

SYNTHESIS AND MASS SPECTRA
OF SOME PYRIDYLFURAN DERIVATIVES.
THE DETERMINATION OF $\bar{\sigma}_m$ CONSTANTS
OF 2-X-5-FURYL SUBSTITUENTS*

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Synthesis of 3-(2-X-5-furyl)pyridines (where X is H, CH₃, C₂H₅, Br, CHO, COCH₃, COOCH₃) by the reaction of 1,3-di(3-pyridyl)triazene with isopentyl nitrite and with the corresponding furan derivative is described. From spectrophotometrically determined pK_a values the $\bar{\sigma}_m$ constants of the 2-X-5-furyl substituents were calculated. The preparation of 2-(2-furyl)pyridine is also described. The structure of the prepared derivatives was determined by mass and ¹H-NMR spectroscopy.

Only a small number of papers dealing with the synthesis and properties of pyridylfuran derivatives can be found in the literature¹. 3-(2-Furyl)pyridine was prepared by photochemical reaction of furan with 3-iodopyridine² or by an arylation reaction³. Several derivatives of 2-(2-furyl)pyridine were prepared by cyclisation reactions⁴. The aim of our present investigation was to prepare substituted 3-(2-X-5-furyl)pyridine derivatives, and on the basis of their pK_a values to determine $\bar{\sigma}_m$ constants of the 2-X-5-furyl substituents.

We prepared 3-(2-X-5-furyl)pyridine derivatives, where X is H, Br, CH₃, C₂H₅, CHO, COCH₃ and COOCH₃, by the reaction of 1,3-di(3-pyridyl)triazene with isopentyl nitrite and with the corresponding furan derivative in 12–28% yields. The best isolation method proved to be chromatography on a silica gel column with benzene or benzene–chloroform (1 : 1) as eluant (depending on the product polarity). In an attempted preparation of 3-(2-furyl)pyridine by reaction of 3-aminopyridine with isopentyl nitrite in furan, using standard conditions (0.5 molar excess of isopentyl nitrite) we obtained only 1,3-di(3-pyridyl)triazene. The structure of this product was proved by mass spectrometry as well as by its synthesis by diazotation of 3-aminopyridine. When the reaction was carried out with a greater excess of isopentyl nitrite (1 molar), after 7 hours the triazene derivative was obtained in a 44%

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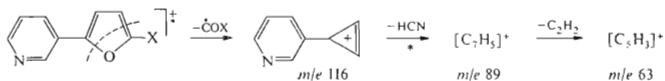
yield and 3-(2-furyl)pyridine in 1% yield. After 30 hours the yield of the triazene was negligible and 3-(2-furyl)pyridine was isolated as the principal product (yield 19%). This reaction appears to be a further proof that the reaction of aromatic amines with alkyl nitrites in furan proceeds *via* triazene derivatives, as we have already pointed out in one of our previous papers⁵.

An attempt to prepare pyridylfuran derivatives by the Meerwein arylation of 2-furancarbaldehyde with 2-, 3-, and 4-pyridyldiazonium salts results⁶ only in products of Sandmeyer reaction and in almost quantitative recovery of 2-furancarbaldehyde. We succeeded in preparation of 3-(2-X-5-furyl)pyridine derivatives, where X is CHO, COCH₃, by the Meerwein arylation of 2-furancarbaldehyde or 2-acetylfuran with the corresponding diazonium salts, the respective yields being 4.2% and 5.3%. The isolation of products was successful only when the reaction mixture after completion of the reaction was neutralised with sodium carbonate. Otherwise, the derivatives *V* and *VI* are soluble in the reaction medium in the form of their pyridinium salts. 3-(2-Formyl-5-furyl)pyridine was transformed into the corresponding hydroxymethyl and cyano derivatives. The reaction of 2-aminopyridine with isopentyl nitrite in furan afforded 2-(2-furyl)pyridine.

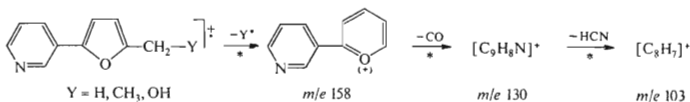
The structure of the prepared derivatives follows from the method of their preparation, as well as from their mass and ¹H-NMR spectra. The base peaks in mass spectra of the compounds *I*, *III*, *V*, *VII*–*X* are represented by the molecular ions, and also in the spectra of other derivatives the molecular ions are very abundant (Table I). The spectra of all the compounds exhibit a fragment ion, *m/e* 116, which arises by cleavage of the radical COX from the molecular ion. Its formation and further decomposition is shown in Scheme 1. A very abundant fragment ion, *m/e* 158, arises from the molecular ions of *III*, *IV* and *IX* by a fission of the β-bond (relative to the furan ring). This fragment ion decomposes further by splitting off the CO molecule and by subsequent loss of HCN under formation of fragments (C₉H₈N)⁺, *m/e* 130, and (C₈H₇)⁺, *m/e* 103. This process is depicted in Scheme 2. The formation of ions *m/e* 106 and *m/e* 78 in compounds *III*–*V*, *VII* and *IX* can be explained by the fission depicted in Scheme 3. Direct elimination of CO molecule from the molecular ion takes place in the case of compounds *I*, *II*, *V* and *VIII*–*X*.

The elimination of CO in the compounds *I* and *X* is followed by the loss of HCN under formation of the fragment ion (C₇H₆)⁺, *m/e* 90.

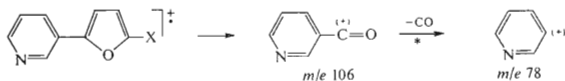
The values of chemical shifts and coupling constants are given in Table II. The position of the substituent on the pyridine nucleus can be determined from chemical shifts and splitting character of the α-pyridine hydrogen signal. 2-Substituted pyridine nucleus has only one α-proton, 3-monosubstituted ring has two protons in the low field with different chemical shifts and splitting character. Two hydrogen atoms with a doublet–doublet splitting are characteristic for a 4-monosubstituted pyridine nucleus⁷. We have proved by the interpretation of the ¹H-NMR spectra, that the



SCHEME 1



SCHEME 2



SCHEME 3

furan ring is attached to the position 3 of the pyridine nucleus. It is known⁷ that, as a result of the electron-accepting character of the nitrogen atom, α -protons of the pyridine nucleus have the highest δ values. According to the character of the splitting (doublet) we assigned the 2-proton to the higher δ values (8.80–8.92) and the 6-proton to $\delta = 8.35$ –8.57 (doublet–doublet splitting). The chemical shifts of the corresponding protons, as well as the value of the coupling constant (3.3–3.8 Hz), support the conclusion of mass spectrometry that the pyridyl moiety is bonded

TABLE I
 Molecular Peaks of the Studied Compounds

No	X	M	No	X	M
<i>I</i>	H	145	<i>VI</i>	COCH ₃	187
<i>II</i>	Br	223 ^a	<i>VII</i>	COOCH ₃	203
<i>III</i>	CH ₃	159	<i>VIII</i>	CN	170
<i>IV</i>	C ₂ H ₅	173	<i>IX</i>	CH ₂ OH	175
<i>V</i>	CHO	173	<i>X</i>	H ^b	145

^a For the isotope ⁷⁹Br; ^b for 2-(2-furyl)pyridine.

to the position 5 of the furan nucleus. As seen from Table II, the chemical shifts of protons in pyridine, and particularly in furan, are influenced by the character of the substituent on the furan ring.

The pK_a values, which were measured spectrophotometrically⁸, are listed in Table III. For pyridine we found pK_a 5.14 (ref.⁸ reports values 5.14–5.19). It is obvious from Table III that the pK_a values depend on the character of the substituent on the furan ring. We determined the σ -constants for the furan-containing substituents in the position 3 of the pyridine nucleus. A suitable system is the equilibrium pyridinium ion \rightleftharpoons pyridine which is known⁹ to be greatly sensitive to the substituent effect. Using a selected series of substituents bonded to the pyridine nucleus (H, 3-CH₃, 3-Cl, 3-Br, 3-COOCH₃, 3-CN and 3-NO₂) Fisher and coworkers¹⁰ determined the slope of the plot pK_a vs σ^0 for the equilibrium pyridinium \rightleftharpoons pyridine,

TABLE II

¹H-NMR Spectra of Substituted 3-(2-X-5-Furyl)pyridines

Compound X	δ , ppm ^a				J , Hz ^b	δ , ppm ^a		$J_{3'4'}$	δ_X , p.p.m.
	H ₂	H ₆	H ₄	H ₅		H _{3'}	H _{4'}		
III CH ₃	8.80 (d)	8.35 (d,d)	7.81 (m)	7.18 (m)	2-4 = 1.6 5-6 = 5.0 4-6 = 1.8 4-5 = 7.9	6.0 (d)	6.56 (d)	3.6	1.17 (s)
IV C ₂ H ₅	8.83 (d)	8.36 (d,d)	7.86 (m)	7.17 (m)	2-4 = 1.6 5-6 = 5.0 4-6 = 1.8 4-5 = 7.9	6.0 (d)	6.55 (d)	3.6	CH ₂ = 2.65 (q) CH ₃ = 1.22 (t) $J = 7.5$ Hz
V CHO	8.89 (d)	8.57 (d,d)	7.93 (m)	7.37 (m)	2-4 = 1.5 5-6 = 4.9 4-6 = 1.6 4-5 = 7.6	7.25 (d)	6.71 (d)	3.6	9.60 (s)
VI COCH ₃	8.96 (d)	8.53 (d,d)	8.01 (m)	7.33 (m)	2-4 = 1.8 5-6 = 5.1 4-6 = 1.5 4-5 = 8.0	7.21 (d)	6.82 (d)	3.8	2.45 (s)
VII COOCH ₃	8.92 (d)	8.48 (d,d)	7.97 (m)	7.3 (m)	2-4 = 1.5 4-6 = 1.6 5-6 = 5.0 4-5 = 8.0	7.16 (d)	6.75 (d)	3.6	3.82 (s)

^a Chemical shifts in δ values, standard hexamethyldisiloxane; ^b $J_{2-5} = 0.5$ Hz, $J_{2-6} = 0$ Hz.

TABLE III
Calculated pK_a Values for 3-(2-X-5-Furyl)pyridine Derivatives

X	c^a , M	λ^b , nm	pK_a	$\bar{\sigma}_m$ (2-X-5-furyl)
H	$1 \cdot 10^{-4}$	263.3	4.59 ± 0.011	0.09
CH ₃	$1 \cdot 10^{-4}$	345	4.63 ± 0.015	0.085
C ₂ H ₅	$5 \cdot 10^{-5}$	345	4.62 ± 0.024	0.086
Br	$1 \cdot 10^{-4}$	333	4.23 ± 0.03	0.15
CHO	$7 \cdot 10^{-5}$	299	3.83 ± 0.023	0.22
COCH ₃	$4 \cdot 10^{-5}$	299	3.67 ± 0.023	0.24
CN	$5 \cdot 10^{-5}$	328	3.62 ± 0.014	0.25
2-(2-Furyl)- pyridine	$1 \cdot 10^{-4}$	333	4.17 ± 0.04	—
Pyridine	$2 \cdot 10^{-5}$	255.3	5.14 ± 0.02	—

^a Concentration; ^b analytical wavelength.

$\rho = 6.01$, taking the σ^0 constants from ref.¹¹. From the equation $\bar{\sigma} = (pK_0 - pK)/\rho$ the authors calculated the effective substituent constants, $\bar{\sigma}$, for the substituents bonded to the pyridine ring. Using this equation we calculated for the 2-X-5-furyl substituents the substituent constants, denoted as $\bar{\sigma}_m(X-C_4H_2O)$ (Table III). The value, obtained for the unsubstituted furan nucleus (0.09) shows a weak electron-accepting character of the furan ring attached to the position 3 of the pyridine nucleus. The same result follows from the mentioned greater chemical shift δ (2 Hd) as compared with the chemical shift δ (6 Hd, d).

EXPERIMENTAL

Mass and ¹H-NMR spectra were measured under conditions described previously¹². Mass spectra of the compounds I, VIII–X were taken also using the GC/MS method on a MAT 111 (Varian) instrument; electron energy 80 eV, current 270 μ A, temperature of the ion source 200°C. The pK_a values were determined on a Specord UV VIS spectrophotometer at $20 \pm 0.2^\circ$ C. The pH values of the buffer solutions, prepared from succinic acid according to ref.¹³, were measured on a Radiometer pH-meter 26 (Copenhagen) at 20°C using a Radiometer 6202 C glass electrode and a Radiometer K 4112 reference calomel electrode. The electrodes were calibrated using aqueous buffers. The pK_a values were calculated from the equation $pK_a = \text{pH} + \log(d - d_M) : (d_1 - d)$, where d_M and d_1 are the respective optical densities of the non-ionised and ionised form. The corresponding extinctions d_M and d_1 were determined by measurement of the spectra of the studied compound in 0.05M-KOH and in 0.1M-H₂SO₄, respectively. The preparation of 2-X-substituted furans was already described¹².

Preparation of 3-(2-X-5-Furyl)pyridine Derivatives

A mixture of 1,3-di(3-pyridyl)triazene (XI, 2.5 g; 0.0125 mol), isopentyl nitrite (2 ml; 0.017 mol) and the corresponding furan derivative (50 ml) was kept at 30°C for 24 hours. The mixture was filtered, washed with water and dried (Na₂SO₄). The excess furan derivative was distilled off and the residue was chromatographed on a silica gel column. Following compounds were prepared by the described procedure:

3-(2-Furyl)pyridine (I), from furan, eluant benzene, yield 28.2%, b.p. 78–80°C/4 Torr. UV spectrum (water) λ_{\max} in nm, (log ϵ): 201 (4.13), 223 (3.77), 279 (4.13), 296 (3.93). For C₉H₇NO (145.2) calculated: 74.45% C, 4.85% H, 9.64% N; found: 74.33% C, 4.79% H, 9.41% N.

3-(2-Bromo-2-furyl)pyridine(II), from 2-bromofuran, eluant benzene, yield 23.3%, m.p. 150 to 152°C (benzene). UV spectrum (water), λ_{\max} in nm, (log ϵ): 203 (4.12), 241 (3.69), 291 (4.09), 304 (4.02). For C₉H₆BrNO (224.1) calculated: 35.37% Br, 6.05% N; found: 35.22% Br, 5.99% N.

3-(2-Methyl-5-furyl)pyridine (III), from 2-methylfuran, eluant benzene, yield 17%, b.p. 72°C/0.5 Torr. UV-spectrum (water), λ_{\max} in nm, (log ϵ): 202 (3.61), 228 (3.43), 287 (3.55), 306 (3.43). For C₁₀H₉NO (159.2) calculated: 75.46% C, 5.69% H, 8.79% N; found: 75.58% C, 5.66% H, 8.75% N.

3-(2-Ethyl-5-furyl)pyridine (IV), from 2-ethylfuran, eluant benzene, yield 16.3%, b.p. 72°C/0.1 Torr. UV spectrum (water), λ_{\max} in nm, (log ϵ): 202 (3.96), 227 (3.79), 290 (4.16), 307 (4.05). For C₁₁H₁₁NO (173.2) calculated: 76.27% C, 6.40% H, 8.08% N; found: 76.01% C, 6.38% H, 7.84% N.

3-(2-Formyl-5-furyl)pyridine (V), from 2-furancarbaldehyde, eluant benzene-chloroform (1 : 1), yield 12.2%, m.p. 113–115°C (light petroleum). UV spectrum (water), λ_{\max} in nm, (log ϵ): 222 (3.85), 250 (3.59), 3.28 (4.05), 372 (3.60). For C₁₀H₇NO₂ (173.2) calculated: 69.35% C, 4.07% H, 8.08% N; found: 69.41% C, 4.11% H, 7.88% N.

3-(2-Acetyl-5-furyl)pyridine (VI), from 2-acetylfuran, eluant benzene-chloroform (1 : 1), yield 15.1%, m.p. 78–80°C (light petroleum). UV spectrum (water), λ_{\max} in nm, (log ϵ): 220 (4.22), 320 (4.50). For C₁₁H₉NO₂ (187.2) calculated: 70.60% C, 4.85% H, 7.49% N; found: 70.52% C, 4.79% H, 7.51% N.

3-(2-Methoxycarbonyl-5-furyl)pyridine (VII), from 2-methoxycarbonylfuran, eluant benzene-chloroform (1 : 1), yield 15.5%, m.p. 110–112°C (light petroleum). UV spectrum (water), λ_{\max} in nm, (log ϵ): 202 (4.09), 215 (4.07), 303 (4.25), 318 (4.09). For C₁₁H₉NO₃ (203.2) calculated: 65.02% C, 4.46% H, 6.89% N; found: 65.13% C, 4.49% H, 6.85% N.

The derivative I was prepared also by the reaction of 3-aminopyridine with isopentyl nitrite in furan in 19.4% yield. This reaction gave also XI, m.p. 176–179°C, as a side product; mass spectrum: M⁺ 199 (10), 173 (3), 106 (58), 94 (9), 78 (100), 51 (41), and 39 (12). The compound II was synthesized in 65% yield also by bromination of I. The derivatives V and VI were prepared also by the Meerwein method from the diazonium salt of 3-aminopyridine according to ref.^{14,15} in 4.2% and 5.3% yield, respectively. After the arylation reaction, the reaction mixture was extracted with ether, neutralised by addition of a sodium hydrogen carbonate solution and the product taken up in ether. The ethereal layer was washed with water, dried (Na₂SO₄) and the ether was evaporated. The derivatives V and VI were obtained by distillation at 100°C/0.1 Torr and 96°C/0.05 Torr, respectively, and were purified by crystallisation.

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