

[CONTRIBUTION FROM THE CANCER CHEMOTHERAPY LABORATORIES, DEPARTMENT OF PHARMACOLOGY, STANFORD UNIVERSITY]

A New Method for Preparation of Dialkylaminostyryl Derivatives of Pyridine and Quinoline and Their *N*-Oxides¹

ELIZABETH D. PARKER² AND ARTHUR FURST

Received April 10, 1957

Ten new nitrogen heterocyclic dialkylaminostyryl derivatives have been prepared by condensing the appropriate *p*-dialkylaminobenzaldehyde with the active methyl group of picoline, quinaldine, or 2-methylquinoxaline. In five cases the heterocyclic starting material was an *N*-oxide. These condensations, conducted in toluene solution, were catalyzed by piperidinium acetate; neither acidic nor basic catalysts alone were effective. In two of the five *N*-oxide condensations a side reaction occurred resulting in a deoxy product. The ultraviolet spectra of the ten styryl derivatives are recorded, and the infrared spectra of the *N*-oxide derivatives briefly discussed.

Preparation of styrylquinolines from 2- or 4-methylquinolines and aromatic aldehydes, using a number of Lewis acids to effect condensation, has previously been reported.^{3,4} These reactions required relatively long periods of heating at 140–160°, and the yields in most cases were only fair (40–80%).

As would be predicted, quaternization of the heterocyclic compound facilitated condensation. Using piperidine as a catalyst, styryl derivatives of the alkylidides of pyridine and quinoline were prepared^{5,6} in yields exceeding 90% by refluxing the reactants for short times in methanol or isopropyl alcohol.

Neither acid catalysts nor piperidine in alcohol would promote condensation of the *N*-oxides of quinaldine or 2- or 4-picoline with the dialkylaminobenzaldehyde. Only starting materials plus tars were obtained after heating the 2-methyl heterocyclic *N*-oxide for long periods of time with *p*-dimethylaminobenzaldehyde, using zinc chloride, acetic anhydride, or concentrated hydrochloric acid as the condensation catalyst. We were unable to repeat the work of Takahashi and Satake,⁷ who reported the isolation of 2-(*p*-dimethylaminostyryl)quinoline *N*-oxide after heating the reactants in concentrated aqueous hydrochloric acid for 16 hours. Nor could condensation be effected by piperidine in alcohol, after periods much longer than required by the quaternary alkylidide compounds.

However, by using piperidinium acetate as catalyst, we have now prepared 2-(*p*-dimethylaminostyryl)- and 2-(*p*-diethylaminostyryl)quinoline *N*-oxides in fair yields (40–60%) by refluxing

the reactants together in toluene under a Stark-Dean trap. It was found necessary to remove the water formed, since only starting materials were recovered when the reactants were refluxed together in ethanol with piperidinium acetate.

When this piperidinium acetate method was applied to certain picoline *N*-oxide derivatives, unexpected products were obtained, and *N*-oxide styryl derivatives were isolated with difficulty. 2-(*p*-Dimethylaminostyryl)pyridine *N*-oxide was isolated in only 13% yield after the heterocyclic compound and the aldehyde were refluxed under a Stark-Dean trap for two days; if the refluxing was continued two days longer the only product isolated (hereafter called "compound A") corresponded in analysis to C₂₃H₂₇N₃. Compound A was also the only product isolated when 2-picoline replaced the *N*-oxide derivative, or when the picoline compound was completely eliminated. Thus compound A was obtained in 21% yield when a mixture of piperidine and acetic acid was refluxed for two days in toluene with excess *p*-dimethylaminobenzaldehyde. At first it seemed that a reaction between piperidine and acetic acid took place since compound A also corresponded in analysis to C₁₆H₂₀N₂. This possibility was eliminated because compound A was also obtained (in 30% yield, with no other isolated products) when propionic acid was used instead of acetic acid. Hence the acid acted as a co-catalyst and was not incorporated in the product. That formation of compound A cannot be attributed to an impurity in the piperidine⁸ originally used was demonstrated by isolation of compound A in 21% yield, when specially purified piperidine⁸ was used. Similarly, when *p*-diethylaminobenzaldehyde, 2-picoline *N*-oxide, piperidine, and acetic acid were refluxed in toluene for 2.5 days, the only product isolated, hereafter called

(1) The research was supported by Grant No. C2798(C) from the U. S. Public Health Service, National Cancer Institute.

(2) Department of Chemistry, Wayne State University, Detroit 2, Mich.

(3) R. S. Tipson, *J. Am. Chem. Soc.*, **67**, 507 (1945).

(4) H. Gilman, J. L. Towle, and R. K. Ingham, *J. Org. Chem.*, **21**, 595 (1956).

(5) A. P. Phillips, *J. Org. Chem.*, **12**, 333 (1947).

(6) L. Horwitz, *J. Am. Chem. Soc.*, **77**, 1587 (1955).

(7) T. Takahashi and K. Satake, *J. Pharm. Soc. Japan*, **72**, 119 (1952).

(8) The piperidine originally used was Eastman "Practical" grade. It was subsequently separated by careful fractionation through a 2 × 64 cm. column packed with single-turn glass helices into only two fractions: piperidine-water azeotrope (b.p. 92°, 6% by volume), and pure piperidine (b.p. 106°, 92% by volume). There remained only 2% of higher boiling material.

"compound B," (20% yield based on piperidine) corresponded in analysis to $C_{27}H_{35}N_3$. The formula $C_{18}H_{24}N_2$ was also considered, but appeared improbable since (as noted above) the carboxylic acid catalyst used was not incorporated into the product.

When the reaction was stopped after 30 hours and the resulting thick dark sirup was chromatographed over alumina, over 95% of the starting materials was recovered, in addition to a very small proportion of a product not the same as compound B, as apparent from comparison of infrared spectra. This material may have been the desired *N*-oxide styryl derivative, but was never obtained in sufficient quantity for characterization.

The unidentified reaction products A and B were colorless solids, m.p. 135° and 102°, respectively, with very similar ultraviolet spectra. Compound A had λ_{max} 215 m μ , ϵ_{max} 28,000; λ_{max} 258.5 m μ , ϵ_{max} 37,000, and a shoulder at 314 m μ . Compound B had λ_{max} 215.5 m μ , ϵ_{max} 28,000; λ_{max} 266.5 m μ , ϵ_{max} 49,000 and a shoulder at 318 m μ . Compound A on oxidation by chromic acid or permanganate (acid, alkaline, or neutral) gave only polymeric material.

These unidentified reaction products were *not* isolated when 4-picoline *N*-oxide was refluxed with either of the aldehydes mentioned, plus piperidinium acetate in toluene, for periods of time varying between 2.5 and 7 days. In both cases, *mixtures* of two products were obtained: the 4-(*p*-dialkylaminostyryl)pyridine *N*-oxide and the corresponding styryl derivative without the *N*-oxide group. The nature of the reduction leading to formation of the deoxy products is not yet clear, for attempts to isolate *p*-dialkylaminobenzoic acids from the reaction mixtures were not successful. In the case of *p*-dimethylaminobenzaldehyde, the reactants were refluxed together for 4.5 days to give a 12% yield of *N*-oxide styryl derivative and an 18% yield of deoxygenated styryl derivative. Decreases in the yields of both products were noted when the mixtures were refluxed for shorter periods of time. The two styryl derivatives were separable by fractional recrystallization from ethanol. The deoxygenated styryl derivative crystallized first under the conditions used. In the case of *p*-diethylaminobenzaldehyde, a seven-day reflux period afforded a 55% yield of *N*-oxide styryl derivative, along with only 3% of deoxygenated styryl derivative. This mixture was separated by chromatography on alumina. If the reflux period was shortened to 3.5 days, 83% of the starting 4-picoline *N*-oxide was recovered; no styryl derivatives appeared to be present.

Certain other styryl derivatives, not *N*-oxides, were also made by the piperidinium acetate method. These included 2-(*p*-dimethylaminostyryl)quinoxaline, a previously unreported compound, which could not be prepared by any other method

described in the literature.³⁻⁶ Also made were 2-(*p*-dimethylaminostyryl)-8-hydroxyquinoline and 2-(*p*-diethylaminostyryl)pyridine. The analog, 2-(*p*-dimethylaminostyryl)pyridine, could not be made by this procedure owing to the preferential formation of compound A described above; nor was it possible to make this styryl compound using either zinc chloride or acetic anhydride as the condensing agent.

Table I summarizes our data on the preparation of the styryl derivatives. The piperidinium acetate method described here gives yields which at best are only fair. The optimum reflux times are seen to vary greatly with the identity of the reactants. Nevertheless, the method deserves consideration in condensation reactions where neither acidic catalysts nor basic catalysts alone promote the reaction.

Table I also lists the ultraviolet spectra of the new styryl derivatives. The previously reported bathochromic effect of quaternization of heterocyclic nitrogen⁵ was also observed here, though to a much smaller degree, in the *N*-oxide styryl derivatives. This was to be expected on the basis of greater stabilization of ionic, excited state forms by the ability of the *N*-oxide oxygen atom to bear the negative charge.

Both 2-(*p*-diethylaminostyryl)pyridine tertiary base and 2-(*p*-dimethylaminostyryl)pyridine *N*-oxide absorbed at shorter wave lengths than did the corresponding 4-styryl derivatives. This may be attributable to some small steric hindrance to coplanarity in the excited state of the 2-styryl derivatives.

Bands between 7.3 m μ and 8.2 m μ in the infrared spectra of quinoline *N*-oxide and certain 4-substituted quinoline *N*-oxides have previously been attributed to N—O stretching.⁹ 4-(*p*-Dimethylaminostyryl)pyridine *N*-oxide and the corresponding diethyl analog had strong bands at 7.97 μ and 8.00 μ , respectively, which the corresponding deoxygenated products did not show. 2-(*p*-Dimethylaminostyryl)pyridine *N*-oxide had a strong band at 8.14 μ , and its diethyl analog had a strong band at 8.10 μ . 2-(*p*-Diethylaminostyryl)pyridine did not absorb in this region. 2-(*p*-Dimethylaminostyryl)quinoline *N*-oxide had a band at 7.76 μ not shown by its deoxy analog.

EXPERIMENTAL

General procedure for preparation of p-dialkylaminostyryl derivatives of heterocyclic free bases or N-oxides. To a solution of 0.020 mole of the active methyl heterocyclic base (or its *N*-oxide) and 0.027 mole of dialkylaminobenzaldehyde in 35 ml. of dry toluene was added one ml. of piperidine and about 0.8 ml. of glacial acetic acid. The mixture was refluxed under a Stark-Dean trap until no more water was collected, or for the optimum number of hours. The toluene

(9) G. Costa, P. Blasina and G. Sartori, *Univ. Studi Trieste, Fac. sci. Ist. chim.* No. 9, 11 (1955); *Chem. Abstr.*, **50**, 1182e (1956).

TABLE I
 STYRYL DERIVATIVES PREPARED BY PIPERIDINIUM ACETATE-CATALYZED CONDENSATIONS

Compound ^a	Reflux Time, Hr.	Yield, %	M.P. ^b	Anal. ^c			Ultraviolet Spectral Data ^d		
				C	H	N	λ_{\max}	ϵ_{\max}	
2-(<i>p</i> -Dimethylaminostyryl)-pyridine <i>N</i> -oxide	47	13	200–201.5°	Calcd.	74.97	6.71	11.66	253	20,000
				Found	75.50	6.98	11.82	282	11,000
quinoline <i>N</i> -oxide	17	60	213–214°	Calcd.	78.59	6.25	9.65	230.5 ^e	35,000
				Found	78.64	6.13	9.7	264.5	38,000
quinoxaline	116	32	166.1–166.9°	Calcd.	78.51	6.22	15.26	224.5	22,000
				Found	78.16	6.34	15.1	261.5	17,000
8-hydroxyquinoline ^f	6	62	164.3–165.1°	Calcd.	78.59	6.25	9.65	217	19,000
				Found	78.18	6.17	9.61	266	25,000
pyridine	69	12	142.8–143.6°	Calcd.	80.91	7.99	11.10	255	>40,000
				Found	81.12	8.17	10.76	377	9,800
quinoline <i>N</i> -oxide	22	42	178.7–179.6°	Calcd.	79.21	6.96	8.80	234	21,000
				Found	79.05	6.74	8.54	269	27,000
4-(<i>p</i> -Dimethylaminostyryl)-pyridine ^g	108	18	239.4–240°	Calcd.	80.32	7.03	12.65	253	16,000
				Found	80.14	7.20	12.56	377	28,000
pyridine <i>N</i> -oxide	108	12	238–239°	Calcd.	74.97	6.71	11.66	221	14,000
				Found	75.00	6.80	11.58	279.5	12,000
4-(<i>p</i> -Diethylaminostyryl)-pyridine	168	3	188–188.6°	Calcd.	80.91	7.99	11.10	255.5	13,000
				Found	80.76	7.87	10.89	387	36,000
pyridine <i>N</i> -oxide	168	55	195–196.5°				10.44	223	15,000
							10.06	281	21,000
							299	15,000	
							416	38,000	

^a All compounds have infrared bands in the 10.2–10.6 μ region and are unchanged on exposure to ultraviolet or visible light. On this basis they may tentatively be assigned the *trans* configuration. ^b Melting points were taken using an electrically heated block with Anschuetz thermometers. ^c Analyses were performed by Drs. Weiler and Strauss, Oxford, England, and Microchemical Specialties Co., Berkeley, Calif. ^d Spectra were determined on a Beckman Model DK-2 ratio-recording spectrophotometer. ^e 2-(*p*-Dimethylaminostyryl)quinoline³ had λ_{\max} 219.5, 253.5, 293, 392; ϵ_{\max} 28,000, 23,000, 13,000, 34,000. ^f Prepared by the method of Tipson³ using acetic anhydride. ^g Also prepared in 12% yield by the method of Tipson³ using acetic anhydride.

was then removed by distillation, about the last 10 ml. under reduced pressure. The dark sirupy residues were cooled to induce crystallization and the crude solids washed with ether to remove the adherent dark oils. The crude solids were purified by recrystallization from 95% ethanol or benzene. In only two cases was more than a single product obtained.

Separation of N-oxide products from deoxy products. The mixture of 4-(*p*-dimethylaminostyryl)pyridine *N*-oxide and 4-(*p*-dimethylaminostyryl)pyridine obtained from reaction of 4-picoline *N*-oxide and *p*-dimethylaminobenzaldehyde was separated by fractional recrystallization from 95% ethanol.

The mixture of 4-(*p*-diethylaminostyryl)pyridine was separated on a 2 × 25 cm. column packed with *Alco F 20* mesh alumina. One gram of the mixture (dissolved in benzene) was put on the column. Unreacted aldehyde was eluted by benzene, then the deoxygenated styryl derivative by benzene-ether mixtures and finally ether, and last the *N*-oxide styryl derivative by ether-methanol mixtures. The two products were then each purified by recrystallization from acetone.

STANFORD, CALIF.