

# NITRATION OF SOME 2,5-DISUBSTITUTED 4-PHENYL PYRIDINES

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2,5-Dimethyl-4-phenylpyridine is nitrated in the para position of the phenyl ring. Further nitration of the resulting nitro compound gives a mixture of isomeric dinitro derivatives. In the case of 4-phenylisocinchomeric acid the nitro group enters the meta position of the phenyl ring.

In the present communication we present the results of nitration of 2,5-dimethyl-4-phenylpyridine (I) [1] and some of its analogs. Nitration of I with the usual nitrating mixture at 0°C gives 2,5-dimethyl-4-(p-nitrophenyl)pyridine (II), the further nitration of which gives 2,5-dimethyl-4-(o,p-dinitrophenyl)pyridine (III) and a small amount of 2,5-dimethyl-4-(m,p-dinitrophenyl)pyridine (IV). The position of the nitro groups in the phenyl rings of II-IV was established by means of spectral data. The character of the splitting of the two-proton multiplets at  $\delta$  7.46 and 8.23 ppm in the PMR spectrum of II is typical for para substitution [2]. The overall character of its UV spectrum is similar to that of the spectrum of 2-(p-nitrophenyl)pyridine [3]. The hypsochromic shift of the longwave maximum in the spectrum of nitro derivative II ( $\lambda_{\text{max}}$  276 nm) as compared with the spectrum of 2-(p-nitrophenyl)pyridine ( $\lambda_{\text{max}}$  295 nm) is due to the noncoplanarity of the II system.

The multiplicities of the signals of the protons of the phenyl ring in the PMR spectra of dinitro derivatives III and IV (Table 1) are identical and constitute evidence for the unsymmetrical character of the substitutions. On the basis of an analysis of the chemical shifts of these signals we arrived at a conclusion regarding the position of the second nitro group in these compounds. The close values of the chemical shifts of the 2'-H and 5'-H protons in IV are due to the identical effects of the nitro groups in the 3' and 4' positions. The diamagnetic shift of the 5'-H signal in its PMR spectrum as compared with the corresponding 3'-H and 5'-H signals

TABLE 1. Chemical Shifts ( $\delta$ , ppm) and Spin-Spin Coupling Constants (J, Hz) of the Protons in the PMR Spectra of I-IV, VI, and IX

Compound	Solvent	6-H	3-H	2'-H	3'-H	4'-H	5'-H	6'-H	2-CH <sub>3</sub>	5-CH <sub>3</sub>	OCH <sub>2</sub> CH <sub>3</sub>	OCH <sub>2</sub> CH <sub>3</sub>
I	CCl <sub>4</sub>	8.15 s*	6.80 s	7.05				7.45 m	2.38 s	2.10 s	—	—
II	CCl <sub>4</sub>	8.33 s	6.90 s	7.46 m	8.23 m	—		8.23 m	7.46 m	2.47 s	2.17 s	—
III	CCl <sub>4</sub>	8.30 s	6.77 s	—	8.82 d	—	8.46 q	7.50 d	2.47 s	2.00 s	—	—
					$J=2.0$		$J_1=9.0$	$J=9.0$				
							$J_2=2.0$					
IV	CDCl <sub>3</sub>	8.39 s	6.96 s	7.79 d	—	—	7.97 d	7.45 q	2.51 s	2.20 s	—	—
				$J=2.0$			$J=9.0$	$J_1=9.0$				
							$J_2=2.0$					
VI	CCl <sub>4</sub> + CDCl <sub>3</sub>	9.04 s	7.96 s	7.44 m	8.22 m	—	8.22 m	7.44 m	—	—	4.14 q	1.09 q
											$J=7.0$	$J=7.0$
											4.41 q	1.38 t
											$J=7.0$	$J=7.0$
IX	CDCl <sub>3</sub>	9.07 s	8.00 s	8.04	—	8.04	7.48	7.68 m	—	—	4.15 q	1.05 m
				8.32 m		8.32 m					$J=7.0$	$J=7.0$
											4.41 q	1.36 m
											$J=7.0$	$J=7.0$

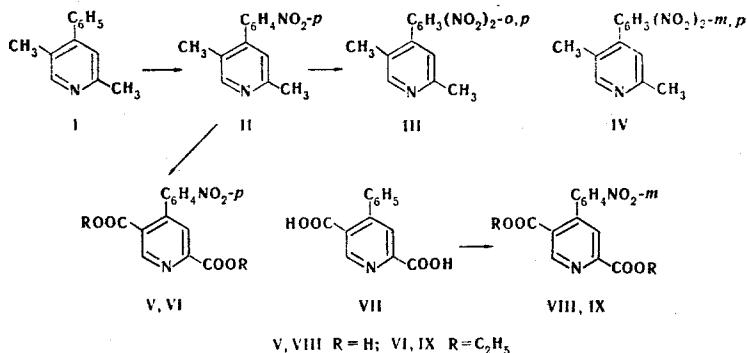
\*Abbreviations: s is singlet, d is doublet, t is triplet, q is quartet, and m is multiplet.

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in the spectrum of II ( $\Delta\delta = 0.26$  ppm) is also in agreement with this orientation of the nitro group in IV. Because of steric interaction, the nitro groups attached to  $C_3'$  and  $C_4'$  are removed from the plane of the phenyl ring, and this leads to a decrease in their deshielding effect on the ortho and para protons.

Oxidation of II gave 4-(p-nitrophenyl)isocinchomeric acid (V), which was identified in the form of diethylester VI. 4-(m-Nitrophenyl)isocinchomeric acid (VIII), which was subsequently converted to diethyl ester IX, was isolated in the nitration of 4-phenylisocinchomeric acid VII [4].

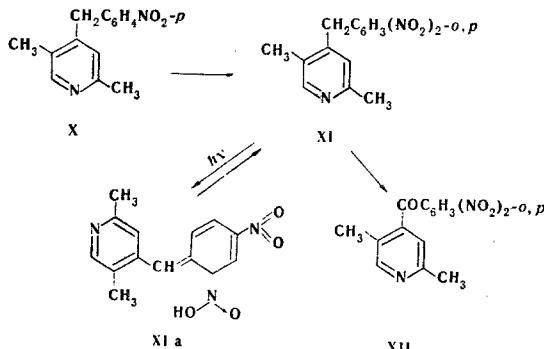


Information regarding the position of the nitro group in the phenyl ring of acid VIII and ester IX was obtained from data from the PMR spectrum of IX, in which the complex two-proton multiplets of different form at  $\delta$  7.48-7.68 ppm and  $\delta$  8.04-8.32 ppm are related to the 5'-H and 6'-H and 2'-H and 4'-H protons, respectively.

The electrophilic substitution of 4-phenylpyridines is evidently analogous to the electrophilic substitution of p-nitrodiphenyl. p,p'-Dinitrophenyl is formed in the nitration of the latter, and this makes it possible to consider the p-nitrophenyl grouping to be a halogen analog [5, 6]. Taking into account the analogy between the p-nitrophenyl and  $\gamma$ -pyridyl groups, para substitution in the nitration of I is in conformity with the established principle. We are inclined to feel that the orienting effect of the  $\gamma$ -pyridyl group in this case is similar to the effect of an alkyl substituent with an electron-acceptor group remote from the phenyl group [7, 8], inasmuch as the conjugation is disrupted because of the noncoplanarity of the system [9]. The change in orientation in the nitration of dibasic acid VII is explained by the effect of strong electron-acceptor carboxyl groups.

We were able to considerably raise the yield of 2,5-dimethyl-4-(o,p-dinitrobenzyl)pyridine (XI) by nitration of 2,5-dimethyl-4-(p-nitrobenzyl)pyridine (X) [10] with fuming nitric acid. Nitration of XI gave 2,5-dimethyl-4-(o,p-dinitrobenzoyl)pyridine (XII).

When a colorless alcohol solution of dinitro derivative XI is illuminated with an electronic pulse photoelectric spark, the solution turns dark-blue and then gradually becomes colorless. The duration of retention of the color increases when the solution is cooled. The photochromism is explained by reversible conversion of nitro form XI to nitronic acid XIa [11]. Nitronic acid XIa is stabilized in the form of a salt by treatment of an alcohol solution of XI with an alcohol solution of alkali (a dark-green solution is produced); the color vanishes when the solution is neutralized with a strong acid.



Preliminary testing of the nitroarylpyridines obtained in this study showed that some of them (II and XI) have nonlinear optical properties. The nonlinear polarizability of II and XI and the photochromic properties of XI apparently hold promise for nonlinear and integral optics.

## EXPERIMENTAL

The PMR spectra of  $\text{CCl}_4$  and  $\text{CDCl}_3$  solutions of the compounds were measured with HA-100D and T-60 spectrometers with hexamethyldisiloxane as the internal standard. The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The UV spectra of ethanol solutions of the compounds were obtained with a Hitachi spectrophotometer.

2,5-Dimethyl-4-(p-nitrophenyl)pyridine (II). A 40-g (0.218 mole) sample of I was added gradually at 0° with vigorous stirring to a nitrating mixture prepared from 208 g (2 moles) of nitric acid (sp. gr. 1.37) and 308 g (3 moles) of sulfuric acid (sp. gr. 1.83), after which the mixture was stirred at 0° for 1 h. It was then poured over ice, and the aqueous mixture was diluted with water and treated with sodium carbonate until it was strongly alkaline. The organic bases were extracted with ether and dried with magnesium sulfate. The ether was then evaporated, and the residue (40 g) was crystallized repeatedly from hexane to give 12.5 g (25%) of colorless crystals with mp 99.5–100.5°. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1520 ( $\text{NO}_2$ , as) and 1350 ( $\text{NO}_2$ , s). UV spectrum,  $\lambda_{\text{max}}$ , nm (log  $\epsilon$ ): 276 (4.14). Found: C 68.5; H 5.5; N 12.2%.  $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_2$ . Calculated: C 68.5; H 5.3; N 12.3%.

2,5-Dimethyl-4-(o,p-dinitrophenyl)pyridine (III) and 2,5-Dimethyl-4-(m,p-dinitrophenyl)pyridine (IV). A 61-g (0.62 mole) sample of fuming nitric acid (sp. gr. 1.5) was added gradually with stirring at 10° to a solution of 10 g (0.044 mole) of II in 90 g (0.87 mole) of sulfuric acid (sp. gr. 1.83), after which the mixture was heated at 100° for 1.5 h. It was then cooled and worked up as in the preparation of II. Successive crystallization of the residue (9.1 g) from hexane yielded 3.6 g (30.6%) of III and 0.47 g (4%) of IV. Compound III was obtained as colorless crystals with mp 114–115°. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1536 ( $\text{NO}_2$ , as) and 1357 ( $\text{NO}_2$ , s). Found: C 57.1; H 4.2; N 15.8%.  $\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}_4$ . Calculated: C 57.1; H 4.0; N 15.4%. Dinitro derivative IV was obtained as colorless crystals with mp 166–168°. Found: C 57.1; H 4.2; N 15.8%;  $M^+$  273.  $\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}_4$ . Calculated: C 57.1; H 4.0; N 15.4%; M 273.

4-(p-Nitrophenyl)isocinchomeronic Acid (V). An 8.5-g sample of potassium permanganate was added in portions at 100° to 2.2 g (9.4 mmole) of II in 40 ml of water, after which the mixture was stirred and heated until the solution became colorless. The manganese dioxide was removed by filtration and washed with 60 ml of hot water. The solution was evaporated to half its original volume and acidified to pH 1 with hydrochloric acid. Workup gave 1 g (36%) of colorless crystals of the acid with mp 226–228° (from aqueous ethanol). Found: N 10.0%.  $\text{C}_{13}\text{H}_8\text{N}_2\text{O}_6$ . Calculated: N 9.7%. The hydrochloride of V had mp 215–216°. Found: N 8.4%.  $\text{C}_{13}\text{H}_8\text{N}_2\text{O}_6 \cdot \text{HCl}$ . Calculated: N 8.6%.

Diethyl 4-(p-Nitrophenyl)isocinchomeronate (VI). A mixture of 0.2 g (0.7 mmole) of acid V, 5 ml of ethanol, and 0.5 ml of sulfuric acid was refluxed for 8 h, after which the alcohol was removed by distillation, and the residue was treated with 10 ml of water. The aqueous mixture was neutralized with ammonia, and the organic bases were extracted with ether. Workup yielded 0.1 g (45.5%) of colorless crystals of ester VI with mp 98–101° (from hexane). IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1731 (CO), 1531 ( $\text{NO}_2$ , as), and 1350 ( $\text{NO}_2$ , s). Found: C 59.3; H 4.7; N 8.3%.  $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_6$ . Calculated: C 59.3; H 4.7; N 8.1%.

4-(m-Nitrophenyl)isocinchomeronic Acid (VIII). A 2.43-g sample of VII was added at 0° to a nitrating mixture obtained from 10.4 g (0.17 mole) of nitric acid (sp. gr. 1.37) and 20.3 g (0.2 mole) of sulfuric acid (sp. gr. 1.83), after which the mixture was stirred at 0–5° for 2 h. It was then poured over ice, and the aqueous mixture was made alkaline to pH 1 with ammonium hydroxide. Workup gave 1.73 g (60%) of colorless crystals with mp 232–234° (from water). Found: C 54.1; H 3.1; N 9.4%.  $\text{C}_{13}\text{H}_8\text{N}_2\text{O}_6$ . Calculated: C 54.2; H 2.8; N 9.7%.

Diethyl 4-(m-Nitrophenyl)isocinchomeronate (IX). This compound was obtained from 0.8 g (2.8 mmole) of acid VIII by the method used to prepare VI. Workup of the reaction mixture gave 0.2 g (20.9%) of colorless crystals with mp 142–144° (from hexane). Found: C 59.6; H 5.1; N 7.8%.  $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_6$ . Calculated: C 59.3; H 4.7; N 8.1%.

2,5-Dimethyl-4-(o,p-dinitrobenzyl)pyridine (XI). A 2.5-g (1.03 mmole) sample of X was added gradually to a nitrating mixture obtained from 18 g (0.179 mole) of sulfuric acid (sp. gr. 1.83) and 14 g (0.234 mole) of fuming nitric acid (sp. gr. 1.5), after which the mixture was stirred at 100° for 0.5 h. It was then cooled and worked up as in the preceding experiments. The ether was removed by distillation, and the residue (2.87 g) was crystallized from hexane to give 1.82 g (63%) of yellow crystals with mp 109–111° [10].

2,5-Dimethyl-4-(o,p-dinitrobenzoyl)pyridine (XII). A 9.5-g sample of potassium permanganate was added with stirring at 70° to 2.5 g (8.7 mmole) of XI in 40 ml of water. The resulting solution was filtered

after it had become completely colorless. The manganese dioxide was washed with 40 ml of hot water and extracted with boiling acetone. The acetone was removed by distillation, and the residue (1.1 g) was crystallized from alcohol to give 0.4 g (15.8%) of yellow crystals with mp 172-174° (from alcohol). IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1690 (CO), 1540 (NO<sub>2</sub>, as), and 1345 (NO<sub>2</sub>, s). UV spectrum,  $\lambda_{\text{max}}$ , nm (log  $\epsilon$ ): 232 (4.12) and 300 (3.56). Found: C 55.9; H 3.9; N 14.2%. C<sub>14</sub>H<sub>11</sub>N<sub>3</sub>O<sub>5</sub>. Calculated: C 55.8; H 3.7; N 14%.

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#### 2,4,6-TRIS(METHYLSULFONYL)-3,5-DICHLOROPYRIDINE

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The reactions of 2,6-bis(methylthio)-3,4,5-trichloropyridine and its N-oxide with sodium hydrosulfide were studied. A method for the synthesis of 2,4,6-tris(methylsulfonyl)-3,5-dichloropyridine was developed.

We originally described 2,6-bis(methylsulfonyl)-3,4,5-trichloropyridine [1]. Continuing our research on the synthesis of polysulfone derivatives of pyridine we obtained 2,4,6-tris(methylsulfonyl)-3,5-dichloropyridine (I). Attempts to obtain sulfone I from 2,6-bis(methylsulfonyl)-3,4,5-trichloropyridine were unsuccessful. Its reaction with potassium hydrosulfide leads to replacement of one methylsulfonyl group by a mercapto group [1]. In addition, the reaction of 2,6-bis(methylthio)-3,4,5-trichloropyridine N-oxide (II) with potassium hydrosulfide does not give the desired results — a methylthio group rather than the chlorine atom in the 4 position is replaced to give 2-mercaptop-6-methylthio-3,4,5-trichloropyridine N-oxide, which was identified in the form of the methyl derivative.

In contrast to N-oxide II, the reaction of 2,6-bis(methylthio)-3,4,5-trichloropyridine (II) with sodium hydrosulfide proceeds readily in dimethylformamide (DMF) with replacement of the chlorine atom in the 4 position by a mercapto group to give 2,6-bis(methylthio)-4-mercaptop-3,5-dichloropyridine (IV) in quantitative yield. The difference in the chemical behavior of II as compared with unoxidized compound III is explained by the electronic effect of the N-oxide group, which activates the  $\alpha$  position considerably more markedly than the  $\gamma$  position in nucleophilic substitution reactions [2]. The manifestation of the electron-acceptor effect of the N-oxide group in II is also confirmed by the PMR spectrum, in which one observes a 0.04-ppm shift of the signals of the protons of the methyl group to the weak-field side as compared with the signals of the protons of III (Table 1). Methylation of IV with dimethyl sulfate in an alkaline medium gives 2,4,6-tris(methylthio)-3,5-dichloropyridine (V).

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