# SYNTHESIS AND PROPERTIES OF STERICALLY HINDERED HYDROXYSTYRLPYRIDINES

G. N. Bogdanov, A. N. Rozenberg, and A. K. Sheinkman

UDC 547.829.07:615.771.7

A number of new sterically hindered hydroxystyrylpyridines were synthesized, and their antioxidative activity as a function of structure was studied. The antitumorigenic characteristics of three of the synthesized compounds are given.

The extensive use of sterically hindered phenols in various fields of chemistry and experimental biology [1, 2] is stimulating further study of the properties of this series of organic compounds. In particular, sterically hindered phenols that contain a polar grouping with a markedly developed system of conjugated bonds in the 4 position seem of considerable interest as potentially active antitumorigenic preparations [3]. Since the broad spectrum of biological action of substituted stilbazoles has been experimentally demonstrated, we undertook research on the synthesis and study of the properties of sterically hindered hydroxystyrylpyridines.

One of the most convenient methods for the synthesis of stilbazoles is the condensation of aromatic aldehydes with the acyl salts of pyridine derivatives [4]. Although styrylpyridines could not be obtained from p-hydroxybenzaldehyde by this method because of side acylation of the OH group [5], it could be expected that, because of the steric shielding of the hydroxyl group in 3,5-dialkyl-4-hydroxybenzaldehydes, they could be used for the synthesis of sterically hindered hydroxystyrylpyridines.

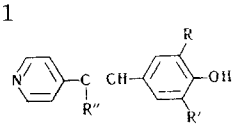
In the present study, we were able to obtain a number of previously unknown hydroxystyrylpyridines by the direct condensation of 3,5-dialkyl-4-hydroxybenzaldehydes with N-acyl-$\alpha$- or $\gamma$-picolinium salts. The pH of the medium plays a substantial role in the isolation of the individual bases of the hydroxystyrylpyridines from the crude hydrochlorides. The pure hydroxystyrylpyridine bases could be isolated in good yields by the slow addition of ammonium hydroxide and subsequent filtration (Table 1).

The structures of the hydroxystyrylpyridines were confirmed by UV and IR spectroscopy. Thus, for example, strong absorption bands (1220 and 1240 $cm^{-1}$) corresponding to the skeletal vibrations of the tert-butyl groups are observed in the IR spectra of Ic, Ie, If, and IIc. In addition, the presence of an absorption band at 1635 $cm^{-1}$ is evidence for the presence of a conjugated double bond, and the intensity of this band may serve as a measure of the conjugation of the aromatic ring and the double bond. The IR spectra of Ic, Ie, If, and IIc contain different absorption bands caused by the deformation vibrations of the ethylene (-CH=CH-) and ethylidene $\left(\rangle C{=}CH{-}\right)$ groupings at 967 and 915 $cm^{-1}$, respectively.

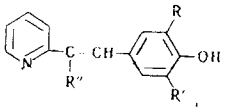
There are two characteristic maxima at 230-240 and 320-340 nm in the UV spectra (Fig. 1). The long-wave absorption band is due to a $\pi-\pi^*$ transition in the conjugated system of bonds, which is attested to by the bathochromic shift of the maximum as the solvent polarity increases (Table 2). In turn, the decrease in the molar extinction coefficients and the hypsochromic shift of the absorption maxima in Ie, If, and Ig are evidence that the presence of R'' substituents in these styrylpyridines induces disruption of the

Donetsk Branch, Institute of Chemical Physics, Academy of Sciences of the USSR. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1660-1664, December, 1971. Original article submitted May 5, 1970.

TABLE 1



I a-g



II a-c

| Compound | R | R′ | R″ | mp, °C | $R_f$ [a] | UV spectrum [b] $\lambda_{max}$ | UV spectrum [b] lg ε | Empirical formula | Found, % C | Found, % H | Calc., % C | Calc., % H | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ia[c] | $CH_3$ | $C_6H_{11}$[d] | H | 176—178 | 0,44 | 315 | 4,10 | $C_{20}H_{23}NO\times$ $\times HCl$ | 72,8 72,7 | 7,3 7,3 | 72,8 | 7,3 | 58 |
| Ib | $CH_3$ | $t$-$C_4H_9$ | H | 165—165,5 | 0,32[e] | 319[f] | 4,30 | $C_{18}H_{21}NO$ | 81,8 81,0 | 7,8 7,8 | 80,9 | 7,9 | 33 |
| Ic | $i$-$C_3H_7$ | $i$-$C_3H_7$ | H | 224—225 | 0,23 | 344[f] | 4,23 | $C_{19}H_{23}NO$ | 79,8 80,1 | 8,3 8,1 | 81,1 | 8,2 | 60 |
| Id | $t$-$C_4H_9$ | $t$-$C_4H_9$ | H | 243—245 | 0,32 | 345 | 4,24 | $C_{21}H_{27}NO$ | 81,8 81,6 | 8,4 8,6 | 81,5 | 8,8 | 23 |
| Ie | $t$-$C_4H_9$ | $t$-$C_4H_9$ | $CH_3$ | 207—207,5 | 0,47 | 320 | 4,16 | $C_{22}H_{29}NO$ | 81,9 82,1 | 9,5 9,6 | 81,7 | 9,1 | 70 |
| If | $t$-$C_4H_9$ | $t$-$C_4H_9$ | $C_6H_5$ | 181—182 | 0,58 | 335 | 4,14 | $C_{27}H_{31}NO$ | 83,9 84,2 | 8,4 8,2 | 84,1 | 8,1 | 70 |
| Ig | $t$-$C_4H_9$ | $t$-$C_4H_9$ | $p$-$O_2NC_6H$ | 199—200 | 0,23 | 342 | 4,24 | $C_{27}H_{30}N_2O_3$ | 75,6 75,3 | 7,2 7,1 | 75,3 | 7,0 | 85 |
| IIa | $CH_3$ | $t$-$C_4H_9$ | H | 142,5—143 | 0,46 | 322 | 4,24 | $C_{18}H_{21}NO$ | 80,1 81,0 | 7,9 7,9 | 80,6 | 7,9 | 39 |
| IIb | $i$-$C_3H_7$ | $i$-$C_3H_7$ | H | 118—119 | 0,57[e] | 320 | 4,24 | $C_{19}H_{23}NO$ | 81,1 80,9 | 8,2 8,3 | 81,1 | 8,3 | 74 |
| IIc[c] | $t$-$C_4H_9$ | $t$-$C_4H_9$ | H | 216—218 | 0,71 | 337 | 4,25 | $C_{21}H_{27}NO\times$ $\times HCl$ | 67,6 67,4 | 8,4 8,3 | 67,6 | 8,4 | 29 |

[a] In a chloroform–benzene–heptane (30 : 6 : 1) system in a loose layer of aluminum oxide. [b] In ethanol. [c] Data for the hydrochloride are given. [d] Cyclohexyl. [e] In a chloroform–benzene (1 : 2) system in a loose layer of aluminum oxide. [f] In methanol.

TABLE 2. UV Spectra of Hydroxystyrylpyridines

| Compound | $\lambda_{max}$, nm (lg ε) hexane | ether | chloroform | ethanol |
|---|---|---|---|---|
| Id | 329 (4,25) | 330 (4,27) | 340 (4,30) | 345 (4,24) |
| Ig | — | 325 (4,10) | 330 (4,14) | 342 (4,24) |
| If | 328 (4,20) | 330 (4,20) | 334 (4,20) | 335 (4,14) |
| Ie | 305 (4,15) | 307 (4,16) | 315 (4,15) | 320 (4,16) |

TABLE 3. Antioxidative Effectiveness of Hydroxystyrylpyridines

| Inhibitor | $K_7/\sqrt{K_6}$ base | $K_7/\sqrt{K_6}$ hydrochloride |
|---|---|---|
| IIc | — | 4,85 |
| Id | 4,52 | 4,00 |
| Ie | 6,60 | 4,60 |
| If | 11,22 | 7,86 |

planar orientation of the benzene and pyridine rings. The intensities of the absorption bands at 1635 $cm^{-1}$ in the IR spectra and in the fluorescence spectra (Fig. 1) also indicate this.

The peculiarities of the structures of the sterically hindered hydroxystyrylpyridines make them an exceptionally interesting subject for diverse physicochemical investigations. This particularly pertains to their possible use as inhibitor-antioxidants.

Using a chemiluminescence method [6], we studied the ability of the hydroxystyrylpyridines to interact with peroxide radicals in the initiated oxidation of ethylbenzene; this ability was characterized by the kinetic parameter $K_7/\sqrt{K_6}$. ($K_6$ and $K_7$, respectively, are the elementary constants of quadratic chain termination and interaction of the peroxide radicals with inhibitor.) The $K_7/\sqrt{K_6}$ values were calculated from the linear anamorphoses of the chemiluminescence extinction curves as a function of the concentration of the hydroxystyrylpyridines, taken as bases and hydrochlorides (Fig. 2). In this case, the $K_7/\sqrt{K_6} = \tan\alpha\sqrt{W_i}/1.1$* parameter characterized the antiradical activity of the compounds. It was found that all of the hydrochlo-

* Under the conditions of azobisisobutyronitrile-induced oxidation of ethylbenzene, the fixed rate of initiation ($W_i$) was $7.6 \cdot 10^{-9}$ mole/liter · sec.

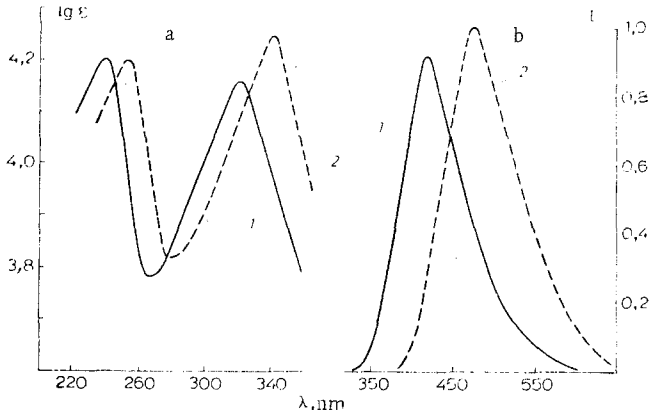



Fig. 1

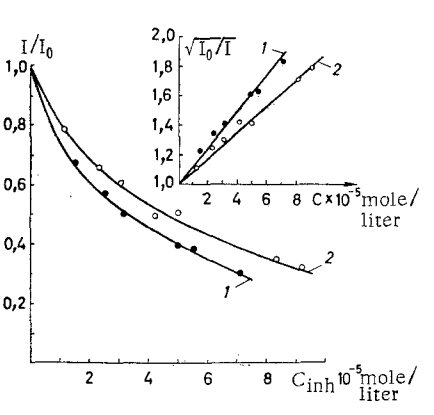



Fig. 2

Fig. 1. UV spectra (a) in ethanol and fluorescence spectra (b) of hydroxystyrylpyridines Ia (1) and Ie (2).

Fig. 2. Chemiluminescence extinction curves and their linear anamorphoses for base Ie (1) and its hydrochloride (2).

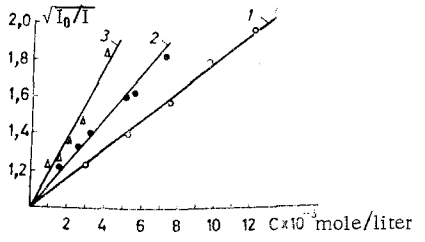



Fig. 3

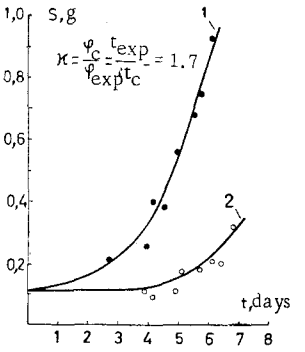



Fig. 4

Fig. 3. Anamorphoses of the chemiluminescence extinction curves for hydroxystyrylpyridine bases Id (1), Ie (2), and If (3).

Fig. 4. Kinetic curves of the change in weight of the spleen in control experiments (1) and when Ia was introduced (2).

rides are less effective as inhibitors than the corresponding bases, which is due to the strong electron-acceptor action of the quaternary nitrogen atom (Table 3). A regular increase in the antioxidative activity is also observed in a number of hydroxystyrylpyridine bases (Fig. 3), which is associated with a change in the polar effect of the pyridine ring as a function of substituent R'', which determines the degree of planarity of the benzene and pyridine rings.

The antitumorigenic action of three of the compounds obtained was studied in experiments on animals with interwoven tumors. The hydroxystyrylpyridines have comparatively low toxicity when they are introduced as a 2% solution in 10% Tween-80: $LD_{50}$ is 150 mg/kg for hydrochloride IIc, 310 mg/kg for hydrochloride Ia, and above 1000 mg/kg for base Ig. The tested compounds display some activity on ascitic ARÉ-G, S-180, and NKLy tumors, retarding the growth of the tumor process by 30-80%. The greatest activity is displayed by the 3-methyl-5-cyclohexyl-4-hydroxystyrylpyridine hydrochloride, which also retards the growth of interwoven La leucosis by a factor of 1.7. The kinetic curves of the increase in the weight of spleen during the growth of the leucosis in control experiments and when Ia was introduced in a 100-mg/kg dose are presented in Fig. 4.

## EXPERIMENTAL

4-(3,5-Di-tert-butyl-4-hydroxystyryl)pyridine. A solution of 1.17 g (5 mmole) of 3,5-di-tert-butyl-4-hydroxybenzaldehyde in 3 ml of freshly distilled absolute pyridine was added with cooling to an acyl salt* obtained from 0.5 ml (5 mmole) of γ-picoline and 0.6 ml (5 mmole) of benzoyl chloride. The reaction mass was held at 125-135° for 5 h and cooled. The mixture was then treated first with 10% and then with concentrated hydrochloric acid, and the unchanged material was removed by steam distillation. The acidic aqueous solution was decanted and cooled, and $NH_4OH$ was added to it slowly in portions. A light-colored precipitate formed at pH ~7. It was removed by filtration, washed with water, and dried to give 23.5% of a colorless crystalline substance with mp 243-245° (first from heptane, and then from alcohol). The product gave a picrate. The hydrochlorides of the hydroxystyrylpyridines were obtained by refluxing the reaction mixture with concentrated sulfuric acid, decantation, and cooling of the acid solution. (The operation was repeated many times.) The precipitates were removed by filtration and dried.

The authors thank L. S. Vasil'eva, R. F. D'yachkovskaya, and N. A. Zakharova for their assistance in this research.

## LITERATURE CITED

1. N. M. Émanuél' and Yu. N. Lyaskovskaya, Inhibition of Oxidation Processes in Fats [in Russian], Pishchepromizdat, Moscow (1961).
2. N. M. Émanuél' in: Routes to the Synthesis and Investigation of Antitumorigenic Preparations [in Russian], Meditsina, Moscow (1967), p. 5.
3. N. P. Konovalova, G. N. Bogdanov, L. S. Vasil'eva, L. M. Dronova, A. A. Matveeva, and N. M. Émanuél', Dokl. Akad. Nauk SSSR, 168, 1419 (1966).
4. A. N. Kost and A. K. Sheinkman, Zh. Obshch. Khim., 33, 2077 (1963).
5. A. N. Kost, A. K. Sheinkman, and A. N. Rozenberg, Zh. Obshch. Khim., 33, 4046 (1964).
6. O. N. Karpukhin, V. Ya. Shlyapintokh, and N. V. Zolotova, Izv. Akad. Nauk SSSR, Ser. Khim., 1718 (1963).

* Because of the ready hydrolyzability of the N-acyl salts of pyridine derivatives in air, the condensation with 3,5-dialkyl-4-hydroxybenzaldehydes was carried out without isolation of the salts.