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Ozonolysis of Styryl Derivatives of Nitrogen Heterocycles

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Ozonolysis of substances containing an ethylenic double bond is a common method for the preparation of aldehydes, ketones and carboxylic acids. Very little has been reported concerning the treatment of nitrogen heterocycles containing an unsaturated side chain with ozone. α-Stilbazole[2,3] has been ozonized both in carbon tetrachloride and in concentrated hydrochloric acid to produce α-pyridylaldehyde and picolinic acid. It was reported that an ozonide precipitated when carbon tetrachloride was used as the solvent. Ozonization of benzoylmetanicotine[2] in hydrochloric acid gave a 15% yield of β-pyridylaldehyde. Indigo has been ozonized by van Alphen[4] but the yield of isatin is not given. Schenck and Bailey[5] obtained 2-methylbutanoic acid by ozonolysis of both 2,4-dimethyl-8-*s*-butyl- and 2,4-dimethyl-6-*s*-butylquinoline while ozonolysis of 2,3,4-trimethyl-8-*n*-propylquinoline gave *n*-butyric acid.

The present paper reports on the ozonolysis of a number of styryl and 3′-nitrostyryl derivatives of pyridine and quinoline. These substances were prepared by condensation of benzaldehyde and *m*-nitrobenzaldehyde, respectively, with α- and γ-picoline, lepidine, quinaldine, and 2,4-dimethylquinoline using three different procedures. 2-Styryllepidine was prepared by heating 2,4-dimethylquinoline with benzaldehyde in the presence of a drop of aqueous alkali. A procedure based on that of Shaw and Wagstaff[6] in which the substance was heated with acetic anhydride and benzaldehyde gave the best results with quinaldine and α- and γ-picoline while anhydrous zinc chloride proved to be the best condensing agent for the preparation of 4-styrylquinoline. Acetic anhydride was used as the condensing agent for the preparation of the 3′-nitrostyryl derivatives.

Ozonolysis studies of these styryl derivatives gave the surprising result that only the carboxylic acids were produced. All attempts to obtain the aldehydes were unsuccessful. Carboxylic acids were obtained in yields of 58–95% (see Table I). Even when the solution of the ozonized styryl derivative was cleaved reductively, the acid was obtained. The use of 90% formic acid as recommended by Dorland and Hibbert[7] also failed to produce the aldehyde.

Ozonolysis of a solution or a suspension of the styryl derivatives could be carried out most successfully either in glacial or 95% acetic acid solution. Except in the case of the α-stilbazole, a finely divided crystalline precipitate separated near the end of the ozonization period; this was shown to be the carboxylic acid instead of the ozonide. The same behavior was noted when anhydrous acetic acid was used. The 3′-nitrostyryl derivatives were only slightly soluble in glacial acetic acid but even a suspension in 95% acetic acid could be ozonized successfully. The unsubstituted styryl derivative gave a higher yield of the carboxylic acid than was obtained from the 3′-nitrostyryl derivative. Ozonolysis of the 3′-nitrostyryl derivatives did not go to completion even when a four molar excess of ozone was used.

Experimental[8]

4-Styrylquinoline.—A mixture of 68.5 g. (0.48 mole) of lepidine, 90 g. (0.85 mole) of benzaldehyde and 8 g. of freshly fused zinc chloride was heated at 160° for eighteen hours in a 250-ml. round-bottomed flask fitted with an air condenser. The hot solution was poured into 100 ml. of warm 20% sodium hydroxide solution, cooled, then the supernatant oil separated and dissolved in 125 ml. of concentrated hydrochloric acid. The acid solution was diluted with 400 ml. of water, the yellow solid removed by filtration and mixed in 100 ml. of water, the suspension made alkaline with sodium hydroxide solution and collected on a Büchner funnel. The substance was dried and recrystallized from a benzene–ligroin mixture. One recrystallization gave a yield of 60 g. (56.5%) of light yellow solid which melted at 91.5–92°.

The melting point checks that reported by Doebner and Miller[9] who prepared the compound by heating benzaldehyde and lepidine in a sealed tube at 180°, using anhydrous zinc chloride as the catalyst.

2-Styryllepidine.—One drop of 10% aqueous alkali was added to a solution of 31.4 g. (0.2 mole) of 2,4-dimethylquinoline in 23.3 g. (0.22 mole) of benzaldehyde contained in a 200-ml. round-bottomed flask fitted with an air condenser and the mixture heated in an oil-bath at 130–135° for thirty hours. The dark-colored viscous oil was shaken with 150 ml. of water containing 4 ml. of concentrated hydrochloric acid, the precipitated solid removed by filtration and washed with successive 50-ml. portions of water, dilute sodium bicarbonate solution and water. The crude 2-styryllepidine (41 g.) was crystallized from 120 ml. of 75–80% ethyl alcohol. A yield of 33.5 g. (74%) of light yellow solid (m. p. 121–122°) was obtained. Further recrystallization either from dilute alcohol or a benzene–ligroin solution did not change the melting point which agrees satisfactorily with that reported by Spallino and Cucchiaroni,[10] who prepared the substance by heating 2,4-dimethylquinoline and benzaldehyde without a catalyst. In a trial using this method, the yield was only 48%.

2-Styrylquinoline.—A solution of 42 g. (0.29 mole) of quinaldine, 35 g. (0.33 mole) of benzaldehyde and 20 g. (0.15 mole) of acetic anhydride was heated at 160° for

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[1] Abstracted from a portion of the thesis submitted by R. Dale Stayner in partial fulfillment of the requirements for the M.A. degree.

[2] Harries and Lenart, *Ann.*, **410**, 95 (1915).

[3] Lenart, *Ber.*, **47**, 808 (1914).

[4] van Alphen, *Rec. trav. chim.*, **57**, 911 (1938).

[5] Schenck and Bailey, THIS JOURNAL, **62**, 1967 (1940).

[6] Shaw and Wagstaff, *J. Chem. Soc.*, 77 (1933).

[7] Dorland and Hibbert, *Can. J. Research*, **18B**, 30 (1940).

[8] All melting points are corrected.

[9] Doebner and Miller, *Ber.*, **18**, 1640 (1885).

[10] Spallino and Cucchiaroni, *Gazz. chim. ital.*, **42**, 517 (1912); *C. A.*, **6**, 2419 (1912).

sixteen hours in a 200-ml. round-bottomed flask fitted with a reflux condenser. The hot solution was poured into 200 ml. of 10% sodium hydroxide solution. After the oil congealed, the solid was removed by filtration, washed with water, then with 30 ml. of ice cold ethyl alcohol and dried at 60°. The yield of crude 2-styrylquinoline was 43 g. (m. p. 96–98°). Recrystallization from a mixture of benzene (80 ml.) and ligroin (100 ml.) gave 36.4 g. (56.8%) of a product which melted at 98–98.5°. This melting point agrees satisfactorily with that reported by Wallach and Wunsten[11] who prepared the substance by condensing quinaldine and benzaldehyde in the presence of anhydrous zinc chloride.

α- and γ-Stilbazole.—These substances were prepared from α- and γ-picoline, respectively, using acetic anhydride as the condensing agent as described above. The yield of α-stilbazole was 28%[12,13] and it melted at 90°. The γ-stilbazole (56% yield) melted at 127–128°. These values correspond to the recorded melting points.[14,15]

2-(3′-Nitrostyryl)-quinoline.—Using the procedure of Shaw and Wagstaff,[6] a mixture of 14.5 g. (0.1 mole) of quinaldine, 15 g. (0.1 mole) of *m*-nitrobenzaldehyde and 8 g. (0.06 mole) of acetic anhydride was heated under reflux in an oil-bath at 160° for four hours. The warm solution was poured into 100 ml. of 20% sodium hydroxide solution. After the oil congealed the solid was pulverized, removed by filtration and washed with water, then dried. When crystallized from a mixture of benzene (100 ml.) and ligroin (100 ml.), a yield of 21.3 g. (80%) of light yellow needles melting at 154.5–155° was obtained. The melting point recorded by Wallach and Wunsten[11] is 154–155°.

The same method was used for the preparation of 4-(3′-nitrostyryl)-quinoline[16] (52%, m. p. 130.5–131.5°), 3′-nitro-α-stilbazole[17] (65%, m. p. 127–128°), and 3′-nitro-γ-stilbazole[18] (60%, m. p. 141–142°).

Ozonolysis Experiments.—As an example the ozonolysis of 2-styrylquinoline may be cited. Ozonized oxygen was bubbled into a solution of 11 g. (0.05 mole) of 2-styrylquinoline in 75 ml. of glacial acetic acid while the reaction flask was cooled. When most of the yellow color was gone, quinaldic acid started to precipitate. At this time about 0.1 mole of ozone had been used. The solution and precipitate was transferred to a 250-ml. round-bottomed flask, 25 ml. of 3% hydrogen peroxide added and the solution refluxed for five minutes. Most of the solvent was removed by vacuum distillation, the residue diluted with 200 ml. of ether and the mixture placed in a refrigerator overnight. The quinaldic acid was removed by filtration, washed with 50 ml. of ether and allowed to dry. The yield was 8 g. (92%) and it melted at 155.5–156.5°. Doebner and Miller[19] recorded a melting point of 156° for this compound.

The other product of the reaction, benzoic acid, may be isolated by extraction of the ether filtrate with sodium carbonate solution and precipitation of the benzoic acid by the addition of dilute hydrochloric acid.

Ozonolysis of the 3′-nitrostyryl derivative proceeded in a similar way. A suspension of 13.3 g. (0.05 mole) of 2-(3′-nitrostyryl)-quinoline in 75 ml. of 95% acetic acid was treated with 0.15 mole of ozone, the mixture refluxed for five minutes with 25 ml. of 3% hydrogen peroxide, cooled, and diluted with 200 ml. of ether. After remaining in the refrigerator overnight, a yield of 5.1 g. (59%) of quinaldic acid melting at 155.5–156.5° was obtained. A product of lower melting point was obtained if the acetic acid was removed by vacuum distillation and the residue diluted with ether.

The other styryl derivatives were ozonized in the same manner as described above. 4-Methylquinaldic acid was characterized as the ethyl ester but the other acids were identified as the amides. The results are summarized in Table I. In each case, 0.05 mole of the styryl derivative was used.

TABLE I

Starting material	Acid obtained	M. p., °C.	Yield, %	Amide, m. p., °C.
2-Styrylquinoline	Quinaldic	155.5–156.5	92	131.5–132[a]
2-(3′-Nitrostyryl)-quinoline			59	
α-Stilbazole	Picolinic[b]	136–136.5	85	106–107[c]
3′-Nitro-α-stilbazole			75	
γ-Stilbazole	Isonicotinic[d]	310	95	155–156[e]
3′-Nitro-γ-stilbazole			82	
4-Styrylquinoline	Cinchoninic[f]	248	82	179.5–180[g]
4-(3′-Nitrostyryl)-quinoline			66	
2-Styryllepidine	4-Methylquinaldic[h]	163–165	84	(i)

[a] Reistert, *Ber.*, **38**, 1612 (1905). [b] Weidel, *ibid.*, **12**, 1992 (1879). [c] Engler, *ibid.*, **27**, 1786 (1894). [d] Behrmann and Hoffmann, *ibid.*, **17**, 2698 (1884). [e] Ternajgo, *Monatsh.*, **21**, 459 (1900); *Chem. Zentr.*, **71**, II, 482 (1900). [f] Skraup, *Ann.*, **201**, 301 (1880). [g] Wenzel, *Monatsh.*, **15**, 456 (1894); *Chem. Zentr.*, **65**, II, 757 (1894). [h] Koenigs and Mengel, *Ber.*, **37**, 1327 (1904). [i] The ester was prepared by refluxing a solution of 4-methylquinaldic acid in absolute ethyl alcohol containing sulfuric acid. Melting point of the ethyl ester, 98.5–99°; saponification equivalent: calcd. 183; found 185.

An attempt was made to prepare the aldehydes by ozonolysis. The ozonized mixture in glacial acetic acid was treated with zinc dust and about 1 ml. of water, dropwise, but no aldehyde could be isolated. Neither could any aldehyde be isolated when ozonolysis was carried out in anhydrous ethyl acetate or anhydrous ethyl bromide. Ozonolysis was tried also using anhydrous, 99%, and 95% formic acid as the solvent but no aldehyde could be obtained. An 82% yield of isonicotinic acid was obtained by ozonolysis of γ-stilbazole in anhydrous formic acid. When γ-stilbazole was ozonized in anhydrous ethyl acetate and the solution treated with formic acid, an 85% yield of isonicotinic acid was obtained.

Summary

1. Satisfactory methods of synthesis have been described for α- and γ-stilbazole, α- and γ-3′-nitrostilbazole, 2- and 4-styrylquinoline, 2- and 4-(3′-nitrostyryl)-quinoline, and 2-styryllepidine.

2. Ozonolysis of the styryl derivatives to carboxylic acids occurred in good yields.

3. The aldehydes could not be obtained by ozonolysis.

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[11] Wallach and Wunsten, *Ber.*, **16**, 2007 (1883).

[12] Shaw and Wagstaff (ref. 6) reported an 87% yield.

[13] Chiang and Hartung, *J. Org. Chem.*, **10**, 21 (1945), have reported a 57.5% yield by refluxing a mixture of benzaldehyde and α-picoline with concentrated hydrochloric acid.

[14] Baurath, *Ber.*, **20**, 2719 (1887).

[15] Friedlander, *ibid.*, **38**, 159 (1905).

[16] Heymann and Koenigs, *ibid.*, **21**, 1427 (1888).

[17] Feist, *ibid.*, **34**, 465 (1901).

[18] Friedlander, *ibid.*, **38**, 2837 (1905).

[19] Doebner and Miller, *ibid.*, **16**, 2472 (1883).