then with sodium bicarbonate solution, and dried with anhydrous sodium sulfate. After the ether is driven off, the residue is fractionated at reduced pressure. There is obtained 8.9 g of pyranone III, which can be additionally purified by low-temperature crystallization from pentane.

Separation of 2,3-Dihydro-3-methyl-6-trifluoromethyl-3-chloro-4H-pyran-4-one (IV). The unpurified product, obtained, as indicated above, by reacting 1.7 g (9 mmole) of hydroxypyranone I with 0.9 ml (13 mmole) of $SOCl_2$ in 3.0 ml (37 mmole) of pyridine, without treatment with triethylamine, is chromatographed on a column with silica gel (chloroform eluent). Subsequently, 0.2 g (10%) of chloride IV and 1.0 g (62%) of pyranone III are separated out.

4-Hydroxy-5-methyl-2-trifluoromethylpyridine (II). To a solution of 9.4 g (0.05 mole) of pyranone III in 20 ml of methanol is added 8 ml (0.12 mole) of 25% aqueous ammonia, and the mixture is heated at a low boil for 8 h. After the methanol is removed, the residue is crystallized from toluene. Hydroxypyridine II is obtained in an amount of 8.8 g.

Methylation of Hydroxypyridine II with Iodomethane in Acetone. A solution of 1.5 g (8.5 mmole) of hydroxypyridine II and 3.7 ml (60 mmole) of iodomethane in 50 ml of dry acetone is boiled for 2 h in the presence of 1.4 g (10 mmole) of potassium carbonate. The cooled mixture is filtered off, the acetone is evaporated, the residue is dissolved in chloroform, and the solution is washed with water, then with 10% of sodium thiosulfate solution, and dried with anhydrous sodium sulfate. After chloroform is driven off, the residue is chromatographed on a column with aluminum oxide (the eluent is ether–methanol with a gradient from 10:1 to 1:10). Methoxypyridine VI in an amount of 0.7 g (41%) and 0.9 g (55%) of pyridinone V are successively separated.

1,5-Dimethyl-2-trifluoromethyl-4(1H)-pyridin-4-one (V). To a solution of 1.5 g (8.4 mmole) of pyranone III in 5 ml of methanol is added 1.7 ml (13 mmole) of a 25% aqueous solution of methylamine, and the mixture is heated for 3 h at a low boil. After the methanol is driven off, the residue is crystallized from ethyl acetate; 1.5 g of pyridinone V is obtained.

5-Methyl-2-trifluoromethyl-4-chloropyridine (VII). To a solution of 29.0 g (0.14 mole) of PCl_5 in 125 ml of $POCl_3$ is added five 12.3 g (0.07 mole) portions of hydroxypyridine II. After the vigorous reaction has ended (approximately 30 min), the mixture is boiled for 16 h, then a large portion of $POCl_3$ is driven off at normal pressure. The remaining mass is cooled over an ice bath and carefully decomposed by adding 100 ml of water, neutralized to a slightly alkaline medium with a solution of potassium hydroxide, the organic layer is separated, and the aqueous layer is extracted with chloroform (5 × 30 ml). The combined extracts are dried with anhydrous sodium sulfate, and after chloroform is driven off, the residue is distilled at reduced pressure; 10.8 g of chloropyridine VII is obtained.

5-Methyl-4-methoxy-2-trifluoromethylpyridine (VI). Sodium in an amount of 0.5 g (20 mmole) is dissolved in 50 ml of dry methanol, 4.0 g (20 mole) of chloropyridine VII is added, and the mixture is boiled for 15 h. After methanol is driven off, the residue is treated with 10 ml of water and extracted with ether (5 × 10 ml), and the organic extract is dried with anhydrous sodium sulfate. The ether is evaporated off, and 3.3 g of methoxypyridine VI is obtained at reduced pressure.

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