HYDROXY-, AMINO, AND MERCAPTOPYRIDINES AND QUINOLINES IN THE REACTION WITH PHENYLACETYLENE

M. A. Andriyankov, M. V. Nikitin, and A. V. Afonin

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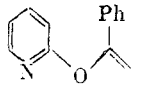
The 2-hydroxy-, amino-, and mercaptopyridines and quinolines react with phenylacetylene under different catalytic conditions with the formation of the corresponding O-, N-, and S-styryl derivatives. In the case of the trans isomer of 1-styryl-2-pyridone, the flat disposition of the olefin fragment and the heterocycle with the S-trans conformation of the sytryl group is proposed. All the cis isomers of the 1-styrylpyridones are noncoplanar.

As was previously shown [1, 2], the vinylation of hydroxy-, amino-, and mercaptopyridines in the presence of the catalysts KOH and cadmium acetate leads to the N-, O-, and S-vinyl derivatives of the pyridine series. The reaction of phenylacetylene (PA) with 2-hydroxypyridine, 2-aminopyridines, 4-hydroxyquinoline, and 2-mercaptoquinoline was investigated under analogous catalytic conditions at 160-210°C in the medium of dioxane in the present work.

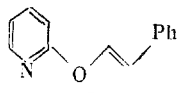
We established that the direction of the addition of the terminal PA to the indicated derivatives of pyridine and quinoline corresponds to the addition of the unsubstituted acetylene. Thus, the reaction of 2-pyridone with PA under the conditions of alkaline catalysis proceeds regio- and stereoselectively with the formation of one product – the cis isomer of 1-styryl-2-pyridone (I). The structure of this and of other compounds synthesized follows from the PMR data which are discussed below.

The most acceptable nucleophilic addition of 2-pyridone at the triple bond of PA may be interpreted by the "rule of consistent trans-nucleophilic addition" of Truce [3]. This scheme explains, in a completely satisfactory way, the preferred formation of the cis adducts, the structural direction of the addition to the monosubstituted acetylenes, and the formation of the β-isomers in the presence of the acceptor substituent (phenyl) at the triple bond and the bulky anion. The formation of precisely the N-styryl derivative (I) is explained by the fact that the 2-pyridone is deprotonated at the nitrogen atom by the action of the alkali.

As was also to be expected [1], mainly the O-addition products are formed from 2-pyridone and PA in the presence of cadmium acetate. Chromatography of the reaction mixture on a column led to the isolation of a light yellow liquid which is the 3:1 mixture of 1-phenyl-1-(pyridyl-2-oxy)ethylene (II) and 2-styryloxypyridine (III), according to the PMR data.



(II)



(III)

The formation of the cis isomers (III) and (I) in this reaction fits into the Truce rule, and the isolation of the compound (II) indicates the addition of 2-pyridone at the α-carbon atom of the PA.

The 4-quinolone reacts analogously with PA with the preferential formation of 1-phenyl-1-(quinolyl-4-oxy)ethylene (IV) (the catalyst is cadmium acetate) or 1-styryl-4-quinolone (V) exclusively by the action of the catalyst KOH.

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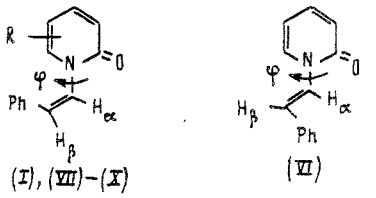
Table 1. PMR Spectral Parameters of the Compounds of the Pyridine Series

Compound	Chemical shifts, δ, ppm				
	H_α	H_β	H^3	H^5	H_{arom}
(I)	6,92	6.48	6.60	5,97	H^4, H^6, H_{arom} 7,00–7.37
	$^3J_{\alpha\beta}$=9,2 Hz				
(VI)	7,98	6.66	6.58	6,23	H^4, H^6, H_{arom} 7,22–7,64
	$^3J_{\alpha\beta}$=14,8 Hz				
(VII)	6,92	6.40	CH_3 2.15	5,86	H^4, H^6, H_{arom} 7,07–7.26
	$^3J_{\alpha\beta}$=9,3 Hz				
(VIII)	6,87	6,41	6,37	5.77	H^6, H_{arom} 7.07–7.42 CH_3–2.10
	$^3J_{\alpha\beta}$=9,3 Hz				
(IX)	6,87	6,42	6,52	CH_3 2,10	H^4, H^6, H_{arom} 7,07–7,28
	$^3J_{\alpha\beta}$=9,3 Hz				
(X)	6,64	6,45	6.46	5,95	H^4, H_{arom} 6.97–7.43 CH_3 – 1,97
	$^3J_{\alpha\beta}$=8,8 Hz				
(II)	$H_{\beta'}$ 5,35	$H_{\beta''}$ 4.90	6,86	H^6 8.11	H^4, H^5, H_{arom} 7,12–7.62
	$^2J_{\beta'\beta''}$ = 1,9 Hz				
(III)		5,66	6,89	H^6 8,18	H_α, H^4, H^5, H_{arom} 7,18–7,76
	$^3J_{\alpha\beta}$=7,1 Hz				

The addition of 2-aminopyridine and its 3-, 4-, 5-, and 6-methyl-substituted derivatives to PA takes place regioselectively, by the pyridine nitrogen at the β-carbon atom of the acetylene bond, in the presence of cadmium acetate. The reaction evidently proceeds via the formation of 1-styryl-2-iminopyridine and the subsequent hydrolysis of the imino group. The steric direction of such a reaction depends on the presence of water in the reaction mixture. Thus, the cis isomer (I) is formed exclusively in the presence of water, and, in its absence, the trans isomer 1-styryl-2-pyridone (VI) is formed with the remaining parameters of the process being identical.

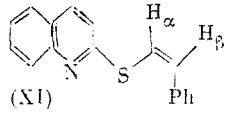


R = H (I), 3-CH_3 (VII), 4-CH_3 (VIII), 5-CH_3 (IX), 6-CH_3(X)

The contemplated thermal (cis–trans) isomerization is excluded in the given case since we only isolate the corresponding stereoisomers on varying the temperature of the reaction (with the addition of water or without it).

One of numerous exclusions to the rule of Truce evidently takes place in the reaction of 2-aminopyridine with PA in the absence of water; this is namely the cis-nucleophilic addition at the triple bond with the formation of the trans isomer (VI). The hydrolysis of the imino group is possible in this case on account of the water of crystallization of the catalyst. The alkaline catalysis of the reaction of 2-aminopyridine with PA leads to the product mixture which is difficult to separate; the products could not identified.

The reaction of 2-mercaptoquinoline with PA proceeds regio- and stereoselectively independently of the nature of the catalyst with the formation of the cis isomer of 2-styrylthioquinoline (XI) with the yield of 60%.



(XI)

Table 2. PMR Spectral Parameters of the Compounds of the Quinoline Series

Compound	Chemical shifts, δ, ppm				
	H_α	H_β	H^3	H^5	H_{arom}
(IV)	$H_{\beta'}$ 5,46 | $H_{\beta''}$ 4,98 $^2J_{\beta'\beta''} = 2,2$ Hz.		6,77	H^2 8.64	H^5–H^8. Harom 7.19–7.62 8.13–8.36
(V)	6,91 | 6.68 $^3J_{\alpha\beta}$=8,6 Hz		6,20	8,43	H^2. H^6–H^8. Harom 7,00–7.67
(XI)	| 6,78 $^3J_{\alpha\beta}$=10,8 Hz				H_α, H^3–H^8. Harom 7.15–8.07

The property of quinoline-2-thione of the reaction at the sulfur atom is evidently determined by the significant polarization of the thiocarbonyl group [4].

The signals of the olefinic protons were identified in the PMR spectra of the compounds synthesized. In the compounds (I), (V), and (VII)-(X), the vicinal spin–spin coupling constants (SSCCs) between the olefinic protons are equal to 8.6-9.3 Hz (Tables 1, 2). Such values of the SSCCs correspond with the cis disposition of the interacting protons [5]. Consequently, the compounds (I), (V), and (VII)-(X) are the cis isomers. The SSCC values for $^3J_{\alpha\beta}$ indicate the addition of the olefin fragment to the nitrogen atom [6]. The SSCC $^3J_{\alpha\beta}$ for the trans isomer of 1-styryl-2-pyridone (VI) is significantly different (14.8 Hz) from that in the compounds (I), (V), and (VII)-(X); this indicates the trans disposition of the olefinic protons (Table 1).

The value of the SSCC $^3J_{\alpha\beta}$ in the 2-styryloxypyridine (III) is characteristic of the cis disposition of the protons (7.1 Hz), but its lower value is associated with the addition of the olefin fragment to the oxygen atom in the given case [7]. The 1-phenyl-1-(pyridyl-2-oxy)ethylene (II) and 1-phenyl-1-(quinolyl-4-oxy)ethylene (IV) have two β-olefinic protons; this follows from the values of the SSCCs between them (1.9-2.2 Hz). Therefore, they are the products of the α-addition to the PA. Finally, the SSCC $^3J_{\alpha\beta}$ of 2-styrylthioquinoline (XI) is equal to 10.8 Hz; this conforms with the cis disposition of the olefinic protons at the sulfur atom [8].

The analysis of the PMR spectra of the compounds synthesized also permits a series of conclusions on their steric structure. The chemical shifts of the olefinic protons in the trans isomer (VI) differ signficantly from those in the cis isomers (I), (V), and (VII)-(X). The abrupt low-field shift of the signal of the α-olefin proton in the trans isomer (VI) relative to the cis isomers (I), (V), and (VII)-(X) can be noted separately; the shift comprises 1.08-1.34 ppm. The analogous low-field shift of the signal of the α-proton of the vinyl group took place for 1-vinyl-2-pyridone [6]. It is caused by the steric proximity of the oxygen atom to the resonating nucleus, which is realized in the S-trans(O)-conformation, being close to planar. In the case of the trans isomer (VI), the planar disposition of the olefinic fragment and the heterocycle can also be assumed. The steric influence of the carbonyl group thereby leads to the S-trans(O)-conformation ($\varphi = 0$), and the H_α nucleus is found to be sterically close to the oxygen atom. In the cis isomers, the steric interaction of the phenyl group and the heterocycle causes a significant disturbance of the coplanar disposition of the olefinic fragment and the heterocycle ($\varphi \approx 45$-$90°$), when the H_α proton becomes sterically removed from the oxygen atom and its chemical shift is shifted to high field.* The introduction of the methyl group at the position 6 of the ring does not lead to significant changes in the chemical shifts of the olefinic protons. In the case of the noncoplanar disposition of the olefin fragment and the heterocycle, the steric influence of the methyl group at the position 6 on the styryl is decreased; it does not therefore induce the further significant emergence of the latter from the plane of the pyridone ring.

Therefore, the trans isomer of 1-styryl-2-pyridone has a planar structure and the S-trans(O)-conformation of the styryl group. All the cis isomers of the 1-styryllactams are noncoplanar.

*This high-field shift is partly caused by the change in the position of the phenyl group relative to the double bond; the value of this effect does not exceed 0.4 ppm [9].

EXPERIMENTAL

The PMR spectra were obtained in the Tesla BS-497 (100 MHz) spectrometer for the 5% solutions in $CdCl_3$ relative to HMDS at ~20°C.

1-Styryl-2-pyridone (I). The mixture of 9.5 g (0.1 mole) of 2-pyridone, 10.2 g (0.1 mole) of PA, 3.0 g (30%) of KOH, and 100 ml of dioxane was heated for 2 h at 180°C in an autoclave. The dioxane was distilled from the cooled mixture, and the residue was extracted with benzene. The extract was repeatedly washed with water and dried with calcined $CaCl_2$. The benzene was evaporated, and the residue was chromatographed on a column with Al_2O_3 in acetone. The yield of 4.5 g (23%) of (I) was isolated; it has the mp 45-48°C. Found: C 79.60, H 5.91, and N 6.70%. $C_{13}H_{11}NO$. Calculated: C 79.16, H 5.62, and N 7.10%.

Reaction of 2-Pyridone with PA in the Presence of Cadmium Acetate. The mixture of 9.5 g (0.1 mole) of 2-pyridone, 10.2 g (0.1 mole) of PA, 5.6 g (0.02 mole) of $Cd(CH_3COO)_2 \cdot 3H_2O$ and 80 ml of dioxane was heated for 1 h in a 0.5 liter autoclave at 205°C. After cooling down the mixture, the dioxane was evaporated from the dark brown liquid using a rotary evaporator; the residue was extracted with benzene, and the extract was repeatedly washed with water and dried with calcined $CaCl_2$. The benzene was distilled off, and the residue was separated on a column with Al_2O_3 in acetone. The yield of 6.0 g (30%) of the liquid with the bp 130-140°C (2 mm) was obtained; this is the 3:1 mixture of 1-phenyl-1-(pyridyl-2-oxy)ethylene (II) and 2-styryloxypyridine (III) according to the PMR data. Found: C 79.31, H 5.80, and N 6.62%. $C_{13}H_{11}NO$. Calculated: C 79.16, H 5.62, and N 7.10%. The yield of 0.9 g (5%) of (I) was isolated together with (II) and (III).

1-Styryl-4-quinolone (V). The mixture of 14.5 g of 4-quinolone, 10.2 g (0.1 mole) of PA, 4.3 g (30%) of KOH, 100 ml of dioxane, and 5 ml of water was heated for 1.5 h at 210°C in an autoclave. In vacuo distillation led to the isolation of the fraction with the bp 200-255°C (3 mm), which was purified by chromatography on a column with Al_2O_3 in the 6:6:1 system of chloroform–ether–acetone. The yield of 4.0 g (16%) of (V) was obtained; it had the mp 108-109°C. Found: C 83.10, H 5.31, and N 5.90%. $C_{17}H_{13}NO$. Calculated: C 82.57, H 5.30, and N 5.66%.

1-Phenyl-1-(quinolyl-4-oxy)ethylene (IV). The mixture of 14.5 g (0.1 mole) of 4-quinolone, 10.2 g (0.1 mole) of PA, 5.6 g (0.02 mole) of $Cd(CH_3COO)_2 \cdot 3H_2O$, and 100 ml of dioxane was heated for 1.5 h in an autoclave at 205°C. The fractional distillation in vacuo with the subsequent chromatography on a column with silica gel L 40/100 in the 20:1 system of chloroform–alcohol led to the isolation of (IV) with the yield of 6.0 g (25%); it had the bp 182-188°C (2 mm), the n_D^{20} 1.6150, and the d_4^{20} 1.1441. Found: C 82.31, H 5.11, and N 6.00%. $C_{17}H_{13}NO$. Calculated: C 82.57, H 5.30, and N 5.66%. Compound (V) was isolated with the yield of 1.5 g (6%) together with (IV).

Reaction of 2-Aminopyridine and Its Derivatives with PA. The mixture of 18.8 g (0.2 mole) of 2-aminopyridine, 20.5 g (0.2 mole) of PA, 8.4 g (0.03 mole) of $Cd(CH_3COO)_2 \cdot 3H_2O$, 100 ml of dioxane, and 10 ml of water was heated in an autoclave for 2 h at 205°C. By treating the reaction mixture analogously to the experiment of the 2-pyridone with PA in the presence of KOH, (I) was isolated in the yield of 10.2 g (26%); it had the mp 42-47°C. Found: C 79.83, H 5.82, and N 7.40%. $C_{13}H_{11}NO$. Calculated: C 79.16, H 5.62, and N 7.10%.

By analogy, the methyl-substituted 2-aminopyridines yielded 1-styryl-2-pyridones (the compound, the bp, the n_D^{20}, the d_4^{20}, and the yield in % are given): (VII), 157-162°C (2 mm), 1.6267, 1.1486, 27; (VIII), 170-173°C (3 mm), 1.6320, 1.2143, 31; (IX), 168-172°C (2 mm), 1.6270, 1.1274, 33; (X), 160-163°C (2 mm), 1.6218, 1.1314, 25.

When the reaction of 2-aminopyridine with PA was performed under analogous conditions but without the added water, the trans isomer (VI) was isolated with the yield of 26%; it had the mp 146-148°C. Found: C 79.62, H 5.70, and N 6.71%. $C_{13}H_{11}NO$. Calculated: C 79.16, H 5.62, and N 7.10%.

2-Styrylthioquinoline (XI). The mixture of 8.1 g (0.05 mole) of 2-mercaptoquinoline, 5.1 g (0.05 mole) of PA, 2.5 g (30%) of KOH, 60 ml of dioxane, and 3 ml of water was heated for 1 h in an autoclave at 160°C. The residue which came out after the cooling of the reaction mixture was washed with water until a neutral reaction was obtained. The remaining product was recrystallized from petroleum ether. The yield of 7.8 g (60%) of (XI) was isolated; it had the mp 115-117°C. Found: C 77.71, H 5.10, N 5.51, and S 12.03%. $C_{17}H_{13}NS$. Calculated: C 77.53, H 4.98, N 5.32, and S 12.18%.

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ALKYLATION OF OXYPURINES BY α,ω-DIHALOALKANES.

1. REACTION OF XANTHINE SODIUM SALTS AND SOME N-METHYL DERIVATIVES WITH α,ω-DIHALOALKANES

I. Sh. Salikhov, V. O. Kuznetsov, and V. S. Reznik

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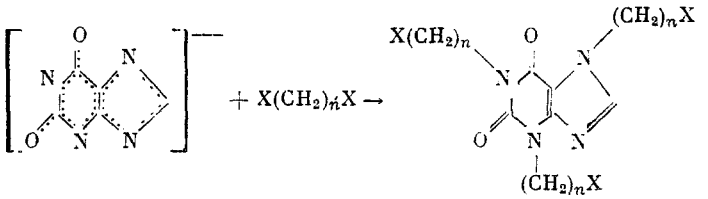
A method was developed for obtaining previously unknown 1,3,7-tris(ω-haloalkyl)-, 1,7-bis(ω-chloroalkyl)-3-methyl-, and 1,3-bis(ω-chloropentyl)-7-methylxanthines.

Purine derivatives have found application in medical practice [1-5]. With the aim of synthesizing N-(ω-haloalkyl)xanthines, we studied the reaction of Na salts of xanthine, 3-methyl-, and 7-methylxanthine with α,ω-dihaloalkanes.

Alkylation of dimethylxanthine salts with α,ω-dihaloalkanes in the presence of quaternary ammonium bases afforded the corresponding 1-(ω-haloaloyl)-3,7-dimethyl- and 7-(ω-haloalkyl)-1,3-dimethylxanthines [6-8]. Romanenko et al. [9] studied the reaction of K salts of 8-bromo-3-methylxanthine with α,ω-dihaloalkanes. 7,7'-Bisxanthylalkanes were isolated at a reagent ratio of 2:1, whereas excess α,ω-dihaloalkane afforded 8-bromo-7-(ω-haloalkyl)-3-methylxanthines; 1,7-bis(ω-haloalkyl)-8-bromo-3-methylxanthines were not formed in this reaction.

Reaction of xanthine trisodium salts (I) with a 10-12 fold molar excess of α,ω-dihaloalkane (II) in absolute DMF at 85-115°C afforded 1,3,7-tri(ω-haloalkyl)xanthines (III) in yields of 32-56%. These compounds are fluid, transparent oils soluble in ether, benzene, and $CHCl_3$:



(I) (II) (III)

$n = 4$, X = Cl (a); $n = 5$, X = Br (b); $n = 5$, X = Cl (c); $n = 6$, X = Cl (d).

A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Branch, Academy of Sciences of the USSR. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 9, pp. 2102-2105, September, 1989. Original article submitted June 3, 1988.

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