[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF COLUMBIA UNIVERSITY AND THE UNIVERSITY OF MICHIGAN]

ALSTONIA ALKALOIDS. IV. THE STRUCTURE OF ALSTONILINE[1]

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In 1942 Elderfield and Hawkins (1) reported the isolation from the bark of *Alstonia constricta*, F. Muell. of a red alkaloid, previously noted by Sharp (2), to which the name alstoniline was given. This is a minor constituent of the total alkaloid fraction of the bark and is characterized by the extreme insolubility in addition to the brilliant red color of its salts. The alkaloid was assigned the formula $C_{22}H_{18}N_2O_3$. It formed two series of salts, one being hydrated and the other anhydrous and was readily oxidized by air to give alstoniline oxide, $C_{22}H_{18}N_2O_4 \cdot 2H_2O$, and on catalytic reduction it rapidly absorbed two moles of hydrogen to yield tetrahydroalstoniline which, however, was easily oxidized by air to alstoniline oxide. On the other hand, reduction of the hydrochloride or sulfate of alstoniline gave the corresponding salts of tetrahydroalstoniline which were stable. The Adamkiewicz reaction for a tetrahydro-β-carboline carrying an unsubstituted indole nitrogen, as modified by Harvey, Miller, and Robson (3, 4) gave the characteristic blue-green color exhibited by tetrahydroalstonine (5) although alstonine, itself, gave a different series of colors. Alstoniline contains two methoxyl groups and is optically inactive.

A new shipment of *Alstonia constricta* bark received from Australia[4, 5] has been found to be relatively rich in alstoniline (about 0.02%) so that a sufficient amount of the alkaloid was at hand to permit a detailed study of its structure.

For the isolation of the alkaloid the procedure described by Elderfield and Hawkins (1) was employed initially. After percolation of the ground bark with hot ethanol, an amount of hydrochloric acid calculated to convert all the alstoniline to its hydrochloride was added to the percolate. On concentration and standing, alstoniline hydrochloride crystallized as bright red crystals. It was subsequently found that addition of hydrochloric acid to the percolate was unnecessary. If the percolate was simply concentrated alstoniline hydrochloride crystallized. Thus, it appears that the alkaloid is found in the bark as the hydrochloride, a comparatively rare occurrence among alkaloid constituents of plants.

[1] The material presented in this paper is taken from a dissertation submitted by Stephen L. Wythe in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Columbia University.

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[4] We wish to acknowledge the valuable cooperation of Dr. C. Barnard, Division of Plant Industry, Australian Commonwealth Scientific and Industrial Research Organization, Canberra, Australia through whom the bark was obtained.

[5] The bark was identified as *Alstonia constricta*, F. Muell. by Dr. Heber F. Youngken of the Massachusetts College of Pharmacy, Boston, Massachusetts.

As will be shown subsequently alstoniline hydrochloride may more properly be regarded as a quaternary ammonium salt.

The crude salt was contaminated with large amounts of waxy material which was removed by washing with chloroform. From the chloroform washings what appeared to be β-sitosterol was obtained.

Although the companion alkaloid, alstonine, readily yields identifiable fragments on dehydrogenation with selenium (2), zinc dust distillation (5), and alkali fusion (5), only fusion with potassium hydroxide gave useful information with alstoniline. From the latter reaction an acid, $C_9H_8O_4$, was obtained. This gave a dimethyl ester and a bisphenylhydrazide. It was stable to hydrobromic acid, did not react with acetic anhydride, and on oxidation with permanganate gave an acid, the melting point of which corresponded to that of hemimellitic acid, although the amount obtained was too small for definite identification. No identifiable basic fragments were isolated. This behavior of alstoniline contrasts with that of alstonine which gives harman in good yield but no well-defined acid fragment on similar treatment (5).

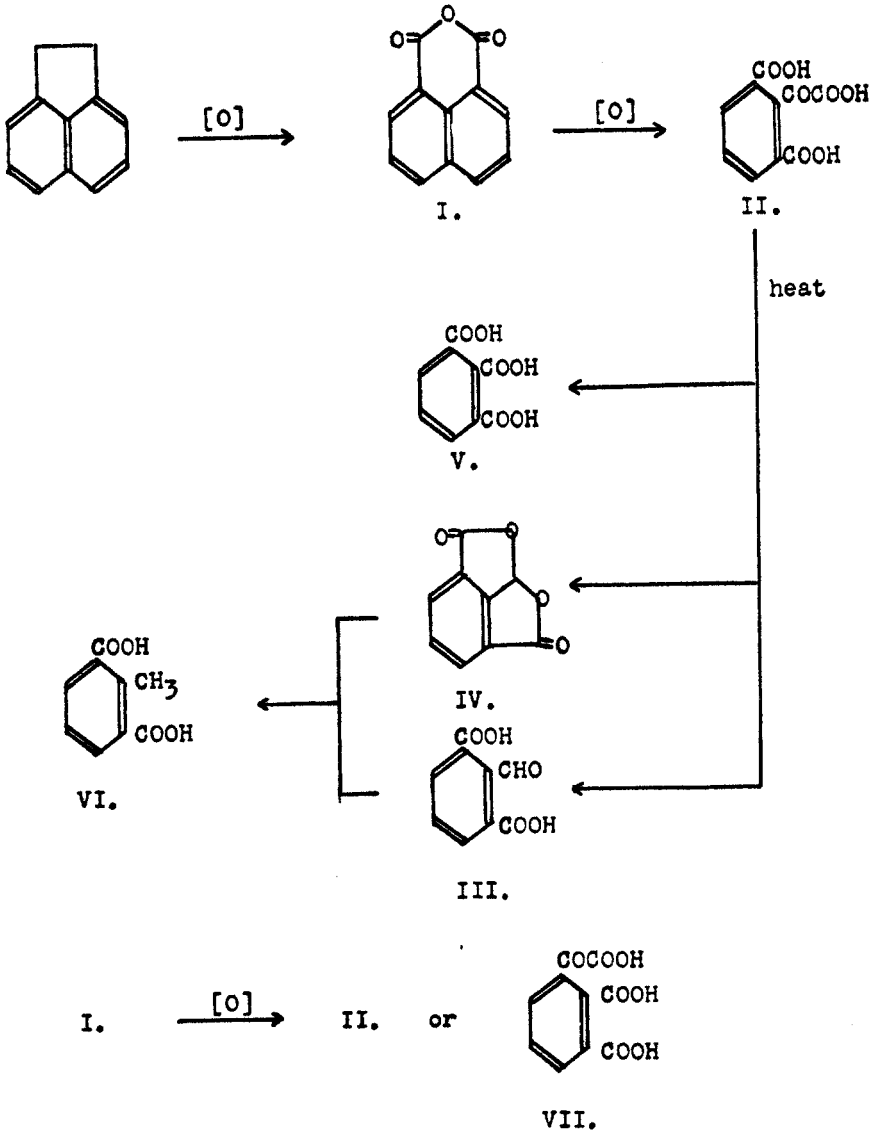
Examination of the literature indicated that the acid, $C_9H_8O_4$, conceivably could be 2-methylisophthalic acid which had been described once before (6, 7). Accordingly this acid was synthesized following in part the synthesis described by Graebe (6, 7).

Acenaphthene was oxidized to naphthalic anhydride (I) which was then reoxidized under controlled conditions to 2,6-dicarboxyphenylglyoxylic acid (II). In his procedure Graebe prepared 2-methylisophthalic acid (VI) by heating II with red phosphorus and hydriodic acid. However II merely on heating above its melting point loses carbon dioxide to give a mixture of 2,6-dicarboxybenzaldehyde (III), the cyclic dilactone of the aldehyde (IV), and hemimellitic acid (V). Reduction of the mixture with Raney nickel-aluminum alloy according to Papa, Schwenck, and Whitman (8) resulted in the formation of VI from III and IV. VI was easily separated from V by sublimation. VI as thus obtained was identical with the degradation product from alstoniline as was its dimethyl ester.

Inasmuch as Graebe did not fully characterize the acid (VI), critical evaluation of the structure assigned the synthetic substance is in order. Oxidation of naphthalic anhydride (I) can only lead to two substances, II or 2,3-dicarboxyphenylglyoxylic acid (VII), with the formation of II much more likely. Since decarboxylation and reduction of VII would give the known 3-methylphthalic acid, the physical constants of which and of its dimethyl ester (9) are distinctly different from those of VI, the structure of II must be as represented and that of the $C_9H_8O_4$ acid from alstoniline must be represented by VI.

Thus of the 22 carbon atoms of alstoniline, the orientation of 9 carbon atoms is determined and 2 more carbon atoms are present as methoxyl groups.

Further information on the structure of alstoniline was obtained from a study of its behavior on reduction. Alstoniline hydrochloride absorbs two moles of hydrogen very rapidly on reduction of a suspension[1] in methanol over Adams' platinum oxide catalyst. By employing a special procedure for working up the product, tetrahydroalstoniline (IX) was obtained in good yield as the free base



which crystallized from methanol with one mole of methanol of crystallization. An explanation of the ready oxidation of tetrahydroalstoniline base by atmospheric oxygen noted by Elderfield and Hawkins (1) was found in the observation that, when pure, the substance is quite stable. However, in the presence of reduced platinum and air or in the presence of its own oxidation products it is rapidly oxidized to orange products.

On reduction with lithium aluminum hydride, tetrahydroalstoniline yields a white cystalline product, $C_{21}H_{22}N_2O_2$, tetrahydroalstonilinol (X) which contains only one methoxyl group. From infrared evidence this substance arises by reduction of a carbomethoxy group to a primary alcohol.

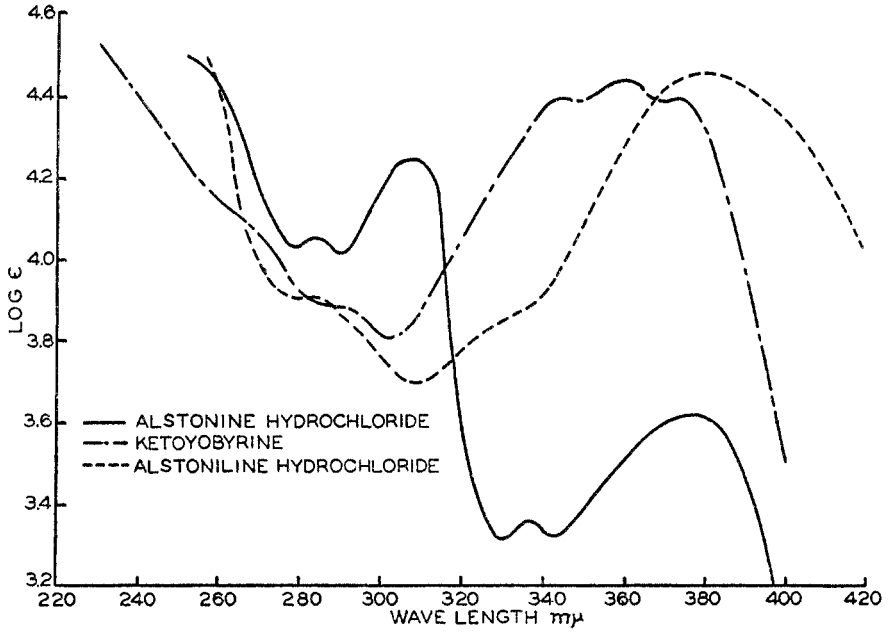
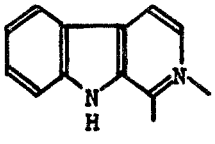


FIG. 1

On the other hand when alstoniline hydrochloride was reduced with lithium aluminum hydride in ether suspension a light yellow substance (XI) which was extremely easily converted to orange products on exposure to air, was formed. This yellow substance appeared to absorb only one mole of hydrogen on catalytic reduction, in contrast to alstoniline itself, and gave the same product, tetrahydroalstonilinol (X), which resulted from the action of lithium aluminum hydride on tetrahydroalstoniline. Thus, one of the double bonds reducible by catalytic hydrogen in alstoniline apparently is also reducible by lithium aluminum hydride. One such type of double bond is the quaternary azomethine linkage $\diagdown\!\!\diagup C{=}N^{+}\diagdown\!\!\diagup$ which is reduced to $\diagdown\!\!\diagup CH{-}N\diagdown\!\!\diagup$ (9).

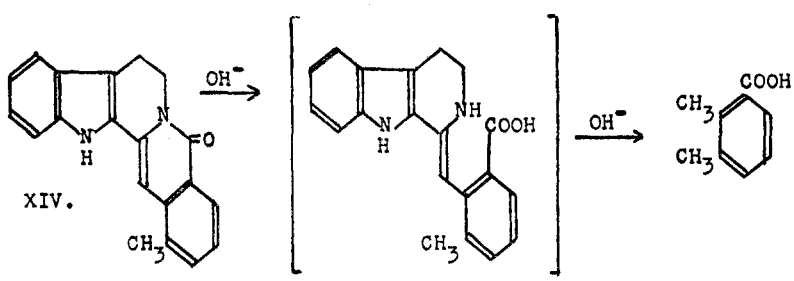
Alternately the ester group in tetrahydroalstoniline was saponified yielding tetrahydroalstonilic acid (XII) which on reduction with lithium aluminum hydride also gave X.

The ultraviolet spectrum of alstoniline is very different from that of its companion alkaloid, alstonine, but it is quite similar to that of ketoyobyrine (XIV) (Fig. 1.). Alstonine and various other quaternary β-carbolinium alkaloids possess the chromophore

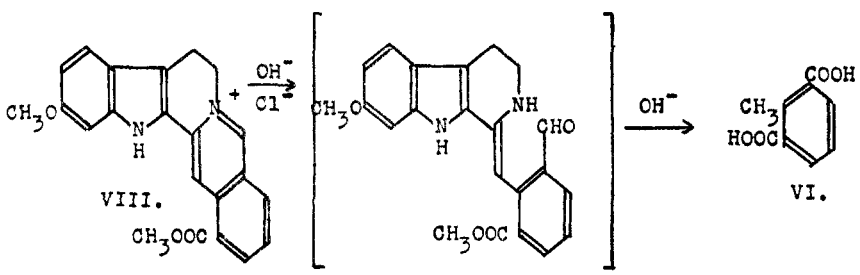


and, in view of the fact that the spectrum of alstoniline does not resemble any of them, it is unlikely that alstoniline contains this unsaturated chromophore. On the other hand the ultraviolet spectrum of tetrahydroalstoniline is quite similar to that of 5- and 6-methoxyindole (10), to that of 6-methoxyindole in particular (Fig. 1 of the following paper). The infrared spectrum of alstoniline shows intense carbonyl absorption at 5.8 microns as well as heavy absorption in the ether region (8–8.5 microns).

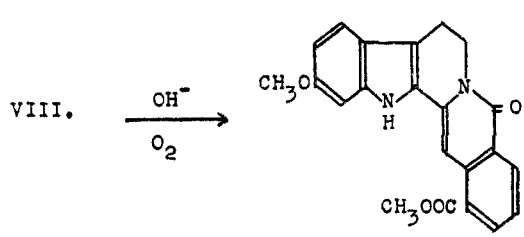
When alstoniline is subjected to the action of hydrobromic acid in glacial acetic acid, a substance, desmethylalstoniline hydrobromide (XIII) $C_{21}H_{16}N_2O_3 \cdot HBr \cdot H_2O$ is formed. This is soluble in aqueous base and is reprecipitated from basic solution by carbon dioxide. The substance is evidently phenolic but it is difficult to obtain pure because of its strong tendency to oxidize. As with alstoniline hydrochloride itself, this compound holds its water of crystallization



KETOYOBYRINE



ALSTONILINE
HYDROCHLORIDE



very tenaciously and satisfactory analytical figures for the anhydrous salt have not been obtained.

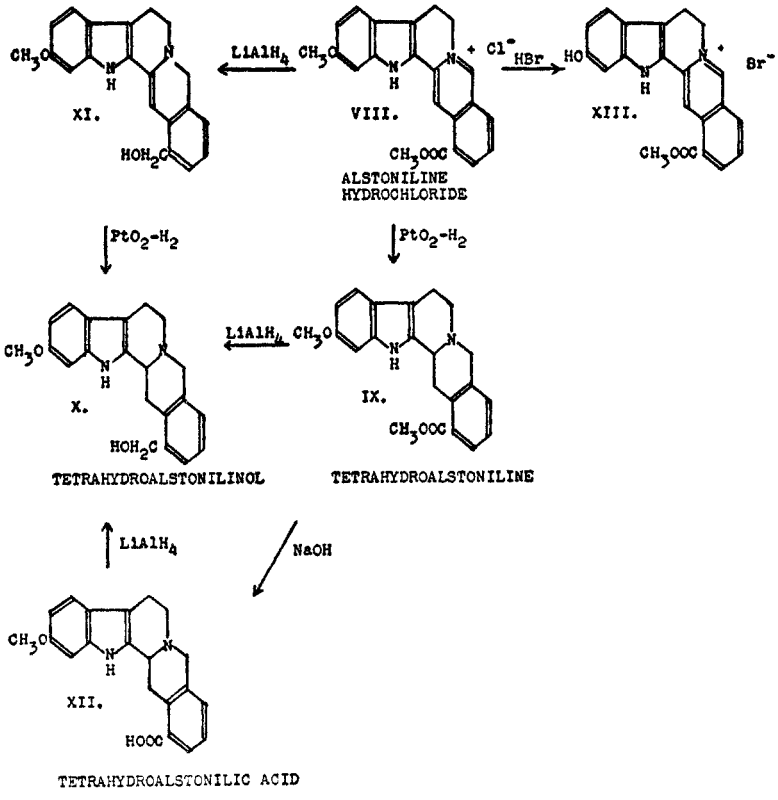
In summary what is known about the structure of alstoniline may be stated as follows. It has two readily reducible double bonds, one of which is probably a quaternary azomethine linkage; it probably contains a benzene ring with substituents in the 1, 2, 3 positions; it carries a methyl ester and probably a methoxyl group in the benzene ring of an indole system; on reduction a tetrahydro-β-carboline is formed.

On this information a structure (VIII) is proposed for alstoniline chloride and other salts.

On this basis the degradation of alstoniline to 2-methylisophthalic acid is analogous to the degradation of ketoyobyrine (XIV) under comparable circumstances (11).

The ultraviolet spectrum of alstoniline also suggests a similarity in structure between ketoyobyrine and alstoniline. The inter conversions discussed above can then be represented as follows.

The methoxyl group is provisionally placed in the 6 position of the indole system on the basis of analogy with harmine and on evidence presented in the following paper. Synthesis of a model compound designed to substantiate these conclusions is described in the following communication.



In conclusion it seems reasonable to formulate alstoniline oxide (1) as XV. Isoquinolinium salts are very susceptible to oxidation by oxygen in basic solution to give the corresponding isocarbostyrils (12).

EXPERIMENTAL[6, 7]

Isolation of alstoniline hydrochloride. The procedure followed was essentially that of Elderfield and Hawkins (1) with some modifications. *Alstonia constricta* bark (800 g., pulverized) was extracted with two 3-l. portions of hot ethanol in a large Silex extractor. The alcoholic extracts were concentrated to 800 ml. On chilling and standing a small amount of red solid separated. After filtration this was recrystallized from 200 ml. of boiling water yielding 235 mg. of crude alstoniline hydrochloride. After washing with chloroform this was recrystallized several times from methanol.

Anal. Calc'd for $C_{22}H_{18}N_2O_3 \cdot HCl \cdot H_2O$: Cl, 8.5. Found: Cl, 8.4.

The mother liquors were reserved for isolation of alstonine.

The bulk of the bark was extracted similarly except that for each 1500 g. of bark 1-ml. of concentrated hydrochloric was added to the alcoholic extract before concentration and the crude alstoniline hydrochloride after the chloroform wash was recrystallized from pyridine-water. Large scale extractions were done at the Lilly Laboratories[8] except for the chloroform washing and recrystallization.

Potassium hydroxide fusion of alstoniline hydrochloride. A mixture of alstoniline hydrochloride (2 g.) and potassium hydroxide (40 g.) was fused in a Pyrex tube in a stream of nitrogen at such a temperature (390°) that mild effervescence occurred. The exit stream of nitrogen was passed into a trap, cooled in solid carbon dioxide in trichloroethylene, and thence through dilute hydrochloric acid. No significant amount of material was isolated from either trap. The melt was fused for 15 minutes, cooled, dissolved in 70 ml. of water, and the resulting solution was extracted with several portions of ether. The aqueous alkaline solution was filtered from insoluble material, acidified, and extracted with three 100-ml. portions of ether-ethanol (9:1). The combined ethanol-ether extracts were dried over sodium sulfate. After removal of the solvent a dark solid remained. On sublimation at 150–180° at 0.2 mm. this gave 250 mg. of a white solid which softened at 130° and melted at 190°. Recrystallization from ethanol-chloroform gave 200 mg. of an acid, m.p. 233–235°. Further recrystallization from water gave needles, m.p. 235–238°. The acid contained no nitrogen.

Anal. Calc'd for $C_9H_8O_4$: C, 60.0; H, 4.5.
Found: C, 59.9; H, 4.8.

Methyl ester of the acid, $C_9H_8O_4$. The above acid (30 mg.) was refluxed for 30 minutes with 2 ml. of thionyl chloride and the solution was added dropwise to 5 ml. of absolute methanol. After refluxing for 30 minutes this solution was concentrated to dryness under reduced pressure leaving a drop of sweet smelling oil. This was dissolved in hot water and on cooling, white needles, m.p. 56–57°, separated.

Anal. Calc'd for $C_{11}H_{12}O_4$: C, 63.4; H, 6.0.
Found: C, 63.4; H, 5.8.

Bisphenylhydrazide of the acid, $C_9H_8O_4$. A solution of 17 mg. of the acid in 2 ml. of phenylhydrazine was refluxed for 1½ hours. On cooling a white solid deposited. This was recrystallized from ethanol, in which it is very sparingly soluble, giving 6 mg. of material which decomposed over a wide range above 250°.

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[6] All melting points are corrected for stem exposure. Boiling points are uncorrected.

[7] Microanalyses were done by Clark Microanalytical Laboratory, Urbana, Illinois; Schwarzkopf Microanalytical Laboratory, Middle Village, New York; and Mr. Goji Kodama of the University of Michigan laboratories.

[8] We wish to express our appreciation to Mr. E. H. Stuart of the Lilly Laboratories, Indianapolis, Indiana who carried out the large scale extractions.

Anal. Calc'd for $C_{21}H_{20}N_4O_2$: C, 70.0; H, 5.6; N, 15.5.
Found: C, 69.7; H, 5.7; N, 15.2.

SYNTHESIS OF 2-METHYLISOPHTHALIC ACID (VI)

A. 2,6-Dicarboxyphenylglyoxylic acid (II). The method of Graebe and co-workers (6, 7) with certain modifications was used. Acenaphthene (25 g., 0.16 mole) was dissolved in 300 ml. of hot glacial acetic acid. After cooling the solution to 80°, 175 g. (0.45 mole) of sodium dichromate heptahydrate was added slowly with stirring at such a rate that the temperature was held below 85°. As the reaction subsided the dichromate was added faster and it was necessary to warm the mixture on the steam-bath to maintain the temperature. Addition of the dichromate took one hour. The solution was held at 100° for an additional two hours, poured into 4 l. of water, and the solid was collected. The product was dissolved in dilute aqueous sodium hydroxide and the filtered solution was acidified with hydrochloric acid. The yield of crude naphthalic anhydride (I) was 24 g. (75%).

The crude naphthalic anhydride obtained above was warmed on the steam-bath with a solution of 8 g. of sodium hydroxide in 100 ml. of water. To the solution was added a solution of 120 g. (0.7 mole) of potassium permanganate in the minimum amount of water as fast as decolorization occurred. As the reduction of the permanganate slowed down, the rest of the solution was added and the mixture was warmed for an additional hour on the steam-bath. The solution was filtered from the manganese dioxide which was washed several times with water. The combined filtrate and washings was boiled one-half hour and the excess permanganate was destroyed with ethanol. After filtering again the filtrate was acidified with a solution of 55 ml. of sulfuric acid (*sp. gr.* 1.84) in 55 ml. of water. After concentration to one-half its volume the solution was exhaustively extracted with ether. Removal of the solvent from the combined ether extracts and recrystallization of the residue from water gave 15 g. of white needles, m.p. 239–241° (dec.). The yield was 40% based on the acenaphthene used. Graebe (6, 7) reports m.p. of 236–238° (uncorr.) for 2,6-dicarboxyphenylglyoxylic acid.

B. Decarboxylation and reduction of 2,6-dicarboxyphenylglyoxylic acid. 2,6-Dicarboxyphenylglyoxylic acid (2 g., 0.008 mole) was heated at 250° until gas evolution ceased. The residual resin was triturated with 15 ml. of warm water and the insoluble material (0.5 g.) was dissolved in warm 10% sodium hydroxide solution and was warmed for one hour on the steam-bath with 1 g. of Raney nickel-aluminum alloy. The solution was filtered, acidified, and chilled, yielding 0.3 g. of white needles, m.p. 190–205°. The aqueous solution from trituration of the resin was treated similarly with Raney alloy in basic solution and gave 0.2 g. of a white solid, m.p. 220–230°. The two solids were combined and sublimed and the sublimate was recrystallized first from ethanol-chloroform and then from water yielding white needles, m.p. 236–238°. This acid on treatment with thionyl chloride and methanol as with the $C_9H_8O_4$ acid described above gave a methyl ester, m.p. 54–55°. Mixtures of this ester with that of the $C_9H_8O_4$ acid from alkali fusion of alstoniline melted at 54–55°.

Tetrahydroalstoniline (IX). A suspension of 5 g. (0.012 mole) of alstoniline hydrochloride in 250 ml. of methanol was shaken with hydrogen and 131 mg. of Adams' platinum oxide catalyst at atmospheric pressure and 27°. In 30 minutes 680 ml. of hydrogen were absorbed (Calc'd for 2 moles: 625 ml.). No further uptake of hydrogen occurred on shaking for an additional half hour. During the reduction the color of the suspension changed from orange to yellow. The mixture of catalyst, tetrahydroalstoniline, and methanol was quickly transferred to a 3-l. separatory-funnel and the funnel was completely filled with methanol and stoppered. In the presence of air and moist catalyst tetrahydroalstoniline is rapidly oxidized to orange products. All the suspended organic material went into solution and the catalyst was allowed to settle and drawn off. The pale, yellow-green solution was filtered, made basic with a few ml. of 10% sodium hydroxide solution, and allowed to stand for two days during which 3.5 g. of broad yellow needles deposited. The mother liquor was concentrated to 500 ml. and an additional 0.75 g. of material was obtained. Both crops of crystals melted at 191–193°. The yield of tetrahydroalstoniline methanolate was 90%.

Anal. Calc'd for $C_{22}H_{22}N_2O_3 \cdot CH_3OH$: C, 70.0; H, 6.6.
Found: C, 70.2; H, 6.7.

On drying the above substance for four days a mole of methanol was lost. For the solvent free material:

Anal. Calc'd for $C_{22}H_{22}N_2O_3$: C, 72.9; H, 6.1.
Found: C, 72.8; H, 6.1.

The *hydrochloride* was formed on recrystallization of the base from ethanol-water containing 1% of hydrochloric acid.

Anal. Calc'd for $C_{22}H_{22}N_2O_3 \cdot HCl$: C, 66.2; H, 5.8.
Found: C, 65.8; H, 5.9.

Tetrahydroalstonilic acid (XII). A solution of 0.4 g. (0.001 mole) of tetrahydroalstoniline methanolate in 25 ml. of ethanol and 20 ml. of 10% aqueous sodium hydroxide solution was refluxed under a nitrogen atmosphere for one hour. The cooled, clear solution was diluted to 100 ml. with water and was filtered from a small amount of insoluble material. The filtrate was heated to boil off most of the alcohol, diluted further with hot water to 120 ml., acidified with hydrochloric acid, and cooled. Tetrahydroalstonilic acid hydrochloride (0.39 g.), m.p. 265–267° (dec.) separated. The yield was quantitative.

Anal. Calc'd for $C_{21}H_{20}N_2O_3 \cdot HCl \cdot H_2O$: C, 62.6; H, 5.7.
Found: C, 62.6; H, 5.8.

Tetrahydroalstonilinol (X). Tetrahydroalstoniline methanolate (0.55 g., 0.0014 mole) was added slowly to a suspension of 0.5 g. (0.013 mole) lithium aluminum hydride in 50 ml. of dry ether. The suspension was stirred under reflux for four hours during which time a white solid formed and most of the yellow color of the starting material was discharged. The excess lithium aluminum hydride was decomposed by dropwise addition of ethyl acetate. After addition of 50 ml. of water followed by 50 ml. of 10% sodium hydroxide solution the mixture was stirred vigorously for 15 minutes. Removal of the ether on the steam-bath left a suspension of a white solid which was collected and recrystallized from methanol. The yield of white needles, m.p. 224–226° (dec.) was 0.39 g. (83%).

Anal. Calc'd for $C_{21}H_{22}N_2O_2$: C, 75.4; H, 6.6; N, 8.4; OCH_3, 9.25.
Found: C, 75.2; H, 6.7; N, 8.0; OCH_3, 8.6.

Tetrahydroalstonilinol forms a *hydrochloride* which crystallizes from ethanol in white needles, m.p. 278–282° (dec.).

Similar reduction of tetrahydroalstonilic acid also gave tetrahydroalstonilinol, m.p. 224–228° (dec.).

Anal. Found: C, 75.1; H, 6.8.

Action of lithium aluminum hydride on alstoniline hydrochloride. Alstoniline hydrochloride (0.5 g., 0.0012 mole) was added in five portions to a stirred suspension of 0.38 g. (0.01 mole) of lithium aluminum hydride in 50 ml. of dry ether. The suspension was orange at first but rapidly turned to a light yellow-green. After refluxing for two hours it was cooled and the excess reagent was decomposed with ethyl acetate. After addition of 100 ml. of 5% hydrochloric acid the ether was boiled off on the steam-bath. The suspension of yellow solid was chilled and the solid was collected. A solution of the solid in methanol displayed an intense green fluorescence. The dried filter cake weighed 0.45 g. and on exposure to air it began to turn from yellow to orange. In view of this rapid reoxidation, 380 mg. of the material was suspended in 100 ml. of methanol and was shaken with hydrogen and 55 mg. of Adams' platinum oxide catalyst at atmospheric pressure. In ten minutes 38 ml. of hydrogen was absorbed and hydrogen uptake ceased. Calc'd for one mole of hydrogen: 44 ml. The solution was decanted from the catalyst and filtered. It was made strongly basic with a few ml. of 10% sodium hydroxide solution, diluted with 10 ml. of water, and chilled. Recrystallization of the precipitate from ethanol gave fine white needles of tetrahydroalstonilinol, m.p. 225–228° (dec.).

Anal. Found: C, 75.9; H, 6.7.

Desmethylalstoniline (XIII). A solution of 0.89 g. of alstoniline hydrochloride in 50 ml. of glacial acetic acid and 150 ml. of 48% hydrobromic acid was refluxed for four hours. On

cooling 0.85 g. of fine red needles separated which were recrystallized from methanol yielding 0.26 g. of red needles, m.p. above 330° with slow decomposition. Concentration of the mother liquors gave additional crops of material of 0.23 g. and 0.16 g. respectively. Both crops melted above 330°. Analytical data indicated that the substance arose by cleavage of an ether group with retention of the carbomethoxy group. This conclusion is substantiated by the fact that the substance is soluble in aqueous sodium hydroxide from which it is precipitated by carbon dioxide, behavior characteristic of phenols but not of acids. In view of its instability the substance was not investigated further.

Anal. Calc'd for $C_{21}H_{16}N_2O_3 \cdot HBr \cdot H_2O$: C, 56.9; H, 4.3; N, 6.3.
Calc'd for $C_{20}H_{14}N_2O_3 \cdot HBr$: C, 58.4; H, 3.7; N, 6.7.
Calc'd for $C_{20}H_{14}N_2O_3 \cdot HBr \cdot H_2O$: C, 55.9; H, 4.0.
Calc'd for $C_{21}H_{16}N_2O_3 \cdot HBr$: C, 59.3; H, 4.0.
Found: C, 56.6, 57.1; H, 4.1, 4.1; N, 6.5.

SUMMARY

1. On the basis of its conversion to 3-methylisophthalic acid on alkali fusion and from a study of its reduction products, a structure is proposed for alstoniline.

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