TRANSFORMATIONS OF 2,6-DIMETHYL- AND 2,3-DIMETHYL-6-ETHYL-4-(2'-FURYL)PYRIDINES INVOLVING THE FURAN AND PYRIDINE RINGS

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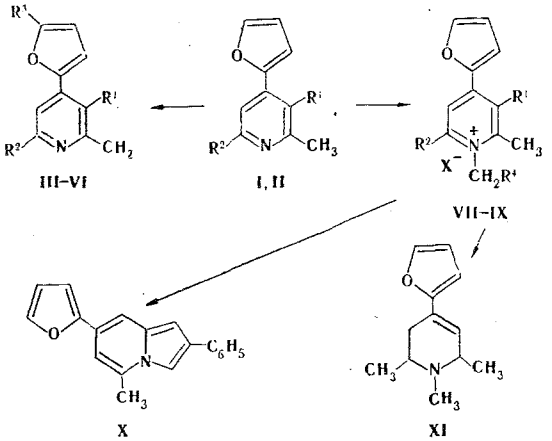
Alkyl-substituted 4-(2'-furyl)pyridines are brominated and nitrated in the C_5' position of the furan ring; however, they do not undergo electrophilic substitution reactions such as acetylation, formylation, and chloro- and aminomethylation. Furyl-substituted indolizines and tetrahydropyridines were obtained from quaternary salts of 2,6-dimethyl-4-(2'-furyl)pyridine.

The study of furylpyridines is important in connection with the fact that a number of biologically active compounds and several alkaloids are compounds of this type [1-4]. Having a relatively practicable method for the preparation of alkylfuryl-substituted pyridine bases [5] at our disposal, we studied their electrophilic substitution reactions, as well as reactions involving the conversion of their quaternary salts to furyl-substituted indolizines and similarly substituted tetrahydropyridines.

We used 2,6-dimethyl(I)[2,3-dimethyl-6-ethyl(II)]-4-(2'-furyl)pyridines as the subjects of our investigation. The hydrobromides of only monobromo-substituted 2,6-dimethyl(III)[2,3-dimethyl-6-ethyl(IV)]-4-(5'-bromo-2'-furyl)pyridines were obtained in high yields when they were brominated.

The fact that the bromine atom is attached to the C_5' atom of the furan ring is confirmed by data from their PMR spectra, viz., by the absence of the signal of the 5'-H proton and the presence of two doublet signals of 3'-H and 4'-H protons with spin–spin coupling constant (SSCC) 3.6 Hz. Similar substitution also occurs in the nitration of pyridine bases I and II with acetyl nitrate. 2,5-Dimethyl(V)[2,3-dimethyl-6-ethyl(VI)]-4-(5'-nitro-2'-furyl)-pyridines were obtained in relatively low yields, since nitration is accompanied by significant resinification of the acidophobic starting substances.



I, III, V, VII, IX R^1=H, R^2=CH_3; II, IV, VI, VIII R^1=CH_3, R^2=C_2H_5; III, IV R^3=Br; V, VI R^3=NO_2; VII, VIII R^4=COC_6H_5, X=Br; IX R^4=H, X=I

Furyl-substituted pyridines I and II do not undergo other electrophilic substitution reactions, viz., formylation, acetylation, and amino- and chloromethylation. In [4] it was reported that a formyl derivative is formed in the formylation of 2-(2'-furyl)pyridine, but the product is obtained in low yield. In comparing these and our data it may be concluded

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that in the case of 4-(2'-furyl)pyridines the pyridine ring has a greater deactivating effect on the furan fragment than in the case of 2-(2'-furyl)pyridines. This is evidently associated with the fact that the two rings are less coplanar in 2-furyl-substituted pyridines.

1-Phenacyl-2,6-dimethyl(VII)[2,3-dimethyl-6-ethyl(VIII)]-4-(2'-furyl)pyridinium bromides were obtained from furyl-substituted pyridines I and II, while methiodide IX was also isolated from base I. The yields of these quaternary salts differ; this is evidently due to steric factors. The highest yield (63%) was obtained in the preparation of salt IX, while the lowest yield (23%) was obtained in the preparation of salt VIII.

Quaternary salt VII was converted by the Chichibabin method (treatment with potassium carbonate solution) to 5-methyl-7-(2'-furyl)indolizine (X) — the structural analog of compounds that have antimicrobial action [6]. The reduction of salt IX with sodium borohydride gave 1,2,6-trimethyl-4-(2'-furyl)-1,2,5,6-tetrahydropyridine (XI) — a subject for pharmacological study. A conclusion regarding the position of the double bond in the nitrogen-containing ring of XI was drawn on the basis of data from its PMR spectrum. The signals of the protons of the two methyl groups attached to C_2 and C_6 appear in the spectrum in the form of two doublets at 1.05 and 1.12 ppm. A broad signal of a vinyl proton (1H) is present at 5.9 ppm. The presence of two signals of an NCH_3 group (at 2.19 and 2.22 ppm) with an overall integral intensity of three proton units is evidently due to the existence of two configurational isomers.

EXPERIMENTAL

The PMR spectra were recorded with a Tesla BS-487C spectrometer (60 MHz) with tetramethylsilane as the internal standard. The mass spectra were measured with an MKh-1303 spectrometer at an ionizing voltage of 70 V. The course of the reactions was monitored by thin-layer chromatography (TLC) (on activity II aluminim oxide).

2,6-Dimethyl-4-(5'-bromo-2'-furyl)pyridine (III). A solution of 1.45 g (9 mmole) of bromine in 15 ml of carbon tetrachloride was added with vigorous stirring in the course of 20 min to a heated (to 40°C) solution of 1.5 g (8.6 mmole) of furylpyridine I in 10 ml of the same solvent, and the resulting precipitate was removed by filtration and washed with CCl_4 to give 2.6 g (91%) of the hydrobromide of bromofurylpyridine III in the form of yellow-orange crystals with mp 232-234°C (from ethanol). Found: Br 47.3; N 4.6%. $C_{11}H_{10}BrNO \cdot HBr$. Calculated: Br 48.0; N 4.2%. A solution of 0.5 g of this salt in 50 ml of water was made alkaline with aqueous sodium carbonate solution and extracted with ether. The extract was purified with a column filled with aluminum oxide (elution with ether) to give 0.2 g (53%) of colorless crystals (from hexane) of bromofurylpyridine III with mp 97-97.5°C. PMR spectrum (in CD_3OD): 2.76 (6H, s, CH_3) and 6.73 (1H, d, $J_{4',3'}$ = 3.5 Hz, 4'-H), 7.57 (1H, d, $J_{3',4'}$ = 3.5 Hz, 3'-H), and 7.90 ppm (pH, s, 3-H and 5-H). Found: C 52.2; H 3.9; N 5.5%; M^+ 251, 253. $C_{11}H_{10}BrNO$. Calculated: C 52.4; H 4.0; N 5.6%; M 251, 253.

The hydrobromide of 2,3-dimethyl-6-ethyl-4-(5'-bromo-2'-furyl)pyridine (IV) was similarly obtained in 85% yield in the form of yellow crystals with mp 193-195°C (from acetone). PMR spectrum (in CF_3COOH): 1.43 (3H, t, C_2H_5), 2.52 (3H, s, 3-CH_3), 2.86 (3H, s, 2-CH_3), 3.13 (2H, q, C_2H_5), 6.65 (1H, d, $J_{4',3'}$ = 3.6 Hz, 4'-H), 7.10 (1H, d, $J_{3',4'}$ = 3.6 Hz, 3'-H), 7.76 (1H, s, 5-H). Mass spectrum, m/z (%): M^+ 281 (59), 279 (69); $[M-H]^+$ 280 (100), 278 (90), 253 (14), 251 (14), 201 (23), 200 (32), 170 (36). Found: C 43.2; H 4.5; Br 43.8; N 3.5%. $C_{13}H_{14}BrNO \cdot HBr$. Calculated: C 43.2; H 4.2; Br 44.3; N 3.9%.

2,6-Dimethyl(V)[2,3-dimethyl-6-ethyl(VI)]-4-(5'-nitro-2'-furyl)pyridines. A 3.5-ml sample of nitric acid (sp. gr. 1.51) was added dropwise with constant stirring at −5°C to a solution of 1 g (5.8 mmole) of furylpyridine I in 10 ml of acetic anhydride, and the mixture was stirred at 0°C for 5 h. It was then poured over ice (100 g), and the aqueous mixture was made alkaline with 10% sodium hydroxide solution and extracted with ether. The extract was purified with a column filled with aluminum oxide to give 0.33 g (26%) of pink crystals of nitro compound V with mp 189-190°C (from hexane). PMR spectrum ($CDCl_3$): 2.60 (6H, s, 2CH_3), 6.95 (1H, d, $J_{3',4'}$ = 3.8 Hz, 3'-H), 7.25 (2H, s, 3-H), and 7.35 ppm (1H, d, $J_{4',3'}$ = 3.8 Hz, 4'-H). Mass spectrum, m/z (%): M^+ 218 (100), 203 (13), 188 (37), 160 (23), 144 (86), 106 (27). Found: C 60.3; H 4.8; N 12.6%. $C_{11}H_{10}N_2O_3$. Calculated: C 60.6; H 4.6; N 12.8%; M 218.

Nitrofurylpyridine VI was similarly obtained in 38% yield from furylpyridine II; the colorless crystal had mp 63-65°C (from hexane), PMR spectrum ($CDCl_3$): 1.15 (3H, t, C_2H_5),

2.58 (3H, s, 3-CH_3), 3.15 (2H, q, C_2H_5), 3.28 (3H, s, 2-CH_3), 6.95 (1H, d, $J_{3',4'}$ = 3.8 Hz, 3'-H), 7.16 (1H, d, $J_{4',3'}$ = 3.8 Hz, 4'-H), and 7.88 ppm (1H, s, 5-H). Mass spectrum, m/z (%): 246 (100), 245 (58), 234 (15), 218 (38), 200 (8), 172 (25), 170 (52), 158 (44), 144 (42), 128 (42), 115 (73). Found: C 63.2; H 6.2; N 11.1%. $C_{13}H_{14}N_2O_3$. Calculated: C 63.4; H 5.7; N 11.4%; M 246.

1-Phenacyl-2,6-dimethyl(VII) [2,3-dimethyl-6-ethyl(VIII)]-4-(2'-furyl)pyridinium Bromides. A solution of 2.3 g (11.6 mmole) of bromoacetophenone and 2 g (11.6 mmole) of furylpyridine I in 50 ml of acetone was refluxed for 6 h, after which the precipitate was removed by filtration and washed with ether to give 2 g (46%) of yellow-green crystals of salt VII with mp 188-190°C (from acetone). Found: Br 19.5; N 3.7%. $C_{21}H_{22}BrNO_2$. Calculated: Br 20.0; N 3.5%.

5-Methyl-2-phenyl-7-(2'-furyl)indolizine (IX). A 40% solution of potassium carbonate was added to a solution of 0.9 g (2.4 mmole) of salt VII in 20 ml of water until the mixture was alkaline, after which it was maintained at 20°C for 30 min. It was then extracted with chloroform, and the extract was purified with a column filled with aluminum oxide to give 0.49 g (75%) of brown crystals of indolizine IX with mp 138-140°C (from hexane). PMR spectrum ($CDCl_3$); 2.56 (3H, s, CH_3), 6.48 (1H, dd, 4'-H), 6.60 (1H, d, 3'-H), 6.69 (s, 1-H), 6.86 (s, 6-H), and 7.77 ppm (d, 5'-H). Mass spectrum, m/z (%): M^+ 273 (65), 245 (8), 244 (14), 196 (15); M^{2+} 136.5 (15), 77 (100). Found: C 83.3; H 5.7; N 4.9%. $C_{19}H_{15}NO$. Calculated: C 83.5; H 5.5; N 5.1%; M 273.

2,6-Dimethyl-4-(2'-furyl)pyridine Methiodide (X). A 3-g (21 mmole) sample of methyl iodide was added to a solution of 1.5 g (8.6 mmole) of furylpyridine I in 20 ml of acetone, and the mixture was heated to 40°C, after which it was allowed to stand at 20°C for 10 h. The resulting precipitate was separated and washed with ether to give 1.7 g (63%) of colorless crystals of salt X with mp 259-260°C (from acetone). Found: C 45.6; H 4.5; N 4.5%. $C_{11}H_{11}NO \cdot CH_3I$. Calculated: C 45.7; H 4.4; N 4.4%.

1,2,6-Trimethyl-4-(2'furyl)-1,2,5,6-tetrahydropyridine (XI). A 2-g (~53 mmole) sample of sodium borohydride was added with stirring at 40°C to a solution of 1.7 g (5.4 mmole) of salt X in 50 ml of methanol, and the mixture was refluxed for 2 h. It was then cooled and treated with 50 ml of water, and the alcohol was removed by vacuum distillation. The reaction products were extracted with ether, and the extract was purified with a column filled with aluminum oxide to give 0.65 g (63%) of XI as an oily substance (which was an individual substance according to the TLC, GLC, and PMR data). Mass spectrum, m/z (%): M^+ 191 (71), 176 (100), 162 (25), 148 (9), 147 (10), 134 (22): M^{+2} 95.5 (11). Found: C 75.0; H 9.3; N 7.2%. $C_{12}H_{17}NO$. Calculated: C 75.4; H 8.9; N 7.3%; M 191. The hydrochloride has mp 123-125°C (from ethanol). Found: N 6.2%. $C_{12}H_{17}NO \cdot HCl$. Calculated: N 6.2%.

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