[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF LOUISVILLE]

Styryl Derivatives of 8-Quinolinol

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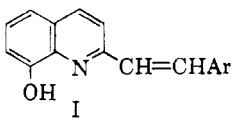
Ultraviolet and infrared spectra of 15 styryl derivatives of 8-quinolinol indicate that these compounds belong to the *trans* series.

Condensations of aromatic aldehydes with 8-hydroxyquinaldine or 8-hydroxylepidine in acetic anhydride yield respectively 2 or 4 substituted styryl-8-hydroxyquinolines (I and II). Fifteen new compounds of this type with hydroxyl and methoxyl substituents have been prepared (Table I) to examine for chelating properties toward metals and to use as intermediates for the preparation of formaldehyde resins containing chelating centers.



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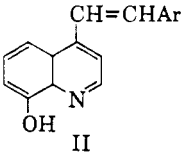


II

in cold ethanol or water containing hydrochloric acid. The solubility of 2-*p*-hydroxystyryl-8-hydroxyquinoline hydrochloride in 5% aqueous hydrochloric acid, for example, is less than 0.1 g. per liter.

The question of whether these compounds are *cis* or *trans* isomers is of interest in determining whether hydroxyl groups located in the styryl part of the molecule could participate in chelation. This could happen only in the *cis* isomers, but these would have somewhat crowded structures and are therefore not as likely to be stable as the *trans* compounds. Infrared spectra of all the hydrochlorides as well as several of the free bases prepared from them show the 10.38 μ band associated with

TABLE I

2-STYRYL-8-HYDROXYQUINOLINE HYDROCHLORIDES

No	Ar in Formula I	Formula	M.P., °C.	Yield, %	Nitrogen	
					Calcd.	Found
1	2,5-(OH)(Cl)C_6H_3	$C_{17}H_{12}ClNO_2\cdot HCl$	198	67	4.19	4.32
2	2,5-(OH)(Br)C_6H_3	$C_{17}H_{12}BrNO_2$[a]	200	62	4.09	4.15
3	2-$MeOC_6H_4$	$C_{18}H_{15}NO_2\cdot BCl$	177–180	—	4.47	4.26
4	[b]	$C_{17}H_{13}NO_2\cdot HCl$	230	25	4.66	4.59
5	4-HOC_6H_4	$C_{17}H_{13}NO_2\cdot HCl$	235	70	4.66	4.31
6	[c]	$C_{18}H_{15}NO_2\cdot HCl$	199	92	4.47	4.43
7	3,4-(MeO)(OH)C_6H_3	$C_{18}H_{15}NO_3$[a]	153	60	4.78	4.97
8	[d]	$C_{18}H_{15}NO_3\cdot HCl$	212	—	4.25	3.80
9	3,4-(EtO)(OH)C_6H_3	$C_{19}H_{17}NO_3\cdot HCl$	212–215	63	4.08	3.90
10	3,4,5-$(MeO)_3C_6H_2$	$C_{20}H_{19}NO_4\cdot HCl$	189	35	[e]	
11	3,5,4-$(MeO)_2$(OH)C_6H_2	$C_{19}H_{17}NO_4$[a]	200–203	55	4.33	4.42
12	2,4-$(MeO)_2C_6H_3$	$C_{19}H_{17}NO_3\cdot HCl$	172–175	60	4.07	3.82
13	2,5-$(MeO)_2C_6H_3$	$C_{19}H_{17}NO_3\cdot HCl$	172	35	4.07	4.13
14	1-Naphthyl	$C_{21}H_{15}NO\cdot HCl$	194	60	4.19	3.98
15	2-HO-1-naphthyl	$C_{21}H_{15}NO_2$[a]	189	90	4.47	4.19

[a] Free base. [b] 4-*o*-Hydroxystyryl-8-hydroxyquinoline hydrochloride. [c] 2-*p*-Hydroxystyryl-8-methoxyquinoline hydrochloride. [d] 4-(3′-Methoxy-4′-hydroxystyryl)-8-hydroxyquinoline hydrochloride. [e] Analyzed for carbon-hydrogen: C, calcd. 64.20; found, 63.90; H, calcd., 5.40; found, 5.83.

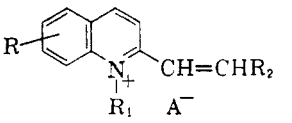
The purification of 2-styryl-8-hydroxquinoline when prepared by this method[1] has been reported to be difficult, perhaps because the reaction is incomplete and some of the aldehyde undergoes the Perkin reaction with acetic anhydride or is air-oxidized to yield acid contaminants. Similar problems in this work were found to be considerably diminished through conversion of the products to the hydrochlorides, intensely fluorescent yellow, orange or red salts with remarkably low solubility

trans RCH:CHR′ structures, especially stilbenes,[2] but not the 10.88 and 12.8 μ. bands expected for the corresponding *cis* isomers. Ultraviolet spectra in acidic ethanol were also determined (Table II). Except for the 4-styryl derivatives and the naphthyl substituted compounds which would be reasonably expected to show the differences observed, these spectra are very similar both to each other and to like compounds previously prepared

(1) H. Irving and A. R. Pinnington, *J. Chem. Soc.*, 3782 (1954).

(2) D. F. DeTar and L. A. Carpino, *J. Am. Chem. Soc.*, **78**, 475 (1956).

TABLE II

ULTRAVIOLET AND VISIBLE SPECTRA IN EtOH-HCl OF 

R	R_1	A	R_2	Wave-length Maxima, mμ (log ε)			
H	H	Cl	3,4-$OCH_2OC_6H_3$	250 (4.10)	272 (4.02)	301 (4.00)	417 (4.47)
H	Me	$MeSO_4$	3,4-$OCH_2OC_6H_3$[a]	246 (4.25)	276 (4.05)	301 (4.04)	425 (4.60)
6-OEt	H	Cl	3,4-$OCH_2OC_6H_3$		272 (3.98)	308 (4.09)	421 (4.46)
6-OEt	Me	$MeSO_4$	3,4-$OCH_2OC_6H_3$[b]		263 (4.21)	302 (4.10)	425 (4.42)
H	H	Cl	3,4-(MeO)(OH)C_6H_3[c]		261 (4.03)	310 (3.94)	430 (4.53)
H	Me	$MeSO_4$	3,4-(MeO)(OH)C_6H_3[d]	251 (4.18)	275[f] (4.03)	310 (4.04)	442 (4.51)
1[e]					267 (4.01)	309 (4.47)	407 (4.43)
2				245[f] (3.96)	—	309 (4.49)	408 (4.44)
3				245[f] (3.89)	268 (3.91)	312 (4.37)	399 (4.46)
4					262 (4.18)		424 (3.93)
5					270 (4.03)	331 (4.00)	415 (4.47)
6					270 (4.21)	328 (4.12)	420 (4.57)
7					280 (4.17)	323 (4.14)	426 (4.58)
8					263 (4.49)		448 (4.32)
9					280 (4.18)	324 (4.15)	430 (4.55)
10					283 (4.56)	327 (4.46)	403 (4.83)
11					283 (4.05)	333 (3.86)	435 (4.41)
12					272 (4.20)	318 (4.00)	427 (4.43)
13					313 (4.41)	364 (4.15)	425 (4.27)
14					286 (4.68)		403 (4.58)
15				230 (4.59)	282 (4.43)	326 (3.96)	445 (4.19)

[a] M.p. 247–250°; ref. 4 gives 261–262° for *cis* isomer, 262–263° for *trans*; principal absorption maxima in MeOH at 348 mμ for *cis* and 423 for *trans*. [b] M.p. 284–286°; ref. 4 gives 281–282° and maxima at 263 and 307 mμ for *cis* isomer; 356 mμ for *trans* isomer. [c] M.p. 222°. [d] M.p. 193–196°. [e] Numbers refer to compounds in Table I. [f] Shoulder.

without the use of acetic anhydride.[3] This implies the same configuration for all, and on the basis of the infrared spectra the structures must be *trans*.

Only two notes concerning *cis-trans* isomerism in the styrylquinolines have been previously published,[4,5] and in both papers configurations were assigned not to the free styrylquinolines but only to quaternary bases obtained from them *via* reaction with dimethyl sulfate or methyl iodide. Reportedly only *cis* structures were obtained by this route, and Horwitz[4] has stated that aldehyde condensations with quinaldine in acetic anhydride appear to require a mechanism similar to that of the Chugaev reaction and thus permit only a *cis* product. However, in the closely related stilbazole series Horwitz[6] could obtain only the *trans* isomers in 10 of 12 examples tried, and in one of the other two trials prolonged refluxing with acetic anhydride produced conversion to the *trans* isomer. Condensation of 1-ethylquinaldinium iodide with vanillin[5] in the presence of acetic anhydride gives only the *trans* isomer. It is therefore rather doubtful that acetic anhydride exerts any special favoritism to the production of *cis* compounds.

Since Horwitz has published only the "principal" absorption maxima of his *cis*-styrylquinolinium methosulfates, direct comparison to our spectra (on the plausible assumption that the hydrochlorides should have spectra essentially similar to the methosulfates except for the relatively minor shifts due to different substituents) proved useless, demonstrating only that our spectra were much different from those of the *cis*-methosulfates.

For a more direct comparison piperonal was condensed with quinaldine and 6-ethoxyquinaldine, yielding the same styrylquinolines previously reported,[4] and the spectra of these in acidic ethanol were determined (Table II). While the piperonal-quinaldine derivative has a spectrum similar to that previously reported for the *trans*-methosulfate prepared by a different route, the 6-ethoxyquinaldine derivative not only shows approximately the same "principal" maxima stated for the *cis*-methosulfate but an additional and unreported strong band at 421 mμ., a longer wave length than any listed for the putative *trans*-methosulfate. By treating the free bases with methyl sulfate according to Horwitz's procedure we obtained methosulfates with spectra quite similar to those of the hydrochlorides, and very substantially in disagreement with Horwitz's data for the *cis* isomers.

Similar repetition of the vanillin-quinaldine condensation[5] also yielded in our hands a hydrochloride and methosulfate having a *trans* rather than *cis* spectrum. The methosulfate formed a phenol betaine by treatment with aqueous alkali, although this has been reported[5] to occur only with the *cis* iodide and not the *trans*. (However, our compound

(3) J. P. Phillips, W. Huber, J. Chung, and L. L. Merritt, *J. Am. Chem. Soc.*, **73**, 630 (1951).
(4) L. Horwitz, *J. Am. Chem. Soc.*, **77**, 1687 (1955).
(5) M. Ito and K. Matsumura, *J. Org. Chem.*, **21**, 1039 (1956).
(6) L. Horwitz, *J. Org. Chem.*, **21**, 1039 (1956).

was a methosulfate, prepared according to Horwitz, and not the methiodide.) This phenol betaine shows the characteristic and very striking color variations with solvent[7]: in acid, yellow; in alcoholic alkali blue; in aqueous alkali, red to purple.

EXPERIMENTAL

Preparation of compounds. The general procedure for synthesis of the 2-styryl-8-hydroxyquinolines is as follows. 8-Hydroxyquinaldine (3.2 g.) is mixed with an equivalent amount of the aromatic aldehyde and 5 ml. acetic anhydride added. The mixture is refluxed 4–6 hr., then poured into water and neutralized with 10% sodium hydroxide solution. The precipitate is filtered, washed with 5% sodium bicarbonate and water, and then heated 1 hr. with 50 ml. 10% sodium hydroxide to hydrolyze the acetate. After neutralization with hydrochloric acid the product is filtered, washed with sodium bicarbonate and water, and recrystallized from ethanol. Since there are usually appreciable impurities at this point, the compound is dissolved in hot ethanol and 3–5 ml. concentrated hydrochloric acid added. A bulky precipitate of the hydrochloride forms quickly and this is recrystallized once or twice from ethanol containing hydrochloric acid.

Compounds 4 and 8 in Table I were similarly prepared from 8-hydroxylepidine, and compound 6 from 8-methoxyquinaldine. An attempt to condense chloral with 8-hydroxyquinaldine produced only extensive decomposition.

All melting points were taken on a Kofler hot stage, and are within a two-degree range of the values in Table I except as noted there. All the hydrochlorides melted with decomposition, and several were observed to sublime from the top of the slide to the cover glass well below the melting point. Melting points for free bases corresponding to some of the hydrochlorides of Table I are as follows: compound 3, 86°; 4, 150°; 5, 215°; 8, 153°; 9, 131°; and 13, 132°. These free bases were obtained by neutralizing the hydrochloride followed by recrystallization from ethanol. No differences in properties of the free bases before and after hydrochloride formation were observed other than minor melting point variations.

The styrylquinolines and methosulfates from quinaldine or 6-ethoxyquinaldine and piperonal were prepared according to the literature.[4] Melting points of the free bases agreed with published values within two degrees. Condensation of quinaldine with vanillin[5] also gave the same free base previously reported; quaternization was performed by Horwitz's method with dimethyl sulfate.

Spectra. All ultraviolet and visible spectra were recorded with a Beckman DK Spectrophotometer in ethanol 0.1*M* in hydrochloric acid, except the methosulfates which were run in ethanol alone. Concentrations ranged from 1 to 4 × $10^{-5}M$.

Infrared spectra were determined by the potassium bromide pellet technique on a Baird AB-2 Spectrophotometer in the range 2–16 μ.

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LOUISVILLE, KY.

(7) S. Hünig and O. Rosenthal, *Ann.*, **592**, 161 (1955).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF CONNECTICUT]

Synthesis of Isoquinoline Alkaloids. I. Lophocerine[1]

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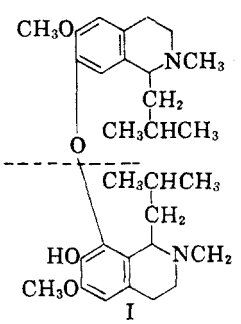
The cactus alkaloid lophocerine (1-isobutyl-2-methyl-6-methoxy-7-hydroxy-12,3,4-tetrahydroisoquinoline) which can be isolated from *Lophocereus Schottii* as its methyl ether has been synthesized.

Three alkaloids have been isolated from the giant cactus *Lophocereus Schottii* by Djerassi and his coworkers. Two of these alkaloids, pilocereine[3–5] and piloceredine[6] (diastereoisomers of I) could be considered *dimeric* since they contain two isoquinoline residues. When the phenolic alkaloidal fraction



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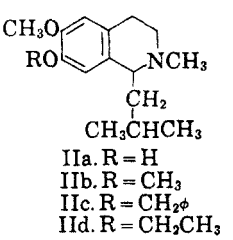

from *L. Schottii* was distilled and methylated, a third compound was isolated and shown to be 1-isobutyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IIb).[6] It was suggested that this methyl ether represented a *monomeric* alkaloid to be called lophocerine. The free phenol group was assigned to the 7-position (structure IIa) by anal-

(1) This investigation was supported in part by Research Grant CY-3905 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(2) Abstracted from the M.S. thesis of Tsu-teh Chou, The University of Connecticut, 1959. Present address: Institute of Materia Medica, Academia Sinica, Shanghai, China.

(3) G. Heyl, *Arch. Pharm.*, **239**, 451 (1901).

(4) C. Djerassi, N. Frick, and L. E. Geller, *J. Am. Chem. Soc.*, **75**, 3632 (1953).

(5) C. Djerassi, S. K. Figdor, J. M. Bobbitt, and F. X. Markley, *J. Am. Chem. Soc.*, **78**, 3861 (1956); **79**, 2203 (1957).

(6) C. Djerassi, T. Nakano, and J. M. Bobbitt, *Tetrahedron*, **2**, 58 (1958).