INSERTION OF ACETYLENIC SUBSTITUENTS IN THE PYRIDINE RING

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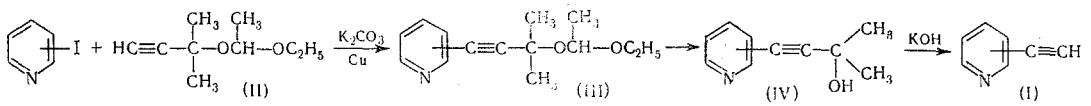
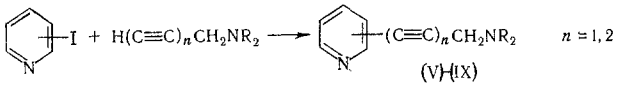
α-Iodopyridine in the presence of copper metal condenses with terminal acetylenic hydrocarbons and the acetals of primary, secondary, and tertiary alcohols, forming substituted pyridylacetylenes [1-3]. The tertiary acetylenic alcohols that are formed here are smoothly converted to the α-ethynylpyridine under the conditions of the reverse Favorskii reaction.

The synthesis of the γ- and β-ethynylpyridines (Iγ) and (Iβ) was accomplished by a similar scheme in the present paper



The time for the condensation of the γ- and β-iodopyridines with acetal (II) was 39-42 h, as compared to 6-7 h for the α-isomer [3]. As a result, the "ortho effect" of the heteroatom is distinctly manifested when a halogen in the pyridine ring is replaced by an acetylenic moiety. The yields of the pyridylacetylenic derivatives (III), despite the long heating during the reaction course, exceeded 90%. Ethynylpyridines (Iγ) and (Iβ) were obtained in 60% yield by the cleavage of the alcohols (IV) when they were vacuum-distilled with traces of KOH. For comparison it might be mentioned that in the literature described syntheses of γ-ethynylpyridine (Iγ) by the classical method from methyl pyridyl ketone the yield hardly reached 5% [4, 5].

Continuing our study of the application of the reaction of haloaromatic derivatives with acetylenes, we used this method to directly insert the N,N-dialkylaminopropynyl and N,N-dialkylaminopentadiynyl groups into various positions of the pyridine ring



α-Iodopyridine was reacted with the propargylamines for 19-23 h, i.e., the reaction rate was 3-4 times slower than when reaction was with the acetals of acetylenic alcohols. With insertion of the diacetylenic grouping into the amine molecule the condensation time dropped to 4 h, but this reaction time still remained approximately the same number of times longer than when reaction was with the acetals of diacetylenic alcohols [3]. In the case of β-iodopyridine the reaction was retarded noticeably less ($\sim$ 1.5 times), while the γ-isomer reacted with the propargylamines and acetal (II) at approximately the same rate. Such a noticeable difference in the relative activity of the propargylamines when substitution is in the α-position can apparently not be explained by the purely electronic effect of the amino group. The reduction we observed in the condensation rate of α-iodopyridine with acetal (II) in the presence of saturated tertiary amines can also serve as confirmation of this. Thus, when one mole of dimethylaniline per mole of iodopyridine was added to the reaction mass the condensation time, with the other conditions kept constant, increased approximately double, which corresponded to 7-10% of unreacted iodide in 7.5 h after the start of reaction. (In this time the replacement of iodine by the aminoacetylenic group goes to the extent of only 55-60%.)

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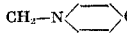
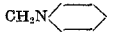
TABLE 1. Acetylenic Condensation of Iodopyridines $C_5H_4NI + HC \equiv CR' \xrightarrow[-HI]{} C_6H_5NC \equiv CR'$

Compound	—R′	Yield, %	Reaction time, h	bp, °C (p, mm of Hg)	n_D^{20}	IR spectrum, $\nu_{C\equiv C}$ cm^{-1} (in CCl_4)	Found N, %	Empirical formula	Calc. N, %
IIIβ	$C(CH_3)_2OCH(CH_3)OC_2H_5$	97	40—42	104—105 (0,5)	1,5050	2240 v. w *	5,99	$C_{14}H_{19}NO_2$	6,00
IIIγ	$C(CH_3)_2OCH(CH_3)OC_2H_5$	90	39—41	107—108 (1,5)	1,4989	2240 w *	5,97	$C_{14}H_{19}NO_2$	6,00
Vα		93	23	135—136 (1)	1,5669	2240 m 2210 w	13,90	$C_{12}H_{14}N_2O$	13,85
Vβ		92	52	mp 57,5—58,5° [6]	—	2245 v. w	—	$C_{12}H_{14}N_2O$	—
Vγ		87	32	mp 69—70°	—	2240 w, sh 2250	13,87	$C_{12}H_{14}N_2O$	13,85
VIα		94	19	132—133 (1)	1,5631	2240 m 2210 w	13,90	$C_{13}H_{16}N_2$	13,99
VIβ		80	70	136—138 (1) [6]	1,5535	2240 v. w	—	$C_{13}H_{16}N_2$	—
VIγ		90	39	mp 30—31°	—	2245 w	14,11	$C_{13}H_{16}N_2$	13,99
VIIα		50	23	— †	1,5650	2240 m 2210 w	14,84	$C_{12}H_{14}N_2$	15,05
VIIIα	$CH_2N(C_2H_5)_2$	70	20	— †	1,5405	2240 m 2210 w	15,12	$C_{12}H_{16}N_2$	14,89
IXα	$C\equiv CCH_2N(C_2H_5)_2$	75	4	— †	1,5914	2250 s ‡ 2170 w	12,98	$C_{14}H_{16}N_2$	13,20

* $\nu_{C-O-C-O-C}$ 1050, 1080, 1120, and 1155 cm^{-1}.

† Purified chromatographically.

‡ In addition, bands of weak intensity at 2215, 2195, 2150, and 2140 cm^{-1}.

The direct synthesis of pyridylacetylenic amines has undoubted advantages over the other methods [6], since it does not require the prior multistep preparation of the ethynylpyridines and proceeds in high yields (70-90%).

EXPERIMENTAL METHOD

The starting iodopyridines were synthesized by the diazotization of the aminopyridines, with subsequent replacement of the diazo group by iodine [7], while the propargylamines were prepared by the reaction of propargyl bromide with the appropriate secondary amines [8, 9]. 5-Diethylamino-1,3-pentadiyne was obtained by the alkaline cleavage of 7-diethylamino-2-methyl-3,5-heptadiyn-2-ol [10], which was synthesized in 50% yield by the Chodkiewics–Cadiot reaction from diethylpropargylamine and 1-bromo-3-methyl-1-butyn-3-ol.

Acetylenic Condensation of Iodopyridines. A mixture of 0.02 mole of the iodopyridine, 0.03 mole of the acetylenic compound, 1 g of activated copper powder [3], and 5.2 g of finely ground anhydrous K_2CO_3 in 50 ml of anhydrous pyridine was refluxed in an N_2 atmosphere until the starting iodide disappeared. The end of reaction was determined employing TLC (Al_2O_3, II activity) and GLC (Pye chromatograph equipped with an ionization detector, column length 110 cm, diameter 6 mm, 0.05% of poly(ethylene glycol adipate) deposited on glass beads, carrier gas = argon, and temperature 70°C). After cooling, the reaction mass was diluted with 500 ml of ether, the precipitate was separated, and the ether solution was washed several times with 10% aqueous NH_3 solution and water, or else it was filtered through a thin layer of Al_2O_3 (II activity). After removal of the solvent, the residue was vacuum-distilled. The yields and constants of the obtained compounds are given in Table 1.

Pyridylacetylenic Alcohols. A mixture of 4.2 g of acetal (IIIβ), 4 ml of dilute HCl solution (1 : 3.5), and 5 ml of dioxane was stirred at 20° for 1-2 h, checking the course of the hydrolysis by TLC. At the end of reaction the mass was diluted with 100 ml of ether and neutralized with finely ground K_2CO_3. After distillation we obtained 2.4 g (83%) of the acetylenic alcohol (IVβ), mp 56-57° (from petroleum ether), and bp 122-123° (2.5 mm) [6]. IR spectrum (ν, cm^{-1} in CCl_4): 2235 (C≡C), 3615 (OH) (broad band of the hydrogen bond with a maximum at 3280 cm^{-1}). 1-γ-Pyridyl-3-methyl-1-butyn-3-ol (IVγ) was obtained in the same manner in 84% yield, mp 111.5-112.5° (from CCl_4). Found: N 8.99%. $C_{10}H_{11}NO$. Calculated: N 8.69%. Infrared spectrum (ν, cm^{-1} in $HCCl_3$): 2240 (C≡C) (shoulder at 2250 cm^{-1}), 3600 (OH) (broad band of hydrogen bond with a maximum at 3210 cm^{-1}).

Ethynylpyridines (Iβ) and (Iγ). A mixture of 2 g of (IVβ) and 0.08 g of powdered KOH was cautiously melted in a distillation flask and, gradually lowering the pressure from 85 down to 25 mm, the acetone and acetylene (Iβ) were distilled off. After repeated sublimation the yield of the chromatographically pure (Iβ) was 0.8 g (61%), mp 37.5-38.5° [6]. Infrared spectrum (ν, cm^{-1} in CCl_4): 2125 (C≡C); 3320 (C≡C–H). NMR spectrum (in CCl_4; hexamethyldisiloxane used as the standard): C≡C–H 3.18 ppm, H of ring – α 8.61 ppm (singlet), α' 8.42 ppm, and γ 7.62 ppm (doublets with additional hyperfine splitting), and β' 7.10 ppm (doublet of doublets).

(Iγ) was obtained in a similar manner in 62% yield, mp 96-96.5° [4]. Infrared spectrum (ν, cm^{-1} in CCl_4): 2125 (C≡C); 3310 (C≡C–H). NMR spectrum (in CH_2Cl_2): C≡C–H 3.34 ppm, H of ring – α 8.50 ppm and β 7.29 ppm (doublets).

CONCLUSIONS

1. An iodine atom in any position of the pyridine ring is easily replaced by an acetylenic moiety when reacted with terminal acetylenic compounds in the presence of copper and potassium carbonate. In their reactivity the isomeric iodopyridines fall into the order: $\alpha \gg \gamma \geq \beta$.

2. A method for the synthesis of ethynylpyridines and their N,N-dialkylaminomethyl derivatives was developed on the basis of the acetylenic condensation.

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