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

Alstonia Alkaloids. VI. The Structure of Alstoniline Oxide

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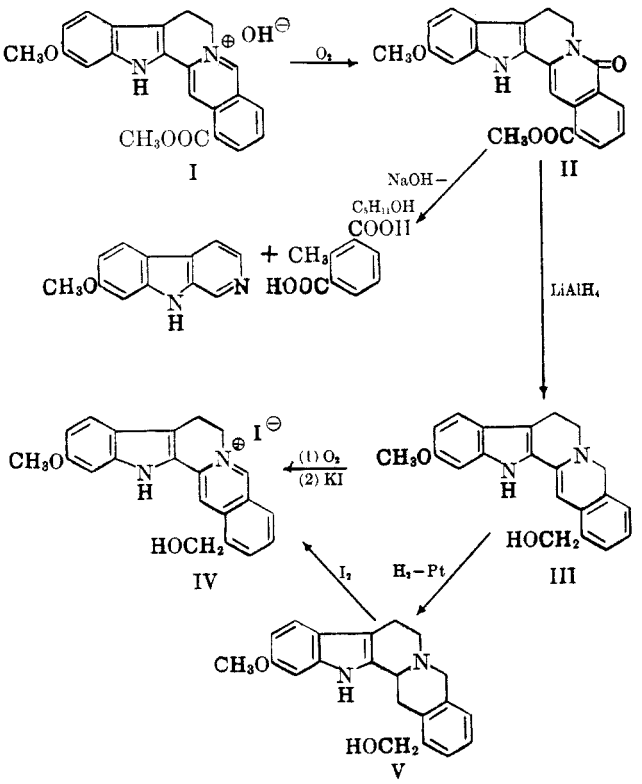
Received November 15, 1955

The structure of alstoniline oxide has been demonstrated, and the position previously assigned to the methoxyl group in alstoniline has been confirmed.

Alstoniline is a brick red alkaloid isolated from the tree bark of *Alstonia constricta*, F. Muell;[2] the structure of the substance was shown in all probability to be represented by I by Elderfield and Wythe.[3] In the course of a study of the reactions of the alkaloid Elderfield and Hawkins[2] noted its extreme susceptibility to atmospheric oxidation with the formation of a substance designated as alstoniline oxide in which one atom of oxygen had been acquired. Formation of the so-called oxide occurred when solutions of the free base in alcohol were aerated or, even more striking, when solutions of the free base of tetrahydroalstoniline were exposed to the air during the process of working up reaction mixtures from catalytic reductions. In contrast, the products of the catalytic reduction of salts of alstoniline were apparently stable to atmospheric oxidation. It was subsequently shown[3] that the oxidation of tetrahydroalstoniline to alstoniline oxide is strongly catalyzed by traces of reduced platinum and that the tetrahydro derivative is stable to oxidation in the absence of platinum. Structure II has been suggested for alstoniline oxide without experimental evidence.[3]



We now wish to present data which substantiate structure II for alstoniline oxide and at the same time provide confirmatory evidence for location of the methoxyl group in alstoniline at position 11.

Alstoniline oxide is soluble in neither dilute acid nor dilute base, hence the basic character of the parent alkaloid has been destroyed during formation of the oxide. It contains no unsaturation which responds to reduction over platinum. Its ultraviolet spectrum[2] (max., 3850 mμ, log ϵ 4.68; shoulder, 2600 mμ, log ϵ 4.15; min., 3000 mμ, log ϵ 3.8) approximates that of alstoniline hydrochloride (max., 3800 mμ, log ϵ 4.4; shoulder, 2800 mμ, log ϵ 3.88; min., 3060 mμ, log ϵ 3.68) and ketoyobyrine (max., 3850 mμ, log ϵ 4.52; 3660 mμ, log ϵ 4.51; 3400 mμ, log ϵ 4.4; shoulder, 2850 mμ, log ϵ 3.88; min., 2900 mμ, log ϵ 3.8). In the carbonyl region of the infrared spectrum alstoniline hydrochloride shows a peak at 5.88 μ, alstoniline oxide at 5.84 μ and 6.10 μ, and ketoyobyrine at 6.13 μ.[4]

On reduction of alstoniline oxide with lithium aluminum hydride the yellow color is discharged and a colorless product (III) is formed which shows an intense blue fluorescence. The latter compound is again extremely susceptible to air oxidation to an orange product which was isolated as the iodide and shown to be identical with alstonilinol iodide (IV) prepared by oxidation of tetrahydroalstonilinol (V) with iodine. Further, the product of reduction of alstoniline oxide by lithium aluminum hydride absorbed one mole of catalytically activated hydrogen to give tetrahydroalstonilinol. These transformations are clearly consistent with formulation of alstoniline oxide as II and may be represented by formulas III–V.

Alstoniline oxide is thus an analog of ketoyobyrine and as such may be expected to undergo cleavage in the manner of ketoyobyrine on vigorous

(1) Eli Lilly and Co. Fellow.

(2) Elderfield and Hawkins, *J. Org. Chem.*, 7, 573 (1942).

(3) Elderfield and Wythe, *J. Org. Chem.*, 19, 683 (1954).

(4) We wish to thank Dr. Percy Julian of The Julian Laboratories, Inc., Franklin Park, Ill., for a generous sample of ketoyobyrine and Dr. B. Witkop of the National Institutes of Health, Bethesda, Md., for a copy of the infrared spectrum of ketoyobyrine.

treatment with alkali.[5] This was shown to be so. On refluxing alstoniline oxide with a solution of sodium hydroxide in amyl alcohol, norharmine and 2-methylisophthalic acid were formed. In addition to providing confirmatory evidence for the structure assigned to alstoniline oxide, the isolation of norharmine furnishes convincing proof for the position of the methoxyl group in alstoniline itself. This had been previously assigned on the basis of spectrographic evidence.[3]

EXPERIMENTAL[6,7]

Alstoniline oxide. This substance is best prepared by platinum-catalyzed oxidation of tetrahydroalstoniline as indicated without experimental details by Elderfield and Hawkins.[2] A solution of alstoniline, prepared from 1.0 g. of the sulfate, in 200 ml. of methanol was shaken with Adams' platinum oxide catalyst under hydrogen at atmospheric pressure. Two equivalents of hydrogen were taken up in 30 min. during which the color of the solution changed from orange to light yellow green. The methanol solution was allowed to stand over the platinum in the presence of air for 3 days, filtered from the catalyst, and taken to dryness under reduced pressure. The light red residue was taken up in benzene and passed over a column of Merck alumina for chromatography. On elution with 1 per cent ethanol-benzene alstoniline oxide moved down the column as a bright yellow band. The substance crystallized as clusters of yellow needles, m.p. 125–130°, from absolute ethanol. The yield was 200 mg. After removal of solvent of crystallization by drying over phosphorus pentoxide at 100° and 0.05 mm. the monohydrate, m.p. 212–213°, remained.

Anal. Calc'd for $C_{22}H_{18}N_2O_4 \cdot H_2O$: C, 67.4; H, 5.2; N, 7.1. Found: C, 67.8; H, 5.1; N, 7.1.

Alstonilinol iodide. A solution of 0.2 g. of tetrahydroalstonilinol[3] in 20 ml. of ethanol was added to a warm solution of 2 g. of potassium acetate in 1 g. of iodine in 20 ml. of ethanol. On warming on the steam-bath for 5 min. a copious orange precipitate separated. After cooling, the solid was collected and a slow stream of sulfur dioxide was passed through a suspension of it in 100 ml. of hot water for 10 min. After recrystallization from ethanol the substance formed fine red needles, m.p. 327° (dec.). The yield was 0.25 g. (92%).

Anal. Calc'd for $C_{21}H_{19}IN_2O_2$: C, 55.0; H, 4.2; N, 6.1. Found: C, 55.4; H, 4.4; N, 6.0.

Reduction of alstoniline oxide with lithium aluminum hydride. A suspension of 0.2 g. of alstoniline oxide in 100 ml. of dry ether was refluxed with stirring with 0.5 g. of lithium aluminum hydride for 2 hr. during which the color changed from yellow to yellow-green. Ethyl acetate was added to destroy excess hydride followed by 10 ml. of 2% hydrochloric acid. Removal of the ether under reduced pressure left a white precipitate which was collected and divided into two equal parts.

One half was shaken with Adams' platinum oxide catalyst under hydrogen at atmospheric pressure in 50 ml. of methanol and 4.8 ml. of hydrogen was absorbed. The color changed from a fluorescent green to a light yellow-green. The filtrate from the catalyst was concentrated under nitrogen to 10 ml. and dry hydrogen chloride was passed through the solution whereupon 60 mg. of fine white needles separated, m.p. 278–280° (dec.). The substance was shown to be tetrahydroalstonilinol hydrochloride by mixture m.p., and identity of the ultraviolet and infrared spectra with those of an authentic sample.

Anal. Calc'd for $C_{21}H_{22}N_2O_2 \cdot HCl$: C, 68.0; H, 6.3; N, 7.5. Found: C, 68.3; H, 6.7; N, 7.4.

The other half of the product was dissolved in 95% ethanol and added to the original mother liquor. After standing exposed to the air for 2 days about 80 mg. of fine red needles crystallized. These were converted to the iodide by solution in 30 ml. of hot water containing 1 g. of potassium iodide. On slow cooling fine red needles separated, m.p. 327° (dec.), after recrystallization from absolute ethanol. Identity of this substance with alstonilinol iodide was shown by mixture m.p. and ultraviolet and infrared spectra.

Cleavage of alstoniline oxide with sodium hydroxide. Alstoniline oxide (0.25 g.) was refluxed with 2 g. of sodium hydroxide in 4 ml. of *n*-amyl alcohol for 40 hrs. The yellow color of the oxide disappeared after 24 hrs. The red solution was poured into 25 ml. of water and extracted with four 25-ml. portions of ether. After drying over sodium sulfate, removal of the ether from the combined extracts left a brown residue which was sublimed at 150° and 0.05 mm. The sublimate was recrystallized twice from benzene and melted at 212–214°. The yield was 20 mg.

Anal. Calc'd for $C_{12}H_{10}N_2O$: C, 72.7; H, 5.1; N, 14.1. Found: C, 72.3; H, 5.1; N, 14.4.

Mixture m.p.'s of this material with authentic norharmine, m.p. 215–216°, prepared according to Perkin, Jr. and Robinson[8,9] were not depressed. The ultraviolet spectra of norharmine obtained by degradation of alstoniline oxide and its methiodide were substantially identical with those of harmine and its methiodide.[10]

A *picrate*, m.p. 205° (dec.) was prepared from norharmine from both sources.

Anal. Calc'd for $C_{18}H_{13}NO_8S$: C, 50.6; H, 3.1; N, 16.4. Found: C, 50.5; H, 3.3; N, 16.4.

The aqueous basic solution from the above ether extraction was acidified with hydrochloric acid and the amorphous white precipitate was filtered off. The filtrate was extracted with ether. After drying the extract over sodium sulfate removal of the ether left a brown residue which was combined with the above amorphous precipitate and sublimed at 150° and 0.05 mm. After recrystallization of the sublimate from dilute ethanol 58 mg. of 2-methylisophthalic acid, m.p. 238–240°, was obtained. Identification was made on the basis of mixture m.p.'s and comparison of ultraviolet and infrared spectra with those of an authentic sample.[3]

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(5) Barger and Scholz, *Helv. Chim. Acta*, **16**, 1343 (1933).

(6) All melting points are corrected.

(7) Microanalyses by Spang Microanalytical Laboratory, Plymouth, Mich.

(8) Perkin, Jr., and Robinson, *J. Chem. Soc.*, **101**, 1775 (1912).

(9) We wish to express our thanks to Dr. R. T. Rapala of the Lilly Research Laboratories for a generous sample of harmine.

(10) Witkop and Pruckner. *Ann.*, **554**, 127 (1943).