[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

ALSTONIA ALKALOIDS. III. FURTHER INVESTIGATION OF ALSTONINE. REDUCTION, OZONOLYSIS, AND SPECTROGRAPHIC STUDIES. THE STRUCTURE OF ALSTONINE[1]

ROBERT C. ELDERFIELD AND ALLAN P. GRAY

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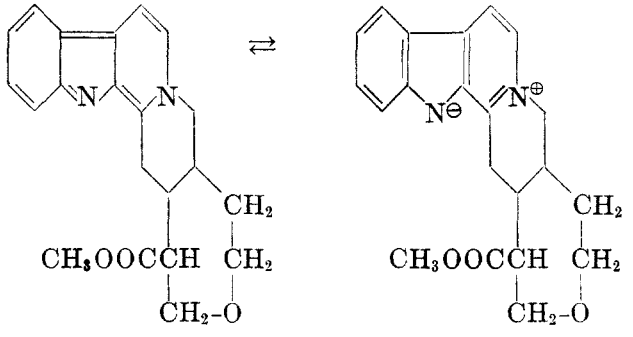
Some years ago a study of the constitution of alstonine, the principal alkaloid of the bark of *Alstonia constricta*, was undertaken in these laboratories (1). From the results of alkali fusion and zinc-dust distillation of alstonine, it was concluded that the β-carboline nucleus was present in the alkaloid.

After this manuscript was submitted, a paper by Schlittler and Schwarz on the closely related alkaloid, serpentine, (2) appeared, and, at the request of the referee, the present paper has been rewritten in part to take this into account. Serpentine differs from alstonine by two hydrogens and can be considered to be either identical to or a stereoisomer of the hitherto unknown dihydroalstonine. Serpentine gives the same selenium dehydrogenation product, alstyrine, as does alstonine and like alstonine absorbs two moles of hydrogen on catalytic reduction. Based on spectrographic evidence Schlittler and Schwarz (2) suggest structure I for serpentine by analogy to the structure of sempervirine put forward by Woodward and Witkop (3) and to that of tetradehydroyohimbine (4).



I

After a lapse during the years of World War II, we have now returned to the study of alstonine. Although the presence of a carbomethoxy group in alstonine has been firmly established (1, 5, 6) the nature of the third oxygen atom has remained an enigma. Failure to obtain acyl derivatives and the liberation of only one mole of methane [possibly from the same source as that given by sempervirine (3)] in the Zerewitinoff determination (1) apparently ruled out the pres-

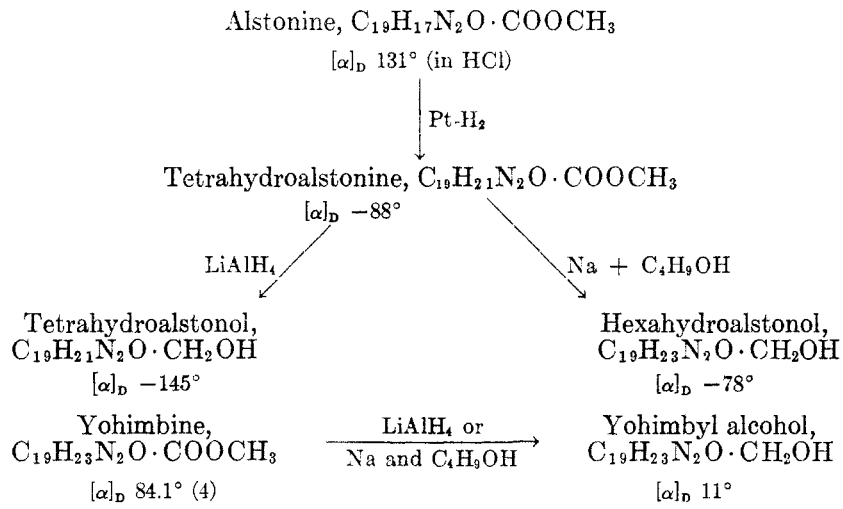
[1] The material reported in this paper is taken from a dissertation submitted by Allan P. Gray in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Columbia University, May 1950.

ence of an hydroxyl group. The presence of an ether linkage seemed unlikely since Sharp (5, 6) reports that tetrahydroalstonine is but little affected on heating with hydrobromic acid at 140°. Further, no carbonyl derivatives have been obtained from alstonine or tetrahydroalstonine.

At the beginning of the present work it was assumed that alstonine conceivably might have the same carbon skeleton as yohimbine. This assumption has been shown to be improbable.

Alstonine and yohimbine were subjected to the series of reductions in Chart I.

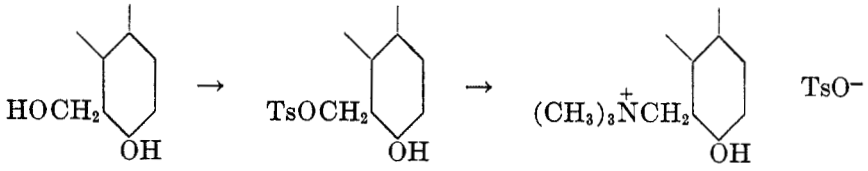
CHART I



All rotations were done in pyridine except that of alstonine hydrochloride which was done in water.

It was then hoped to open the rings of yohimbyl alcohol and hexahydroalstonol (1) by degradation proceeding from the respective primary alcohol groups. When yohimbine was reduced with either sodium and butanol, or better with lithium aluminum hydride, yohimbyl alcohol, a substance first described by Schomer (5), was obtained. After the work was completed, the preparation of yohimbyl alcohol by the lithium aluminum hydride reduction of yohimbine was described by Chatterjee and Karrer (7). Yohimbyl alcohol was isolated as either the hemihydrate or monoalcoholate and was not identical with the isomeric hexahydroalstonol.

Preliminary to attempted degradation, yohimbyl alcohol was converted to the mono-*p*-toluenesulfonate, which was isolated as the alcoholate. Treatment of the *p*-toluenesulfonate with trimethylamine led to the formation of a substance for which no formulation other than as a quaternary salt appears satisfactory. However when the free quaternary hydroxide derived from II was heated either in 50% sodium hydroxide or alone, no trimethylamine was evolved and no pure product could be isolated from the reaction.



II

When tetrahydroalstonine was reduced with lithium aluminum hydride a new substance, tetrahydroalstonol, $C_{20}H_{24}N_2O_2$, was formed. In this reduction, the

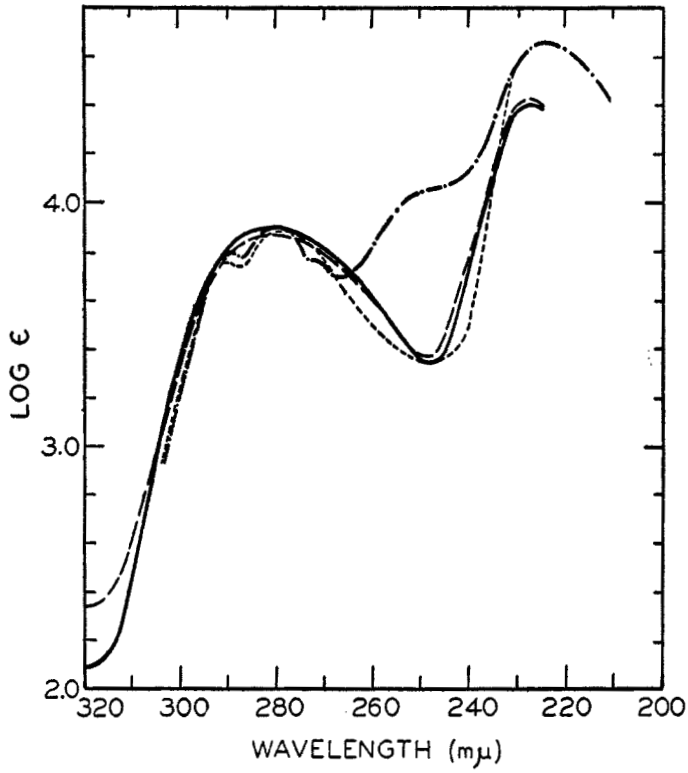
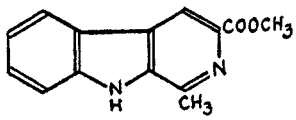


FIG. 1. ULTRAVIOLET SPECTRA. ——— Tetrahydroalstonol — — — Desoxyhexahydroalstonol -·-·- Tetrahydroalstonine (1) - - - - Hexahydroalstonol (1).

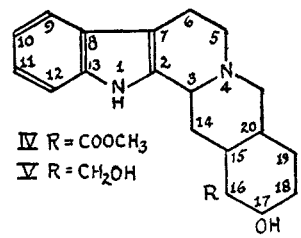
two additional hydrogens taken up by tetrahydroalstonine during reduction with sodium and butanol were not involved. Since lithium aluminum hydride is a very effective reagent for the reduction of carbonyl groups, it appears unlikely that the third oxygen of tetrahydroalstonine is a carbonyl oxygen.

The ultraviolet absorption spectra (Fig. 1) of tetrahydroalstonol, hexahydroalstonol, and tetrahydroalstonine show quite clearly that the double bond of tetrahydroalstonine is conjugated with the ester group and is not conjugated also with the indole system.

Further significant information concerning alstonine and its reduction products is provided by the infrared absorption of these substances in comparison with 5-carbomethoxyharman (III) and yohimbine (IV) (Figs. 2 and 3). No suggestion of the presence of a hydroxyl group in tetrahydroalstonine, and hence in alstonine, was found. Likewise the shift of the ester peaks from 1736 cm.$^{-1}$ in yohimbine to 1710–1720 cm.$^{-1}$ in alstonine, tetrahydroalstonine, and III confirms the conjugation of the double bond in question with the ester group in tetrahydroalstonine (8). The peak at 1668 cm.$^{-1}$ shown by tetrahydroalstonol is characteristic of this compound and occurs at a frequency suggestive of a strained or cyclic double bond.



III



IV R = $COOCH_3$
V R = CH_2OH

In order to secure further confirmation of the nature of the unsaturated ester group in tetrahydroalstonine, which is reduced by sodium and butanol but unaffected by lithium aluminum hydride, Zerewitinoff active hydrogen determinations were made with tetrahydro- and hexahydro-alstonol (Table I).

These results show that a carbon-carbon double bond must have been reduced during the sodium and butanol reduction. If a C=O or a C=N double bond had been involved, hexahydroalstonol would have been expected to show three active hydrogens and tetrahydroalstonol should have added one mole of Grignard reagent. If an ether linkage had been cleaved, hexahydroalstonol should have shown three active hydrogens.

The above evidence together with that previously available appears conclusive that a double bond and a carbonyl group cannot both be present in tetrahydroalstonine and that a carbonyl group (aside from the ester) is absent in the compound.

In order to obtain more direct evidence as to the position of the double bond in tetrahydroalstonine, oxidative cleavage was attempted. No pure products could be isolated after oxidation with chromic oxide, neutral potassium permanganate, or performic acid. When tetrahydroalstonine in aqueous acetic acid was treated with approximately one equivalent of ozone, considerable tar was produced, but a small amount of a crystalline compound was isolated. Analysis of this indicated it to have the empirical formula, $C_{20}H_{22}N_2O_4$, which would result from loss of one CH_2 group and gain of one oxygen. However, no formaldehyde or other one-carbon-atom fragment was isolated from the reaction products. That the reaction product was the result of oxidation by ozone and not by any other reagents which could have been present was indicated by the failure of tetrahydroalstonine to react with either hydrogen peroxide or oxygen under

conditions comparable to those of the ozonization. Methoxyl determinations showed retention of the ester group in the product of ozonization. The substance was a base and furnished a hydrochloride and a picrate. On the other hand it was

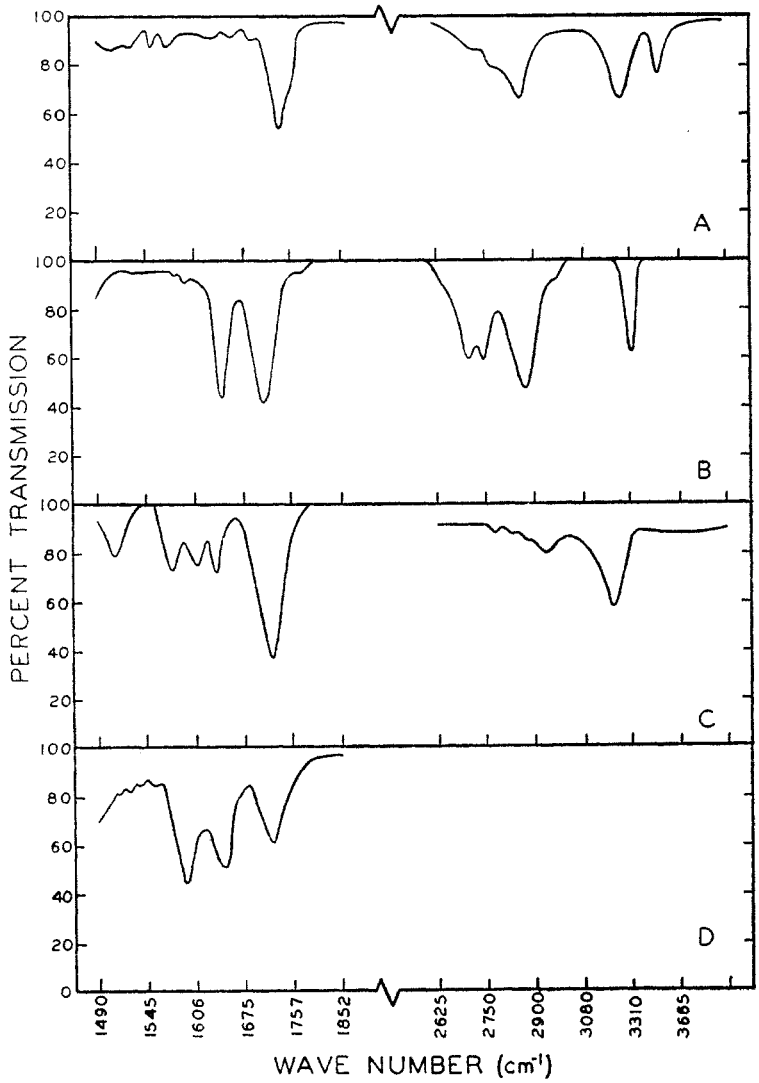


FIG. 2. INFRARED SPECTRA. Samples in chloroform solution below 1850 cm^{-1}, as solid films above 2600 cm^{-1}. A. Yohimbine; B. Tetrahydroalstonine; C. 5-Carbomethoxyharman; D. Alstonine—Spectrum not shown above 1850 cm^{-1}.

readily soluble in 5% sodium hydroxide and insoluble in sodium carbonate, but too weakly acidic to be titrated potentiometrically. It gave a negative enol test with ferric chloride and did not react with 2,4-dinitrophenylhydrazine. Reaction with diazomethane gave about 50% of recovered material and 50% of a tar

which was insoluble in 5% sodium hydroxide. *p*-Toluenesulfonyl chloride in pyridine gave tarry products and acetic anhydride in pyridine did not attack the substance.

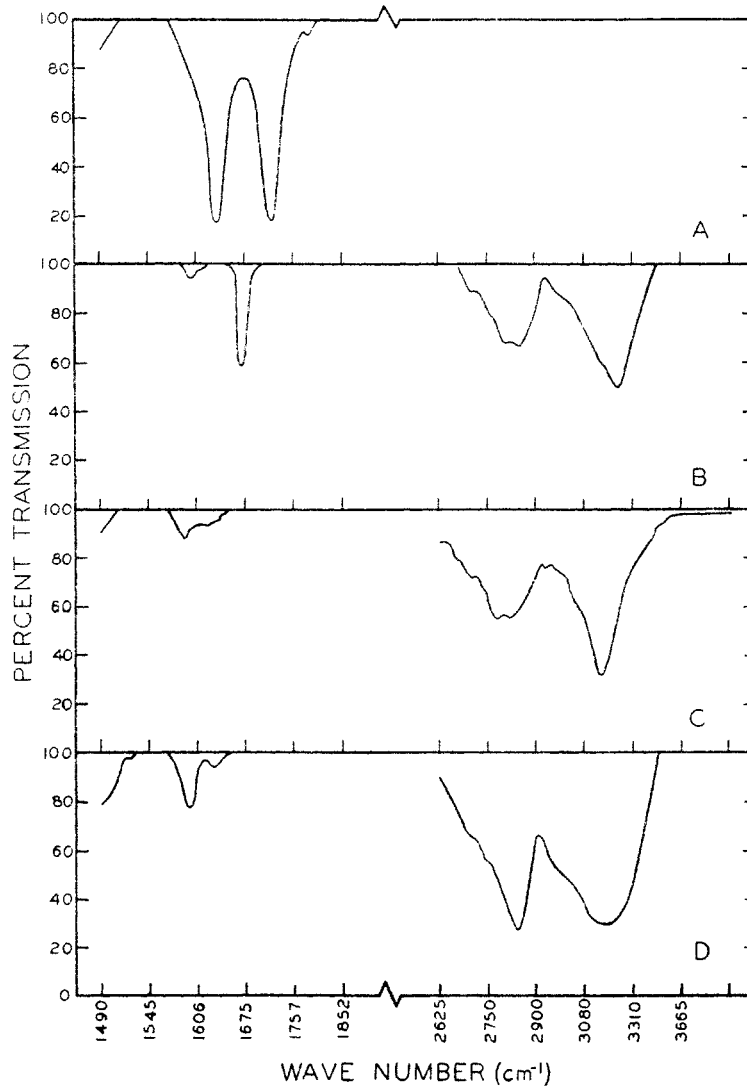


FIG. 3. INFRARED SPECTRA. Samples as solid films. A. Tetrahydroalstonine—For spectrum above 1850 cm^{-1} cf. Fig. 2.; B. Tetrahydroalstonol; C. Hexahydroalstonol; D. Yohimbyl alcohol.

The ultraviolet absorption spectrum of the compound is completely different from that of tetrahydroalstonine and indicates the presence of a highly conjugated system (Fig. 4). The infrared spectrum of the compound (Fig. 5) also

presents marked contrasts to that of tetrahydroalstonine. Pending the accumulation of additional evidence, it is not possible to explain the course of the ozonization satisfactorily at this time.

TABLE I

ACTIVE HYDROGEN DETERMINATIONS

COMPOUND	MOLES METHANE EVOLVED		MOLES GRIGNARD ADDED	
	Calc'd	Found (avg.)	Calc'd	Found (avg.)
Yohimbyl alcohol hemihydrate	4	4.1	0	0.0
Yohimbyl alcohol monoalcoholate	4	3.8	0	0.0
Tetrahydroalstonol		2.0		0.0
Hexahydroalstonol		1.9		0.0

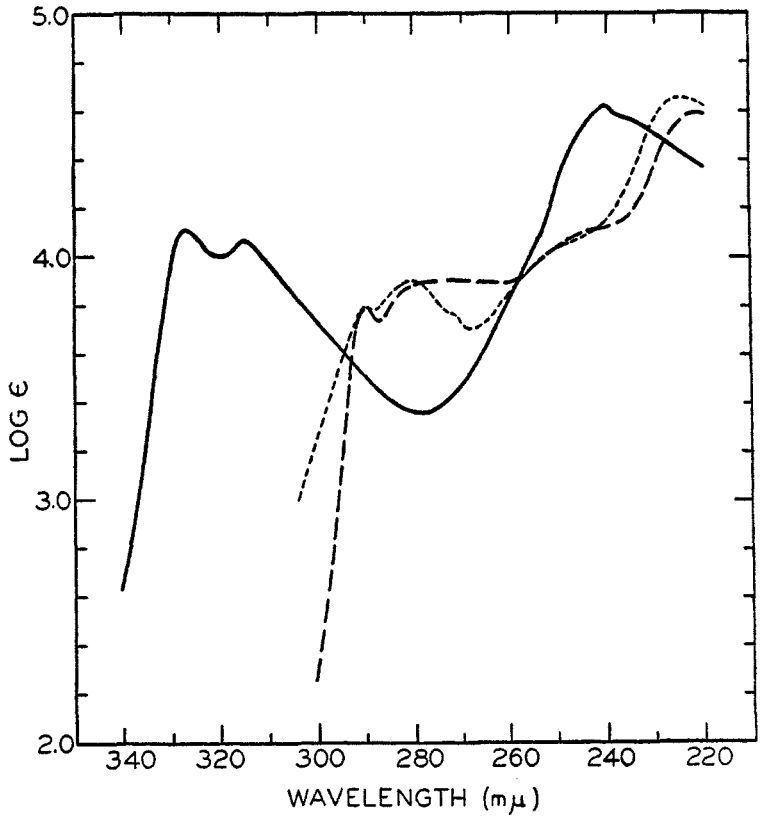


FIG. 4. ULTRAVIOLET SPECTRA. ——— Ozonolysis product — — — Tetrahydroalstonine in 0.1 N hydrochloric acid - - - - - Tetrahydroalstonine (1).

During the course of the investigation of tetrahydroalstonol it was observed that the substance is unusually labile to acid and is not recoverable from strongly acid solutions. The behavior of tetrahydroalstonol in the presence of several acidic reagents is summarized in Chart II.

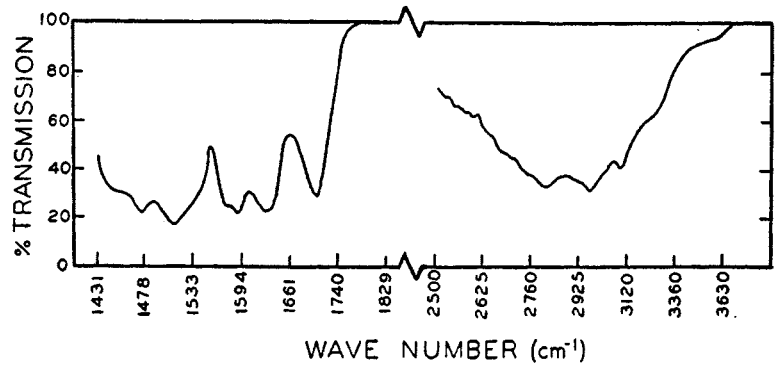
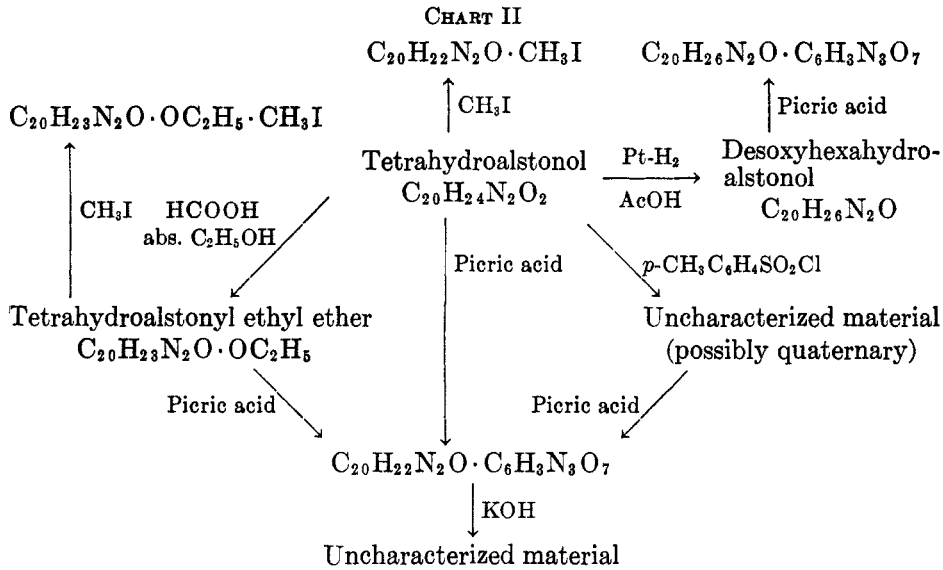


FIG. 5. INFRARED SPECTRUM. Ozonlysis product as solid film.

CHART II



Although tetrahydroalstonol is not a hydrate (*cf.* Zerewitinoff results), its picrate came out of a saturated picric acid solution in 95% ethanol as the salt of a base, $C_{20}H_{22}N_2O$. This has been designated anhydrotetrahydroalstonol picrate since it seems quite clear that it is the picrate of a base formed by dehydration of tetrahydroalstonol with the acid.

Since methyl iodide is not an acid in the same sense as picric acid, it was somewhat surprising that the analysis of tetrahydroalstonol methiodide was in agreement with the formula $C_{20}H_{22}N_2O \cdot CH_3I$. When tetrahydroalstonol was treated with either *p*-toluenesulfonyl chloride or acetic anhydride in pyridine at room temperature, reaction ensued and a brown amorphous material was formed. The product of neither reaction could be crystallized, but both products gave the same picrate in good yield. This picrate appeared to be identical with anhydrotetrahydroalstonol picrate.

Gentle refluxing of a solution of tetrahydroalstonol in 4% formic acid in ab-

solute ethanol yielded a mixture from which only one crystalline compound was isolated. Elementary analyses and ethoxyl determinations indicated the formula, $C_{20}H_{23}N_2O \cdot OC_2H_5$. If the substance is a solvate, it is a very stable one, since it suffered no loss in weight when dried at 100° *in vacuo*. It has been designated tetrahydroalstonyl ethyl ether. The ultraviolet spectrum was identical, within experimental error, with that of tetrahydroalstonol. Although the picrate prepared from tetrahydroalstonyl ethyl ether was identical with anhydrotetrahydroalstonol picrate, a different methiodide in which the ethoxyl group apparently was retained was formed.

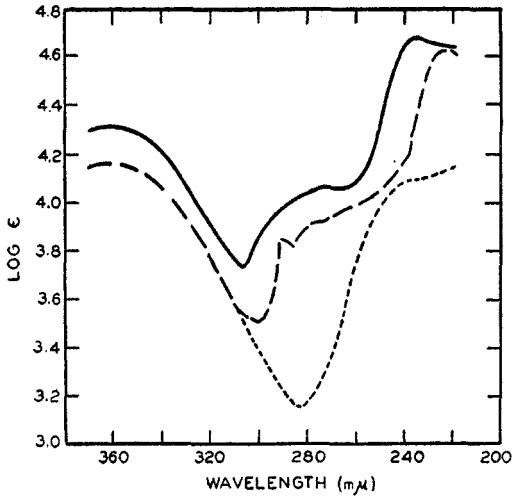


FIG. 6. ULTRAVIOLET SPECTRA. ——— Anhydrotetrahydroalstonol picrate — — — Desoxyhexahydroalstonol picrate - - - - - Tri-*n*-butylamine picrate.

In attempting to rationalize the above reactions, it must be borne in mind that the behavior of hexahydroalstonol is in no way similar (1). This gives a normal picrate and acetate. It therefore appears that the unsaturated system is involved in the peculiar reactivity of tetrahydroalstonol. The α,β-unsaturated ester system present in tetrahydroalstonine is converted into an allyl alcohol system in tetrahydroalstonol, and it is possible to formulate a reasonable explanation for the behavior of the latter substance on this basis. This point is discussed in greater detail later.

Tetrahydroalstonol was not reduced by hydrogen over platinum oxide (of verified activity) in methanol solution. However in methanol containing 30% acetic acid, 3 to 4 moles of hydrogen were smoothly absorbed with the formation of a mixture of products from which one crystalline substance, $C_{20}H_{26}N_2O$, which has been designated desoxyhexahydroalstonol, was isolated. This yielded a normal picrate which was different from that of anhydrotetrahydroalstonol picrate. The ultraviolet absorption spectrum of desoxyhexahydroalstonol (Fig. 6) is almost identical with that of tetrahydroalstonol indicating that the indole nucleus is still intact. The absorption of the extra hydrogen during the reduction

may well have been due to side reactions (*e.g.* reduction of the indole nucleus) since a large amount of unpurifiable oil was obtained. It therefore appears that acetic acid accomplishes a shift in the position of the double bond in tetrahydroalstonol from a position in which it is unreactive to catalytically-activated hydrogen to a position in which it may be attacked and that this shift is accompanied by a newly acquired lability of the hydroxyl group.

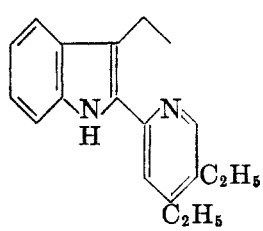
When a solution of tetrahydroalstonol in 30% acetic acid was allowed to stand for five hours at room temperature, only tetrahydroalstonol was recovered. However, this was in a highly impure state, and it was obvious that some change had occurred in at least a part of the material.

At this point it appears to be profitable to review the available evidence for the structure of alstonine, and to put forward tentative structures for the alkaloid and certain of its derivatives.

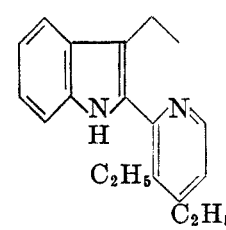
Sharp (6) obtained alstyrine on selenium dehydrogen of alstonine. Karrer and Enslin (9) isolated a substance, corynanthrine, from the products of the selenium dehydrogenation of corynantheine. Corynanthine and alstyrine were shown to be in all probability identical and structure VI was put forward for the substance on the basis of degradation experiments although VII is not excluded (9). On this evidence Karrer and Enslin suggested that alstonine and corynantheine (for which the tentative structure VIII was suggested) may be related, and that both possess the pentacyclic ring system of yohimbine. However, Janot and Goutarel (10) have produced evidence that corynantheine is tetracyclic rather than pentacyclic.

We now wish to put forward the tentative structure IX for tetrahydroalstonine and structure X for tetrahydroalstonol. By the Kuhn-Roth method, tetrahydroalstonine and anhydrotetrahydroalstonol picrate both contain at least one terminal C-methyl group. This is confirmed by the infrared spectra. Formulation of the carbon skeleton as in IX takes this into account and also accounts for the formation of alstyrine (VI) on selenium dehydrogenation of alstonine, if one assumes that no rearrangements occur during the dehydrogenation.

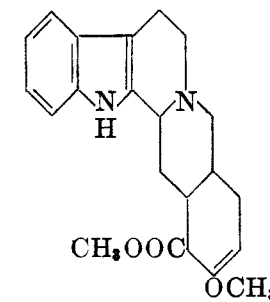
The double bond external to and not conjugated with the indole nucleus in tetrahydroalstonine must be conjugated with the ester group and, further, it is in a position such that it resists catalytic hydrogenation. These conditions are met by placing the double bond in the 15, 16 position.



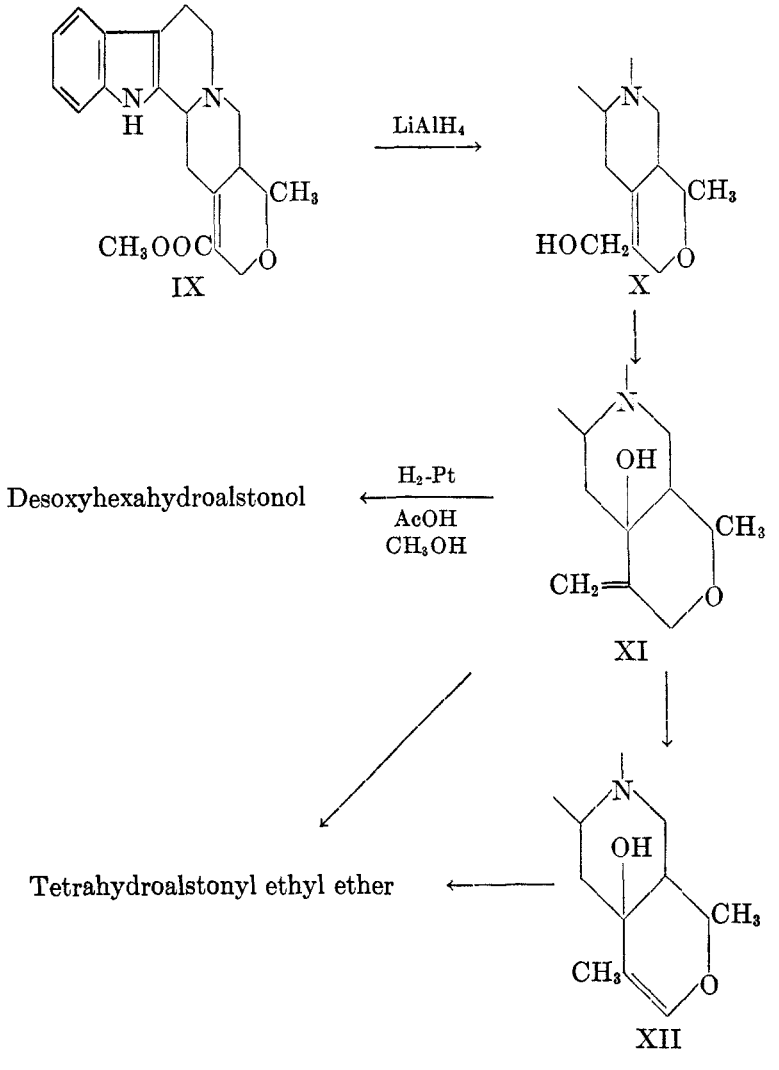
VI



VII



VIII



The formulation of tetrahydroalstonol is in good accord with the properties of a labile allyl alcohol shown by this substance. Allyl alcohols are exceedingly susceptible to rearrangement under the influence of even the mildest reagents. For example, crotyl alcohol and methyl vinyl carbinol are interconvertible under the influence of acid (11) and the interconvertibility of linalool and geraniol (12) may be cited. Further, allyl alcohols undergo ether formation with exceptional ease (11). Thus the action of acid on the labile allyl system of tetrahydroalstonol would lead to the rearranged product XI. The double bond in XI can be expected to shift into the ring with the formation of XII. In acid, then, tetrahydroalstonol can reasonably be expected to exist as X, XI, or XII.

On the above basis the reactions of tetrahydroalstonol can be reconciled. Failure of the substance to undergo catalytic hydrogenation in neutral solution is

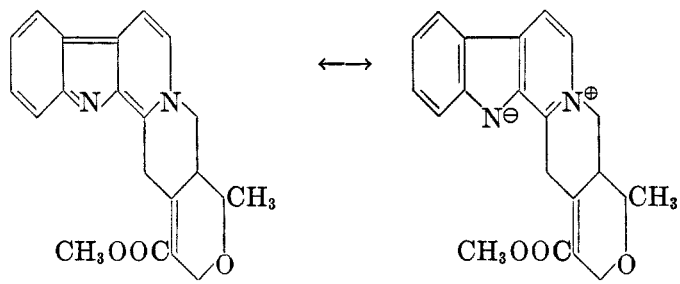
ascribable to the position of the double bond in X. However, in the presence of acid, structure XI apparently controls. Here the double bond is extracyclic and hence susceptible to hydrogenation. Further, the hydroxyl group is tertiary in addition to being allylic, a combination which renders elimination of the hydroxyl with the formation of desoxyhexahydroalstonol easy. Tertiary alcohols undergo ether formation readily under the influence of very mild acidic reagents (13).

Finally the failure of tetrahydroalstonol to yield acyl derivatives, but rather to undergo dehydration to anhydrotetrahydroalstonol is explicable on the basis of structure XI or XII.

Several anomolies remain to be explained. When formulated as IX tetrahydroalstonine is an allyl ether which might be expected to undergo hydrogenolysis on reduction. This has not been noted. Likewise the reported stability of alstonine to hydrobromic acid (6) is difficult to reconcile with an ether formulation. At least one instance, that of seven membered cyclic ether—phenanthrene-4,5-dimethylene oxide, of stability to hydrobromic acid at temperatures up to 150° may be cited (14). The answers to these points await accumulation of further data.

An obvious formulation for tetrahydroalstonine in which Ring E is seven membered in accordance with the structure of serpentine put forward by Schittler and Schwarz (2) is apparent. The formulation of tetrahydroalstonine as IX is dependent only on the presence of one C-methyl group as shown in the Kuhn-Roth determination and by the infrared spectra.

In view of the observations of Schittler and Schwarz (2) a structure (XIII) may now be written for alstonine.



XIII

With 2,4-dinitrophenylhydrazine, what appeared to be an addition compound was formed with alstonine hydrochloride.[2] The substance was not a carbonyl derivative since no water was eliminated in its formation. It was not a hydrazide since the ester methoxyl group was retained. The case for its formulation as an addition compound involving the unsaturated ester system is weakened considerably by the fact that its ultraviolet spectrum did not indicate disruption of the unsaturated ester system. Rather, the observed curve was merely the algebraic sum of the curves for alstonine hydrochloride and 2,4-dinitrophenylhydra-

[2] This reaction was first noted by Dr. B. M. Pitt of these laboratories, and has been repeated by the present authors.

zine in hydrochloric acid. The substance, therefore, appears to be merely a molecular addition compound.

EXPERIMENTAL[3, 4]

Tetrahydroalstonine. This was prepared most conveniently by an unpublished procedure developed by Leonard in these laboratories.

A solution of 4.0 g. of alstonine hydrochloride (15) in 200 ml. of absolute methanol was brought to about *p*H 10 with 10% potassium hydroxide under an atmosphere of nitrogen. Reduction was then carried out as rapidly as possible over 0.4 g. of Adams platinum oxide catalyst at 30 lb. hydrogen pressure. The resulting pale yellow solution, after filtering from the catalyst, was concentrated under reduced pressure until precipitation of salts began. Water and a small amount of *N* ammonium hydroxide was added. The precipitate was recrystallized from aqueous ethanol; 3.1 g. of lustrous white plates, m.p. 230–231°; $[\alpha]_D^{27}$ −108° ±2° (*c*, 0.504 in chloroform).

Anal. Calc'd for one C-methyl: 4.3. Found: 4.3.[5]

Tetrahydroalstonol. A solution of 2.09 g. of dry tetrahydroalstonine in 15 ml. of tetrahydrofuran (distilled twice from sodium and stored over sodium) was added dropwise with stirring to a suspension of 0.675 g. of lithium aluminum hydride in 40 ml. of anhydrous ether. Addition required less than 15 minutes with no external cooling. Stirring was continued and the reaction mixture was heated to gentle reflux for one hour. After cooling in an ice-bath, water was added dropwise to decompose the excess lithium aluminum hydride. After addition of 30 ml. of 10% sodium hydroxide, the ether and tetrahydrofuran were distilled off under reduced pressure under nitrogen. The white precipitate was washed with a large volume of water and exhaustively extracted with hot alcohol. From the alcohol extract after addition of water and cooling, 1.35 g. of almost white needles separated. After recrystallization from dilute alcohol, tetrahydroalstonol formed long colorless needles, m.p. 226–227° (dec.); $[\alpha]_D^{27}$ −145 ±2° (*c*, 1.01 in pyridine).

Anal. Calc'd for $C_{20}H_{24}N_2O_2$: C, 74.0; H, 7.5; N, 8.6.

Found: C, 73.6, 73.9, 73.9; H, 7.6, 7.2, 7.3; N, 8.7.

Anhydrotetrahydroalstonol picrate. When preparation of the picrate of tetrahydroalstonol was attempted in the usual manner in hot 95% alcohol, the picrate of anhydrotetrahydroalstonol slowly crystallized, m.p. 198–202° (dec.). On recrystallization from absolute alcohol, it formed long, soft, light yellow needles which became black at 223–225° and finally melted at 225.5–226°.

Anal. Calc'd for $C_{20}H_{22}N_2O \cdot C_6H_3N_3O_7$: C, 58.3; H, 4.7; N, 13.1; C—CH_3, 2.8.

Found: C, 58.3, 58.4, 58.3, 58.4; H, 4.5, 4.9, 4.8, 4.6; N, 12.8, 13.2; C—CH_3, 2.6.

When decomposition of this picrate with methanolic potassium hydroxide solution was attempted, only brown amorphous material which could not be crystallized was obtained.

Anhydrotetrahydroalstonol methiodide. When 50 mg. of tetrahydroalstonol was refluxed with 2 ml. of methyl iodide in sufficient alcohol to effect solution, the methiodide of the anhydro compound was formed. After three recrystallizations from absolute alcohol-ethyl acetate, it formed colorless rods, m.p. 270–271° (dec.).

Anal. Calc'd for $C_{20}H_{22}N_2O \cdot CH_3I$: C, 56.3; H, 5.6; N, 6.3; I, 28.3.

Found: C, 56.7; H, 6.0; N, 6.5; I, 28.7.

Action of acetic anhydride on tetrahydroalstonol. The procedure which was used by Leonard and Elderfield (1) for the acetylation of hexahydroalstonol was employed. To a solution

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[3] All melting points are corrected for stem exposure.

[4] Microanalyses were performed by The Clark Microanalytical Laboratories, Urbana, Ill., Dr. Francine Schwarzkopf, Elmhurst, L. I., or the Micro-tech Laboratories, Skokie, Ill.

[5] When the oxidation was carried out in a bomb tube, only 0.5% of C-methyl was noted. The result reported was obtained by the reflux method.

of 100 mg. of tetrahydroalstonol in 5 ml. of dry pyridine 1 ml. of freshly distilled acetic anhydride was added. After standing in the dark at room temperature for five days, the yellow-orange solution was concentrated under reduced pressure. The brown resinous solid resisted all attempts at crystallization. However, it formed a picrate in good yield which after one recrystallization from alcohol formed long, soft, yellow needles identical in appearance with anhydrotetrahydroalstonol picrate. The m.p., 224–226° (dec.) was not depressed on admixture with anhydrotetrahydroalstonol picrate.

Action of p-toluenesulfonyl chloride on tetrahydroalstonol. When tetrahydroalstonol was allowed to stand with *p*-toluenesulfonyl chloride in dry pyridine at room temperature overnight an amorphous brown solid was obtained which could not be crystallized. Anhydrotetrahydroalstonol picrate was obtained from this. The m.p., 223–226° (dec.), after one recrystallization from alcohol was not depressed on admixture with an authentic sample.

Tetrahydroalstonyl ethyl ether. To a boiling solution of 108 mg. of tetrahydroalstonol in 5 ml. of absolute alcohol was added 0.2 ml. of 90% formic acid. The color of the solution became greenish-yellow immediately. The solution was refluxed for 30 minutes, cooled, and made basic with 3 ml. of 10% potassium hydroxide in methanol. On addition of water 100 mg. of white amorphous material, m.p. 140–155° (dec.) was obtained. The m.p. was not substantially improved by recrystallization from hexane, but after five recrystallizations from dilute alcohol, tiny white needles, m.p. 187–189° (dec.) were obtained. The analytical sample was dried at 80° *in vacuo* over phosphorus pentoxide. Further drying at 100° for four hours caused no loss in weight, indicating that the ethoxyl was not present as alcohol of crystallization.

Anal. Calc'd for $C_{20}H_{23}N_2O \cdot OC_2H_5$: C, 75.0; H, 8.0; N, 8.0; OC_2H_5, 12.8.
Found: C, 74.8; H, 8.0; N, 8.1, 8.0; OC_2H_5, 12.1.

The *picrate* prepared from the above substance melted at 225–226° (dec.) and was identical with anhydrotetrahydroalstonol picrate.

Anal. Calc'd for $C_{26}H_{22}N_2O \cdot C_6H_3N_3O_7$: C, 58.3; H, 4.7; N, 13.1.
Found: C, 58.2; H, 5.2; N, 13.2.

The *methiodide* of the compound, prepared by refluxing the base in methyl iodide, gave analytical figures indicating retention of the ethoxyl group. After five recrystallizations from absolute alcohol-ethyl acetate, it formed almost white crystals, m.p. 222–223° (dec.).

Anal. Calc'd for $C_{20}H_{23}N_2O \cdot OC_2H_5 \cdot CH_3I$; C, 55.9; H, 6.3; N, 5.7; I, 25.7.
Found: C, 55.5, 56.0; H, 6.4, 6.2; N, 6.2; I, 25.1.

Desoxyhexahydroalstonol. Catalytic reduction of tetrahydroalstonol. Reduction of tetrahydroalstonol over Adams platinum oxide under neutral conditions could not be accomplished. In one experiment a solution of 125 mg. of tetrahydroalstonol in 15 ml. of twice-distilled methanol was introduced into an all glass hydrogenation apparatus containing 50 mg. of previously reduced catalyst, from a batch of known activity. No uptake of hydrogen was noted after shaking for 48 hours. The solution had turned yellow, and some decomposition had evidently occurred as only 90 mg. of tetrahydroalstonol was recovered.

When a solution of 125 mg. of tetrahydroalstonol in 15 ml. of absolute methanol and 8 ml. of purified glacial acid was shaken over platinum oxide, hydrogen uptake proceeded smoothly until it ceased after about seven hours. In one experiment 3.4 moles of hydrogen and in another 3.8 moles were absorbed. After filtration from the catalyst, the solvent was steam-distilled *in vacuo* under nitrogen. The aqueous residue was extracted with ether and the ether extract was washed with 5% sodium hydroxide solution and water, and dried over magnesium sulfate.

The aqueous solution remaining from the ether extraction was made strongly basic with 5% sodium hydroxide, and the oil which separated was extracted with ether. After drying and removal of the solvent, 50 mg. of resinous material which resisted crystallization was obtained.

The original ether extract yielded 70 mg. of a white crystalline substance which formed long colorless needles on recrystallization from alcohol-water. It darkened above 245° and melted with decomposition at 253–256°.

Anal. Calc'd for $C_{20}H_{26}N_2O$: C, 77.4; H, 8.4; N, 9.0.
Found: C, 77.3; H, 8.6; N, 9.0.

The *picrate* crystallized from absolute alcohol as orange-yellow rods, m.p., 215–217° (dec.).

Anal. Calc'd for $C_{20}H_{26}N_2O \cdot C_6H_3N_3O_7$: C, 57.9; H, 5.4; N, 13.0.
Found: C, 57.8, 58.1; H, 5.9, 5.3; N, 12.4, 12.6.

In an attempt to determine the effect of acetic acid on tetrahydroalstonol, 100 mg. of the substance was dissolved in 3.5 ml. of absolute ethanol and 1.5 ml. of glacial acetic acid was added. After standing at room temperature for five hours, addition of alkali and water precipitated 84 mg. of semi-crystalline material, m.p. 190–220° (dec.). After recrystallization from dilute alcohol white needles of tetrahydroalstonol, m.p. 225–227° (dec.) alone and mixed, were obtained.

Ozonization of tetrahydroalstonine. Careful control of experimental conditions was found to be essential for successful ozonolysis and for the reduction of the amount of tar formed. Use of about 0.8 to 1 mole of ozone per mole of tetrahydroalstonine appeared to give optimum results. When ozone up to 2 moles per mole of tetrahydroalstonine was used, the yield of product decreased and the amount of tars formed increased. The success of the reaction was notably dependent on the rate of flow of the gas as well as on the total amount of ozone. At relatively rapid rates—10 to 20 liters of oxygen containing 5% of ozone—tarring was extremely marked and satisfactory yields of crystalline material could not be obtained. Rates of gas flow of 500 to 1000 ml. per hour seemed to give the best results.

A small homemade ozonizer[6] was found suitable. This consisted essentially of a piece of 6-mm. glass tubing about 18 in. long, inside of which was fastened a length of copper wire and around the outside of which about 25 turns of wire were wrapped. The inner wire was connected to a Tesla coil and the outer wire was grounded. When a commercial ozonizer was used, the results were unfavorable.

A stream of ozonized oxygen containing 6 to 7% of ozone was passed through a solution of 950 mg. of tetrahydroalstonine in 40 ml. of glacial acetic acid and 5 ml. of water cooled in an ice-bath at the rate of 600 ml. per hr. for 80 minutes. Practically quantitative absorption of ozone occurred. In one experiment the effluent gas was passed through a solid carbon dioxide trap and in another through a barium hydroxide solution. Neither volatile carbonyl compounds nor carbon dioxide could be detected.

At the end of the reaction, the deep orange solution was shaken with 3 g. of zinc dust. It gave a negative test for peroxide with starch-potassium iodide paper. During this treatment the flask was connected to a solution of dimedon in aqueous alcohol. Although the reaction mixture was finally warmed on the steam-bath no volatile aldehydes were detected.

The zinc dust was filtered off and washed with a small amount of fresh acetic acid. The acetic acid was steam-distilled from the filtrate *in vacuo* under nitrogen. The colorless distillate did not decolorize a drop of 2% permanganate solution during an hour, indicating the absence of formic acid, and gave no test with 2,4-dinitrophenylhydrazine. The aqueous residue was acidified with hydrochloric acid and extracted with ether. From the ether extract only a trace of dark resin remained.

Solid sodium carbonate was added to the acid solution from the above ether extraction to *p*H 8 or 9. Orange resinous material separated. The solution was extracted continuously with ether. The ether extract was washed with one 10-ml. and two 5-ml. portions of 5% sodium hydroxide solution. After drying the ether solution it was evaporated to 15 ml. and chromatographed through a column of Fisher absorption alumina, 80–200 mm. Elution of the column with anhydrous ether gave 130 mg. of tetrahydroalstonine.

The dark colored sodium hydroxide extract obtained above was neutralized with 10% hydrochloric acid with cooling. After adjusting the *p*H to 8 with sodium carbonate, a greyish solid precipitated. After recrystallization from dilute alcohol, 112 mg. of soft white needles were obtained. The substance softened and darkened above 170°, became a red bub-

[6] Obtained through the courtesy of Mr. M. A. Fugier of these laboratories.

bly mass at 183–185° and turned to a black melt above 190°. $[\alpha]_D^{27}$ 113 ±3° (*c*, 0.477 in chloroform).

Anal. Calc'd for $C_{20}H_{22}N_2O_4$: C, 67.8; H, 6.3; N, 7.9; OCH_3, 8.8; C—CH_3, 4.2.
Found: C, 67.7; H, 6.5; N, 7.7; OCH_3, 7.6, 8.8; C—CH_3, 5.2.[7]

The *hydrochloride* of the above compound was prepared in chloroform and recrystallized first from moist alcohol and finally from methanol-ethyl acetate. It formed clumps of microscopic needles which darkened above 240° and melted at 268–270° (dec.).

Anal. Calc'd for $C_{20}H_{22}N_2O_4 \cdot HCl$: C, 61.4; H, 5.9; N, 7.2; Cl, 9.1.
Found: C, 61.3; H, 5.8; N, 7.3; Cl, 8.7.

The *picrate* formed tiny needles from absolute alcohol, m.p. 202–203° (dec.).

Anal. Calc'd for $C_{20}H_{22}N_2O_4 \cdot C_6H_3N_3O_7$: C, 53.5; H, 4.3; N, 12.0.
Found: C, 54.0, 54.0; H, 4.3, 4.3; N, 11.4.

The ozonolysis product gave no derivative with 2,4-dinitrophenylhydrazine or hydroxylamine. It gave a negative test for an enol with alcoholic ferric chloride and was too weak an acid to be titrated potentiometrically with 0.02 *N* sodium hydroxide. It was unattacked by acetic anhydride in pyridine, and *p*-toluenesulfonyl chloride in pyridine caused the formation of a black tar. When a chloroform solution of the compound was allowed to stand with diazomethane in the dark, about half of the material was recovered unchanged. The remainder was an alkali-insoluble tar which could not be crystallized.

Reaction of alstonine with 2,4-dinitrophenylhydrazine. A solution of 104 mg. of alstonine hydrochloride and 104 mg. of 2,4-dinitrophenylhydrazine in 30 ml. of absolute ethanol and 0.4 ml. of conc'd hydrochloric acid was boiled under reflux for one hour. On cooling small yellow-brown plates separated from the solution. After recrystallization from absolute alcohol they melted at 228–230° (dec.).

Anal. Calc'd for $C_{21}H_{20}N_2O_3 \cdot C_6H_6N_4O_4 \cdot HCl$: C, 52.4; H, 4.6; N, 13.6; Cl, 11.4; OCH_3, 5.0.
Found: C, 52.5; H, 4.9; N, 13.4; Cl, 11.1; OCH_3, 5.4.

When an aqueous solution of 10 mg. of this compound was made alkaline, the characteristic blue color of the 2,4-dinitrophenylhydrazine anion appeared and disappeared after a few seconds. No precipitate of alstonine formed.

Yohimbyl alcohol. Method A. The alcohol was first prepared by a modification of the procedure described by Schomer (5). To a boiling solution of 10 g. of yohimbine (from Mallinckrodt yohimbine hydrochloride which was recrystallized) in 500 ml. of anhydrous *n*-butanol, 26 g. of sodium was added with stirring. When all of the sodium had dissolved, the cooled solution was poured into 900 ml. of 5% hydrochloric acid and ice. The butanol was steam-distilled under reduced pressure in nitrogen and the residual aqueous solution was made ammoniacal which precipitated orange resinous material. This was extracted into chloroform-alcohol, and the extract was concentrated to dryness. The residue was dissolved in absolute alcohol, the solution was warmed on the steam-bath, and dry hydrogen chloride was passed through it. Yohimbyl alcohol hydrochloride (2.5 g.) separated as yellowish needles. After recrystallization from absolute methanol, the salt melted at 306–309° (dec.). $[\alpha]_D^{27}$ 34 ±3° (*c*, 0.371 in water). Schomer (5) reports $[\alpha]_D^{29}$ 37.5° but gives no m.p.

Anal. Calc'd for $C_{20}H_{26}N_2O_2 \cdot HCl$: C, 66.2; H, 7.2.
Found: C, 65.9; H, 7.7.

Method B. Yohimbyl alcohol was prepared in 85–90% yield by reduction of yohimbine with lithium aluminum hydride using essentially the same procedure described above for the preparation of tetrahydroalstonol [*cf.* also (9)].

On making an aqueous solution of yohimbyl alcohol hydrochloride ammoniacal, the base separated as small colorless plates which softened at 152–155°, rehardened at about 175°, and finally melted at 204–206° (dec.). Schomer (5) describes yohimbyl alcohol as a hydrate

[7] In checking their procedure, the Schwarzkopf Laboratory also obtained a somewhat high terminal methyl value (4.9%) for tetrahydroalstonine. The terminal methyl values on tetrahydroalstonine and anhydrotetrahydroalstonol picrate reported earlier were obtained by the Clark Microanalytical Laboratories.

which softens at 148–149° and melts at 202°. When dried at 80° over phosphorus pentoxide no change in melting behavior was observed. The compound is a hemihydrate.

Anal. Calc'd for $C_{20}H_{26}N_2O_2 \cdot 0.5\ H_2O$: C, 71.6; H, 8.1; N, 8.4.

Found: C, 71.4; H, 8.0; N 8.1.

On recrystallization of the hemihydrate from dilute alcohol, although the hydrate was occasionally recovered, most frequently a monoalcoholate crystallized as white needles. After drying at 80° *in vacuo*, the monoalcoholate softened at 127–128° and melted at 206–208° (dec.). $[\alpha]_D^{25}$ 11 ±1° (*c*, 0.991 in pyridine).

Anal. Calc'd for $C_{20}H_{26}N_2O_2 \cdot C_2H_5OH$: C, 70.9; H, 8.7; N, 7.5; Neut. equiv., 373.

Found: C, 70.8; H, 8.5; N, 7.6; Neut. equiv., 373.

Further data on the solvates of yohimbyl alcohol is given in Table I.

Yohimbyl alcohol mono-p-toluenesulfonate. To a cooled solution of 2 g. of yohimbyl alcohol monoalcoholate (the hemihydrate gave equally satisfactory results) in 10 ml. of dry pyridine a solution of 2.1 g. of distilled *p*-toluenesulfonyl chloride in 5 ml. of pyridine was added dropwise with stirring. After stirring for four hours, chloroform and absolute alcohol were added and the solvents were removed in *vacuo*. The solid residue was taken up in absolute alcohol and the red solution was made alkaline with 5 % sodium hydroxide solution. Addition of several volumes of water gave a white precipitate which was recrystallized from absolute alcohol yielding 2.3 g. of white needles; these had no definite m.p. but gradually softened and decomposed above 133°, $[\alpha]_D^{29}$ 11 ±2° (*c*, 0.470 in pyridine). The substance contained an alcohol of crystallization which was not lost on drying at 80° *in vacuo*, but was lost at 100°.

Anal. Calc'd for $C_{27}H_{32}N_2O_4S \cdot C_2H_5OH$: C, 66.1; H, 7.3; N, 5.3; S, 6.1.

Found: C, 66.3, 66.3; H, 6.8, 7.1; N, 5.3; S, 6.2.

Yohimbyl trimethylammonium-p-toluenesulfonate. A solution of 3.05 g. of the above *p*-toluenesulfonate monoalcoholate and 5 ml. of liquid trimethylamine in 25 ml. of benzene was heated in a pressure bottle on the steam-bath for 1½ hours. After cooling, excess trimethylamine was distilled off and the yellowish crystals were washed with cold benzene. After four recrystallizations from alcohol-ethyl acetate, the colorless needles began to darken at 180° and decomposed to a red mass at 190–193°.

Anal. Calc'd for $C_{23}H_{34}N_3O \cdot C_7H_7O_3S$: C, 66.8; H, 7.7; N, 7.8; S, 5.9.

Found: C, 66.2; H, 7.8; N, 7.7; S, 6.1.

The Zerewitinoff active hydrogen determinations were done in an apparatus designed in these laboratories (16). Anisole was the solvent for the methyl Grignard reagent, and dry pyridine for the compound under examination. Excess aniline was used to estimate the amount of addition of the Grignard reagent.

The infrared spectra. Most of the spectra reported were obtained with a Perkin-Elmer spectrophotometer equipped with an automatic recorder.[8] The spectrum of the ozonolysis product was determined with a Perkin-Elmer instrument which had been refined with a split beam arrangement and detector of increased sensitivity (17). In all cases a rock salt prism was used.

The samples were run at a concentration of 30 mg./ml. in dry chloroform with a cell (sodium chloride) thickness of 0.1 mm. To obtain the film spectra, the compounds were dissolved in a suitable solvent (chloroform or pyridine) and the solutions were evaporated to a solid film on a silver chloride plate. The films, made as nearly uniform in thickness as was feasible, were dried at 80° *in vacuo* over phosphorus pentoxide before being run.

A satisfactory spectrum of alstonine could not be obtained with a solid film because so much tar formation occurred during preparation of the film as to render it almost opaque. Therefore, an aqueous solution of its salt was made alkaline, the alkaloid was extracted into chloroform, and the solution was dried over magnesium sulfate and then run.

The 5-carbomethoxyharman used was prepared by Dr. H. A. Hageman in these laboratories.

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[8] The help of Professor T. I. Taylor is gratefully acknowledged.

The ultraviolet spectra were obtained using a Beckman model DU quartz spectrophotometer with 95% alcohol as solvent.

SUMMARY

Alstonine and some of its derivatives have been examined further. Structures for alstonine and tetrahydroalstonine have been proposed.

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