[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

ALSTONIA ALKALOIDS. I. DEGRADATION OF ALSTONINE TO β-CARBOLINE BASES AND THE REDUCTION OF TETRAHYDROALSTONINE WITH SODIUM AND BUTYL ALCOHOL

NELSON J. LEONARD AND ROBERT C. ELDERFIELD

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The bark of various species of *Alstonia* has enjoyed a local reputation as a febrifuge in the treatment of malaria for a number of years in China and the Pacific Islands. Studies on the total alkaloids isolated from the bark of two varieties, *Alstonia constricta* and *Alstonia scholaris* (1) led to the conclusion that perhaps a slight action on birds infected with *Plasmodium inconstans* was present in both cases, with the alkaloids of the latter being somewhat more potent than those of the former. Furthermore, similar studies on individual alkaloids isolated from certain species (1, 2) have failed to substantiate the purported action attributed to the barks. However, since it has been a somewhat common experience that native remedies in the past occasionally have a sound basis for use, and since knowledge of the chemistry of these alkaloids is scanty, it appeared worth while to undertake a new investigation of the latter subject. At the same time the question of isolation and characterization of alkaloids hitherto not well described, has been studied (3). From results obtained so far on the latter phase of the work, it appears that the alkaloidal constituents of *Alstonia constricta* are unusually susceptible to atmospheric oxidation, and that the observed pharmacological action of total alkaloid fractions or of individual constituents thereof, may not be representative of the action of freshly prepared infusions of the bark. Furthermore, it was felt that elucidation of the structure of the constituent alkaloids might suggest new approaches to the preparation of antimalarial agents by modification of the molecules.

In the present communication we wish to present the results of certain phases of the study of alstonine obtained from *Alstonia constricta*. The bark used was purchased on the open market and was identified as that of *Alstonia constricta*, F. Muell. by Dr. Heber W. Youngken, of Boston, Mass. Alstonine was isolated in the earlier work according to Sharp (2a) and later by a procedure developed in these laboratories (3).

The early investigations on this alkaloid have been adequately reviewed by Sharp, who, at the same time, investigated several of its reactions (2a, 4). The formula, $C_{21}H_{20}N_2O_3$, was accepted for the base, on the basis of analyses of various salts, although for the nitrate, hydrochloride, and acid sulfate, the figures obtained agreed better with the formula, $C_{22}H_{22}N_2O_3$. The free base could not be obtained crystalline, although hydrates of the base were described as crystalline. The presence of one methoxyl group in the form of a methyl ester, one basic tertiary nitrogen atom, and one apparently inert nitrogen atom, was noted. Alstonine does not contain an N-alkyl group, and neither phenolic nor alcoholic hydroxyl groups. On catalytic reduction with platinum oxide, tetrahydroal-

stonine was formed, although it was reported that salts of the base were not reduced under similar conditions. The methyl ester group of tetrahydroalstonine was described as being very resistant to alkaline hydrolysis, suggesting a quaternary carbomethoxy group. Tetrahydroalstonine is unaffected by acetic anhydride, benzoyl chloride, and semicarbazide, as is alstonine, and is little affected by hydrobromic acid. Sharp also noted the formation of a dibromide by substitution when alstonine sulfate was treated with bromine water. At the same

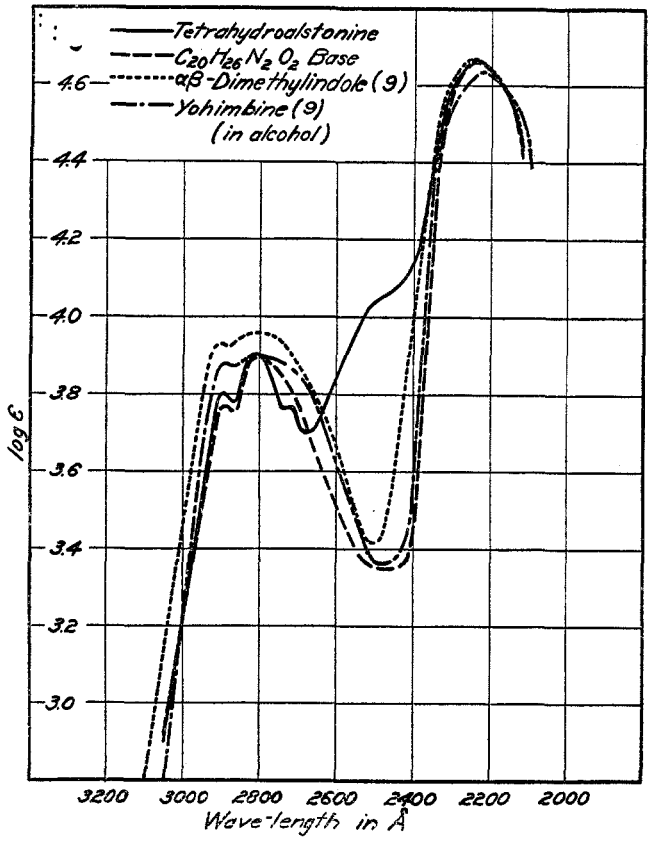


FIGURE 1

time an oxygen atom was introduced. No clue to the structure of this substance was obtained by a study of its catalytic reduction. However, when alstonine was oxidized with permanganate, oxalic acid and N-oxalylanthranilic acid were obtained, from which Sharp concluded that either an indole or quinoline nucleus was present in the alkaloid. On selenium dehydrogenation, a base, alstyrine, to which the formula, $C_{19}H_{22}N_2$ or $C_{18}H_{20}N_2$, was assigned, was obtained. Finally, attempted exhaustive methylation, by a variety of procedures, of alstonine, tetrahydroalstonine, and alstyrine did not result in elimination of nitrogen, although poorly defined products of an indole-like nature were obtained from the latter.

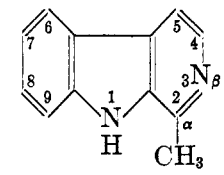
At the start of the present work, a clue to the presence of a tetrahydro-β-carboline ring system in tetrahydroalstonine was furnished by the observation that this base gave a color similar to that obtained with yohimbine in the Adamkiewicz test, as modified by Harvey, Miller, and Robson (5), who noted development of a similar color with other tetrahydro-β-carbolines. The color developed at the interface of a solution of the compound in glacial acetic acid plus half a drop of 10% ferric chloride solution, layered on concentrated sulfuric acid, was taken as the test. Tetrahydroalstonine and yohimbine both showed an original blue to violet color which changed through green to a final yellow green. It is interesting that salts of alstonine give only a yellow color. Likewise the ultra-violet absorption curve for yohimbine and tetrahydroalstonine showed similarity except for the inflection point at about 2500 Å displayed by the latter (Fig. 1). The presence of a β-carboline ring system in tetrahydroalstonine and alstonine was definitely confirmed by the nature of the products formed on various degradations of both substances.

When alstonine was fused with potassium hydroxide, no volatile amine was noted, and from the fusion mixture, harman (I) was isolated. No significant amount of neutral product was formed, and while a considerable acid fraction was found, it has not been possible to isolate any pure substance from this at present.

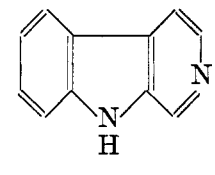
On the other hand, when tetrahydroalstonine was similarly fused with potassium hydroxide, several products were isolated. Harman (I), as well as norharman (II), was found in the basic fraction. In addition to these bases, three other bases have been isolated, but with the amounts available it has not been possible to identify them at present, although tentative empirical formulas are suggested. The separation of the above five bases was achieved by chromatographic adsorption on aluminum oxide, as described in detail in the experimental part. The first of the three unidentified bases, Base A, is assigned the formula, $C_{17}H_{16}N_2$, on the basis of analyses of the free base and its picrate. In alcoholic hydrochloric acid solution it shows a strong blue fluorescence and it is probably a substituted β-carboline. Base B is assigned the tentative formula, $C_{16}H_{16}N_2$, or $C_{16}H_{18}N_2$, on the basis of analysis of its picrate. It likewise showed a blue fluorescence in hydrochloric acid solution, as did Base C, to which is assigned the tentative formula, $C_{17}H_{18}N_2$, on the basis of analysis of its picrate. From the acidic products of the fusion, indole-α-carboxylic acid (III) was isolated. No pure substance could be isolated from the neutral fraction, although the general behavior of this part suggested the presence of indole derivatives.

Thermal decomposition of alstonine likewise resulted in the formation of a variety of bases, all apparently derived from β-carboline, although none of them has been definitely identified. The bases were separated by fractional crystallization of their picrates. The picrate of one of these substances (Base D) is characterized by its extreme insolubility in alcohol, and was easily isolated, although in small amounts. The picrate furnished analytical figures corresponding to those required for the picrate of a base of formula, $C_{17}H_{18}N_2$. However, this picrate melts some 50° higher than the picrate of the above Base C, and the

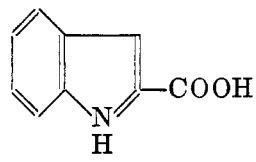
crystalline form of the two is different. The two bases, therefore, can be considered isomeric. The most soluble of the three picrates furnished analytical figures agreeing with those required for the picrate of a base of composition, $C_{18}H_{20}N_2$, or $C_{19}H_{22}N_2$ (Base E). The two suggested formulas are the same as those put forward by Sharp (4) for alstyrine. However, identity of Base E with alstyrine is unlikely since the picrates differ both in melting point and crystalline form. The third base (Base F) was formed in relatively larger quantities. It is



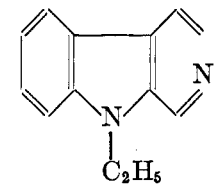
I



II



III



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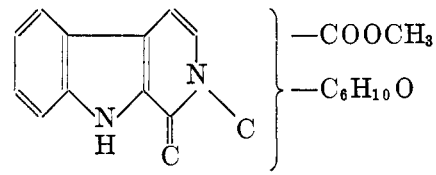

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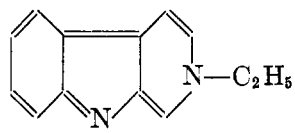

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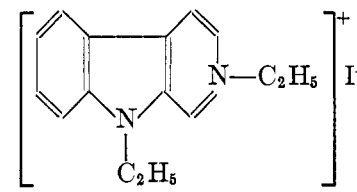

VII

assigned the formula, $C_{13}H_{12}N_2$, on the basis of analysis of the free base, its picrate, and methiodide. The hydrochloride exhibits a strong blue fluorescence in water or alcohol solution. The ultra-violet absorption curve for Base F shows close similarity to that for 2-ethyl-β-carboline (Fig. 2), from which it may be concluded that a β-carboline structure is present. Of the β-carboline derivatives of empirical formula corresponding to Base F, 2-ethyl-β-carboline (6), 1,2-dimethyl-β-carboline (6), and 2,3-dimethyl-β-carboline (7) are known and are not identical with Base F. Since an N-alkyl determination indicated the possible presence of an N-ethyl group, 1-ethyl-β-carboline (IV) was synthesized by a

combination of the procedures of Manske (8) and Späth and Lederer (6) for the preparation of the corresponding methyl derivative, and was not identical with Base F. Likewise 3-ethyl-β-isocarboline (VI) was prepared and was not identical with Base F.

When alstonine was distilled with zinc dust, the only product isolated was a base presumably identical with Base F, although this identification is not unequivocal.

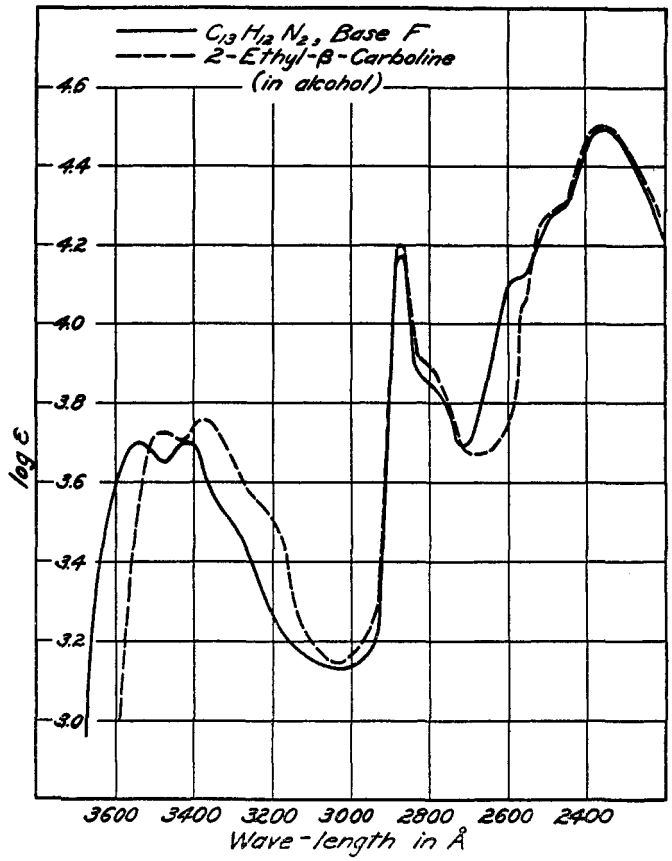

FIGURE 2

We have also investigated the reduction of tetrahydroalstonine with sodium and butyl alcohol. In the preparation of tetrahydroalstonine, our results agree with those of Sharp, in that while alstonine itself in methanol solution readily absorbs two moles of hydrogen in the presence of platinum oxide catalyst, alstonine hydrochloride in methanol and alstonine in acetic acid solution are not reduced with the same catalyst. Further, a methanol solution of alstonine is not reduced in the presence of palladium black. When tetrahydroalstonine was further reduced with sodium and butyl alcohol, the methyl ester group was re-

duced to a primary alcohol and an additional mole of hydrogen was introduced into the molecule. The reduction product, for which we suggest the name hexahydroalstonol, has the empirical formula, $C_{20}H_{26}N_2O_2$. The newly formed primary alcoholic hydroxyl group can be easily acetylated, which contrasts with the reported difficult hydrolysis of the ester group in tetrahydroalstonine. While the ultra-violet absorption curve for the new base clearly indicates that it is an α,β-disubstituted indole (Fig. 1), the relationship of tetrahydroalstonine to its reduction product is not so clear. Likewise, the point of addition of the two additional hydrogens is not clear. The two hydrogens in question can conceivably have been taken up by the reduction of a double bond conjugated with either the carbomethoxy group or indole system of tetrahydroalstonine, by the reduction of a $\rangle C{=}O$ or $\rangle C{=}N-$ group, or by the cleavage of an allyl ether type of linkage. It seems unlikely that a double bond occurs in conjugation with the carbomethoxy group; if this were so, such a double bond should have been reduced in the formation of tetrahydroalstonine. Whether a similar argument applies to a double bond conjugated with the indole system must be left open for the present, although the disappearance of the inflection point at 2500 Å in the absorption curve of tetrahydroalstonine on passing to hexahydroalstonol suggests that some sort of conjugation has been attacked. If a $\rangle C{=}O$, $\rangle C{=}N$ or allyl ether had been reduced, an acylatable group should have resulted and acetylation of hexahydroalstonol, under the strong conditions employed, should have resulted in the formation of a diacetate.

At this point it may be profitable to summarize the information at present at hand concerning the structure of alstonine. From the results here obtained the partial formula V appears to be justified. Results of Zerewitinoff active hydrogen determinations indicate the presence of one active hydrogen which is accounted for by the indole hydrogen and failure to detect any hydroxyl groups either by ourselves or Sharp (4). The tertiary nature of the pyridine nitrogen of the β-carboline system is indicated by the failure of both alstonine and tetrahydroalstonine to show reactions characteristic of both primary and secondary amines. Furthermore, the number of active hydrogens is the same in both alstonine and tetrahydroalstonine, indicating that the basic nitrogen function does not undergo any change on catalytic reduction. The presence of two double bonds closely adjacent to the indole nucleus is indicated by the easy formation of tetrahydroalstonine, although some tautomeric shift of these double bonds must occur when the salts of the base are formed because of the failure of the latter to undergo catalytic reduction. Alstonine hydrochloride absorbs ultraviolet light of longer wave length than any of the related compounds with which it is compared in Fig. 3. It may be concluded that alstonine hydrochloride possesses greater conjugation than lysergic acid, where one double bond is conjugated with the benzene ring, and also greater conjugation than 2-ethyl-β-carboline hydrochloride and harmol, where the additional unsaturation lies in the pyridine ring fused to the α- and β-carbons of indole. Since there is a difference

in the absorption curves of 2-ethyl-β-carboline and its hydrochloride (*cf.* Figs. 2 and 3), there is most likely a difference between the absorption curve of alstonine and that of its hydrochloride. The absorption spectrum of alstonine itself could not be measured because of the instability of the free base, but the probability of the difference in spectra is borne out by the visible difference in the color of alstonine and of its salts; the former is a deeper orange, both as a solid and in solution. The nature of the third oxygen atom remains unknown. Furthermore, the exact location of the double bond external to the indole nucleus in

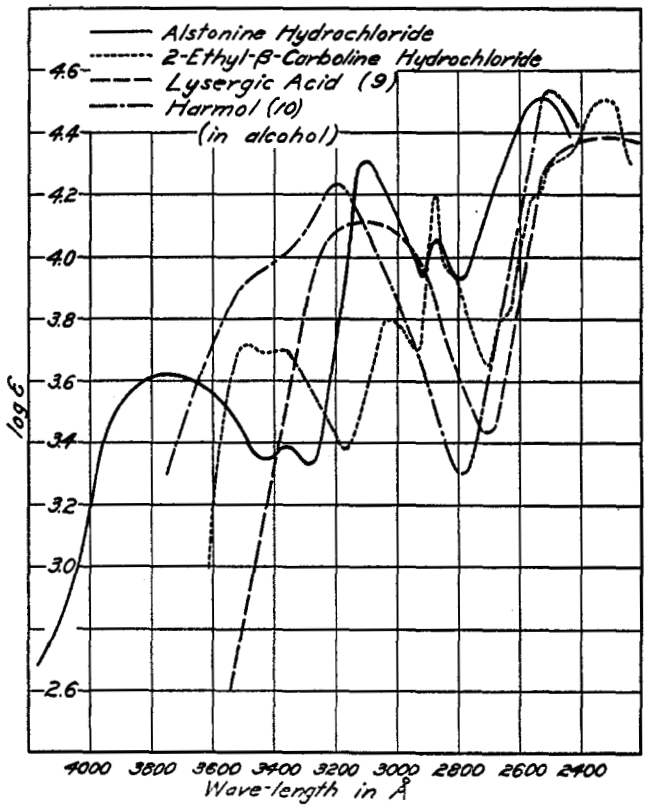

FIGURE 3

tetrahydroalstonine must be left open for the present. It is also now possible to formulate the entire ring structure of alstonine as either a tetracyclic or pentacyclic system, depending on the nature of the oxygen atom not accounted for.

Through the kind cooperation of Dr. John Maier of the Rockefeller Foundation, pharmacological tests were performed and it was found that alstonine is inactive in doses of 35 mg. per day in birds infected with avian malaria.

EXPERIMENTAL

All melting points are corrected for stem exposure.

Alstonine was originally obtained from the dry, powdered *Alstonia constricta* bark, according to the method of Sharp (2a), but later according to a modification developed in

this laboratory (3). Salts were prepared for identification purposes and in order to establish definitely the empirical formula which was left in some doubt from the analyses obtained by Sharp for the hydrochloride, nitrate, and acid sulfate.

Alstonine sulfate (*dihydrate*) crystallized as yellow prisms from absolute alcohol, melted at 195–196°, and foamed at 208°; $[\alpha]_D^{25}$ 127° ± 2° (c = 0.492 in water); $[\alpha_M]_D^{25}$ 527°.

Anal. Calc'd for $(C_{21}H_{20}N_2O_3)_2H_2SO_4 \cdot 2H_2O$: C, 60.7; H, 5.6; N, 6.7; S, 3.9.
Found: C, 60.4; H, 5.9; N, 6.4; S, 4.0.

Alstonine sulfate (*tetrahydrate*) formed nearly colorless needles from absolute alcohol-ethyl acetate and melted at 203–204°; $[\alpha]_D^{25}$ 120° ± 2° (c = 0.548 in water); $[\alpha_M]_D^{25}$ 520°.

Anal. Calc'd for $(C_{21}H_{20}N_2O_3)_2H_2SO_4 \cdot 4H_2O$: C, 58.2; H, 5.8; N, 6.4.
Found: C, 58.6; H, 5.6; N, 6.3.

Alstonine acid sulfate crystallized as yellow rosettes of prisms from absolute alcohol and melted at 243–244° with decomposition; $[\alpha]_D^{25}$ 120° ± 2° (c = 0.588 in water); $[\alpha_M]_D^{25}$ 535°. Sharp reports the melting point 246–248° with decomposition and $[\alpha]_D$ 113.1° in water.

Anal. Calc'd for $C_{21}H_{20}N_2O_3 \cdot H_2SO_4$: C, 56.5; H, 5.0.
Found: C, 56.8; H, 5.0.

Alstonine chloroplatinate formed small orange-yellow prisms from absolute alcohol which melted at 220–221° with decomposition.

Anal. Calc'd for $(C_{21}H_{20}N_2O_3)_2 \cdot H_2PtCl_6 \cdot H_2O$: C, 44.8; H, 4.0; Pt, 17.3.
Found: C, 44.5; H, 4.3; Pt, 17.2.

Alstonine hydrochloride crystallized as nearly colorless plates from absolute alcohol-ethyl acetate and melted at 278–279° with decomposition; $[\alpha]_D^{25}$ 141° ± 2° (c = 0.422 in water); $[\alpha_M]_D^{25}$ 545°. Sharp reports the decomposition melting point 286° and $[\alpha]_D$ 131.9° in water. Neutralization equivalent of alstonine hydrochloride: calc'd: 385; found: 391.

Anal. Calc'd for $C_{21}H_{20}N_2O_3 \cdot HCl$: C, 65.5; H, 5.5.
Found: C, 65.5; H, 5.6.

Alstonine nitrate formed stout yellow monoclinic prisms from absolute alcohol and melted at 252–254° with decomposition. Sharp reports the melting point 262–263°.

Anal. Calc'd for $C_{21}H_{20}N_2O_3 \cdot HNO_3$: C, 61.3; H, 5.2.
Found: C, 61.2; H, 5.3.

Alstonine hydriodide formed pale yellow plates from absolute alcohol and melted at 270° with decomposition. Sharp reports 291°.

Anal. Calc'd for $C_{21}H_{20}N_2O_3 \cdot HI$: C, 52.9; H, 4.5.
Found: C, 53.1; H, 4.6.

Alstonine perchlorate crystallized as stout yellow prisms from absolute alcohol and melted at 239–240°.

Anal. Calc'd for $C_{21}H_{20}N_2O_3 \cdot HClO_4$: C, 56.2; H, 4.7.
Found: C, 56.3; H, 4.9.

Tetrahydroalstonine was obtained on reduction of alstonine in absolute methyl alcohol with platinum oxide but not with palladium. No tetrahydroalstonine was obtained on attempted reduction of alstonine salts or of alstonine in acetic acid solution with platinum oxide. The substance formed colorless plates from 90% alcohol and melted at 230–231°; $[\alpha]_D^{26}$ −110° ± 2° (c = 0.672 in chloroform), $[\alpha]_D^{27}$ −88° ± 2° (c = 0.412 in pyridine). Sharp (4) reports the substance as melting at 230–231° and showing $[\alpha]_D$ −107.0° in chloroform. Molecular weight by the Rast method in camphor: calc'd: 352; found: 354.

Fusion of alstonine with potassium hydroxide. An intimate mixture of 10 g. of alstonine hydrochloride and 75 g. of finely-ground potassium hydroxide was placed in a nickel crucible and fused for 1 hr. at 300–350° under a slow stream of nitrogen, with continual stirring. When cold, the melt was dissolved in water and exhaustively extracted with ether. The ether extract contained basic and neutral fractions and was subsequently extracted ten times with 2 *N* hydrochloric acid, after which the ether layer was washed with water. The ethereal solution was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness, leaving a negligible amount of impure neutral material. The combined hydrochloric acid extracts, containing basic compounds as their hydrochloride salts, were made strongly alkaline with sodium hydroxide solution and extracted with ether. The total

ether extract was dried and the solvent removed, leaving 2.2 g. of impure brownish crystals. These were dissolved in 250 cc. of dry benzene and chromatographed on 35 g. of aluminum oxide (Brockmann). The column was eluted exhaustively with dry benzene, and the total benzene eluate was evaporated to dryness, yielding 1.5 g. of white crystals. These were recrystallized five times from benzene; they appeared to have different crystal habits, separating out both as needles and as small regular prisms. The prisms are evidently the more stable form, since the needles, on standing a sufficient length of time either at room temperature or at 0°, reverted to the prismatic form. Both forms melted at 239–241°. The analytical figures, as well as physical properties, correspond to those of harman (11).

Anal. Calc'd for $C_{12}H_{10}N_2$: C, 79.1; H, 5.5; N, 15.4.
Found: C, 79.2; H, 5.7; N, 15.4.

Accordingly, *harman* (2-methyl-β-carboline) was prepared by the method of Kermack, Perkin, and Robinson (11), who did not note the occurrence of the two crystalline forms. Our synthetic material crystallized both as needles and prisms and was exactly similar in properties to the base (I) obtained from alstonine. It melted at 239–241° and the melting point of mixtures of varying percentage composition of the two specimens showed no depression.

For further identification the *picrate*, melting at 257–258° with decomposition after recrystallization from alcohol, the *chloraurate*, melting at 229.5–230° with decomposition after recrystallization from dilute alcohol acidulated with hydrochloric acid, and the *benzal derivative* (11) melting at 204–205°, after recrystallization from dilute alcohol, were prepared from material from both sources. All pairs of these derivatives were identical and showed no depression of melting point when mixed.

While other bases were formed in this reaction, we have been unable to isolate any chemical individual as yet. Likewise, no pure substance has been obtained from the acidic fraction.

Fusion of tetrahydroalstonine with potassium hydroxide. A mixture of 5 g. of pure tetrahydroalstonine and 75 g. of potassium hydroxide was fused in a nickel crucible, under a stream of nitrogen, for one hour above 310°. When cold, the melt was dissolved in water and exhaustively extracted with ether. The ether solution was extracted ten times with 1 *N* hydrochloric acid, and then washed with water, leaving the neutral compounds in the ether. The total acid extract was then made strongly alkaline with sodium hydroxide and extracted with ether. The ethereal solution was dried and the solvent removed, leaving about 500 mg. of basic material, which was distilled *in vacuo* at 140–200° bath temperature and 0.1 to 0.15 mm. The distillate was dissolved in benzene (*ca.* 350 mg. in 175 cc. of dry benzene) and chromatographed on aluminum oxide (Brockmann).

The column was eluted exhaustively with benzene, the benzene removed at atmospheric pressure, and the oily residue kept at 0° for several days. Upon standing, the residue partially crystallized. The crystals were separated mechanically from the oily upper layer and recrystallized twice from ligroin, b.p. 77–116° (Skellysolve D). After two more recrystallizations from petroleum ether, b.p. 60–71° (Skellysolve B), rosettes of needles were obtained (15 mg.), melting at 171.5–172.5°.

Anal. Calc'd for $C_{17}H_{16}N_2$: C, 82.2; H, 6.5.; N, 11.3.
Found: C, 82.4; H, 6.4; N, 11.4.

The *picrate* was prepared in alcohol and recrystallized five times from 90% alcohol, in which it is sparingly soluble. It formed yellow rhombic prisms melting, with decomposition, above 267°.

Anal. Calc'd for $C_{17}H_{16}N_2 \cdot C_6H_3N_3O_7$: C, 57.9; H, 4.0.
Found: C, 58.3; H, 3.8.

The free base (Base A) gives no color with vanillin-hydrochloric acid solution, nor with Ehrlich's reagent. In alcoholic hydrochloric acid solution, it exhibits a strong blue fluorescence. It is probably a substituted β-carboline.

The oily portion of the residue obtained above from the benzene eluate did not crystallize

on long standing at 0°; therefore, the oil was dissolved in absolute alcohol and the basic picrates were precipitated by addition of a saturated picric acid solution in absolute alcohol. The insoluble yellow picrates obtained were once recrystallized from aqueous alcohol and then fractionally crystallized from the same solvent. This was done by taking up the picrates in about 100 cc. of hot 90% alcohol. The material which remained insoluble was in turn recrystallized from a large volume of aqueous alcohol, from which monoclinic rods separated on cooling. These were recrystallized three times from aqueous alcohol and yielded 10 mg. of yellow monoclinic rods which melted at 261°, with decomposition and foaming.

Anal. Calc'd for $C_{16}H_{16}N_2 \cdot C_6H_3N_3O_7$: C, 56.8; H, 4.1; N, 15.1.
Calc'd for $C_{16}H_{18}N_2 \cdot C_6H_3N_3O_7$: C, 56.5; H, 4.5; N, 15.0.
Found: C, 56.6; H, 4.4; N, 15.1.

It is not possible to decide the empirical formula of this substance (Base B) merely on the basis of the analysis of the picrate alone, although $C_{16}H_{18}N_2$ is favored.

The more soluble of the picrates was obtained crystalline upon concentration and cooling of the original 90% alcoholic solution, after previous filtration from the insoluble picrate. The more soluble picrate was then recrystallized five times from absolute alcohol, yielding 15 mg. of long yellow needles which melted with decomposition at 203.5-205.5°.

Anal. Calc'd for $C_{17}H_{18}N_2 \cdot C_6H_3N_3O_7$: C, 57.6; H, 4.4; N, 14.6.
Found: C, 57.6; H, 4.6; N, 14.6.

The empirical formula for this base (Base C) is probably $C_{17}H_{18}N_2$; it is certainly not identical with Base A, of empirical formula, $C_{17}H_{16}N_2$, since their picrates have different crystalline forms and different melting points.

The aluminum oxide column, after benzene elution, was eluted with dry ether. The ethereal solution was evaporated to dryness, leaving 100 mg. of impure crystals. These were recrystallized three times from benzene, giving needles and prisms, with the latter as the stable form, melting at 238–240°. A mixed melting point with an authentic sample of harman was 238–241°, thus proving its identity with *harman* (I). It should be noted that harman is obtained in much smaller yield (100 mg. from 5 g.) from potassium hydroxide fusion of tetrahydroalstonine than from similar fusion of alstonine itself (1.5 g. from 10 g.).

Following ether elution, the aluminum oxide column was eluted with acetone, and 10 mg. of solid crystalline material was obtained upon evaporation of the acetone solution to dryness. After five recrystallizations from benzene, the substance formed white needles (approximately 2 mg.) which melted at 195.5°.

The *picrate* of the above base was made in alcohol solution from the mother liquor obtained above. It was recrystallized, with decolorizing carbon, from alcohol. After eight more recrystallizations from alcohol, golden yellow needles were obtained which melted at 262–263°, with decomposition. The amount of material was insufficient for analysis. However, the melting point of the base was suggestive of that of norharman (II). Therefore, the latter was prepared according to Kermack, Perkin, and Robinson (11), and melted at 196°. The melting point of mixtures of the base in question and norharman was not depressed. Similarly synthetic norharman picrate melted at 261–263° with decomposition and showed no depression of melting point when mixed with the picrate of the above base which is, therefore, *norharman* (β-carboline).

The original potassium hydroxide solution, following fusion, solution, and ether extraction, was made acid to *p*H 3 with hydrochloric acid and thoroughly extracted with ether. The ethereal solution was then extracted in turn with water, 5% sodium bicarbonate, 5% sodium carbonate, and finally with 10% sodium hydroxide solution. Each of the aqueous extracts obtained was subsequently acidified with hydrochloric acid and extracted with ether. Each ether solution was dried and the solvent removed. The ethereal solution obtained from the water-soluble fraction had the odor of a low molecular weight fatty acid, but the residue remaining after removal of the ether underwent decomposition, leaving a dark, oily, intractable tar. The carbonate and hydroxide fractions did not yield any appreciable residues upon evaporation of their respective ether extracts. Upon evaporation of

the ether solution obtained from the bicarbonate fraction, a brown oil remained which was distilled in a vacuum-sublimation apparatus. Two fractions were obtained: (a) 110–170° bath temperature and 0.2 mm.; (b) above 170° bath temperature and 0.2 mm. Decarboxylation took place during the distillation. Fraction (a) was redistilled at the same bath temperature and pressure, and the distillate was recrystallized, with decolorization, from benzene. After five recrystallizations from benzene, 55 mg. of colorless plates was obtained, melting at 205.5–206°.

Anal. Calc'd for $C_9H_7NO_2$: C, 67.0; H, 4.3; N, 8.7.
Found: C, 67.0; H, 4.4; N, 8.7.

The compound gave no color with vanillin-hydrochloric acid reagent and no color with Ehrlich's reagent, indicating that, if it is an indole derivative, it has not a free α-position. The compound was insoluble in cold water, but readily soluble in cold, dilute alkali. It gave a red-brown color with ferric chloride solution. The empirical formula of the acid, its melting point, and crystalline form, together with its chemical properties, suggested its identity with *indole-α-carboxylic acid* (III). Ciamician and Zatti (12) described this acid as separating from benzene as platelets, melting at 203–204° and giving a red-brown color with ferric chloride solution. They also describe the methyl ester as needles melting at 151–152°.

The *methyl ester* of the acid obtained above was prepared according to Ciamician and Zatti, using methyl alcohol saturated with hydrogen chloride. It was recrystallized twice from benzene, from which it was obtained as needles which melted at 150–151.5°. Since the melting point of this methyl ester corresponds to that for methyl indole-α-carboxylate, and since the melting point of the compound in question corresponds to that for indole-α-carboxylic acid, the identity of the acid obtained above may be considered established.

Thermal decomposition of alstonine. Alstonine was freshly prepared from 4 g. of alstonine hydrochloride and the calculated amount of potassium hydroxide. The free alstonine formed (*ca.* 3.6 g.) was dried and heated rapidly in a sublimation apparatus to 300° sand-bath temperature, then kept at 310–330° bath temperature for 1 hr. The sublimate was dissolved in ether and the solution was extracted five times with 10% hydrochloric acid. The ethereal solution was then washed with water, dried, and evaporated to dryness. The neutral residue, in alcoholic solution, gave a blue-violet color with Ehrlich's reagent reminiscent of β-substituted indoles such as skatole. No attempt was made to purify this small amount of neutral material pending accumulation of larger amounts.

The combined hydrochloric acid extracts were made alkaline with sodium hydroxide, extracted with ether, and the ethereal solution was dried and evaporated to dryness. The residue was distilled over a wide temperature range *in vacuo* and then redistilled at 120–170° bath temperature and 0.15 mm. pressure. The sticky orange distillate was dissolved in alcohol and treated with a saturated alcoholic solution of picric acid, yielding a copious yellow precipitate. The precipitated picrates were separated by fractional crystallization, following the course of the separation by means of melting points and microscopic examination of the crystals obtained at each crystallization. The picrates were digested in about 250 cc. of hot absolute alcohol; that which remained undissolved was filtered off and recrystallized twice from a large volume of absolute alcohol and then twice from 95% alcohol, in which it was more soluble. Yellow monoclinic prisms were obtained, melting, with decomposition, at 254–256° (picrate of Base D).

Anal. Calc'd for $C_{17}H_{18}N_2 \cdot C_6H_3N_3O_7$: C, 57.6; H, 4.4; N, 14.6.
Found: C, 57.4; H, 4.5; N, 14.8.

This picrate is not identical with the picrate of Base C, which has the same empirical formula on the basis of analysis: the melting-decomposition points of the picrates are 50° apart.

The picrates which dissolved originally in the hot absolute alcohol (above) were further separated into two fractions: a more insoluble picrate, separating as very small, fine needles, and a more soluble picrate, obtained on concentration of the mother liquors, which separated as long, slender needles. The latter, or more soluble picrate, was recrystallized several

times from absolute alcohol and formed long yellow needles which melted at 193.5–195° (picrate of Base E).

Anal. Calc'd for $C_{18}H_{20}N_2 \cdot C_6H_3N_3O_7$: C, 58.5; H, 4.7; N, 14.2.
Calc'd for $C_{19}H_{22}N_2 \cdot C_6H_3N_3O_7$: C, 59.1; H, 5.0; N, 13.8.
Found: C, 58.7; H, 4.9; N, 13.9.

The less soluble picrate, which separated as very small, fine needles, was recrystallized several times from absolute alcohol and twice from 80% alcohol. The clusters of yellow needles melted, with decomposition, at 261–262.5° (picrate of Base F).

Anal. Calc'd for $C_{13}H_{12}N_2 \cdot C_6H_3N_3O_7$: C, 53.7; H, 3.6; N, 16.5.
Found: C, 53.9; H, 3.8; N, 16.7.

The *free base* (Base F) was prepared by dissolving the picrate in a large amount of water, in which it is sparingly soluble. The resulting solution was made strongly acid with conc'd hydrochloric acid and the picric acid was removed by exhaustive extraction with ether. The aqueous solution, which exhibited a strong blue fluorescence, was rendered strongly alkaline with sodium hydroxide and extracted with ether. The total ether extract was dried and the solvent removed, leaving a brownish-yellow oil. This was taken up in ligroin (Skellysolve D) plus just sufficient benzene to dissolve it at the boiling temperature. On cooling, some oily material settled out; this was centrifuged down, the supernatant liquor was poured off and concentrated. After standing 1 week in the ice-box, crystals formed, which were recrystallized from ligroin plus the minimum quantity of benzene. Fifteen milligrams of long white, rectangular rods were obtained, melting at 79–81°. The compound gave no color with Ehrlich's reagent or with vanillin-hydrochloric acid reagent.

Anal. Calc'd for $C_{13}H_{12}N_2$: C, 79.6; H, 6.2.
Found: C, 79.5; H, 6.4.

The *hydrochloride* of the $C_{13}H_{12}N_2$ base separated in clusters of fine white needles from alcohol, turning brown at 227° and undergoing final decomposition and liquefaction at about 275°. The hydrochloride is hygroscopic; it exhibits a strong blue fluorescence in water or alcohol solution.

The *methiodide* of Base F was prepared by refluxing the base in benzene solution with excess methyl iodide. Recrystallized from absolute alcohol, it separated as fine, pale yellow needles, melting, with decomposition, at 283–284°. The methiodide also exhibits a blue fluorescence in solution. Considerable difficulty was encountered in burning the methiodide on analysis, so that the figures left something to be desired.

Anal. Calc'd for $C_{14}H_{15}IN_2$: C, 49.7; H, 4.5.
Found: C, 49.1; H, 4.5.

Since the empirical formula of Base F corresponded to an ethyl-, or dimethyl-β-carboline, and since the fluorescence, absorption spectrum, and other general properties of the base showed close similarity to a carboline, 1-ethyl-β-carboline (IV) was prepared on the basis of an experimentally determined value of 3.5% of N-alkyl groups (calculated as ethyl) found with the picrate of Base F.[1]

N-nitrosoethylaniline. The method for N-nitrosomethylaniline described in "Organic Syntheses" (13) was employed, starting with 242 g. (2 moles) of ethylaniline and using proportionate amounts of the other reagents. A 270 g. or 90% yield of N-nitrosoethylaniline was obtained as a light yellow liquid, boiling at 125–126° at 17 mm. Schmidt (14) describes boiling points of 119.5–120° at 15 mm. and 133° at 19 mm.

α-Ethyl-α-phenylhydrazine. The method for α-methyl-α-phenylhydrazine described in "Organic Syntheses" (15) was employed, starting with 270 g. (1.8 moles) of N-nitrosoethylaniline and using proportionate amounts of the other reagents. The product was twice fractionally distilled, and two main fractions were obtained: (a) 59.0 g. boiling at 102–110° at 13.5 mm., n_D^{26} 1.5567; (b) 121.0 g. (49% yield) boiling at 114–116° at 13.5 mm., n_D^{26} 1.5642. The boiling point under vacuum has not been recorded previously; the boiling point of α-methyl-α-phenylhydrazine, obtained by this method in 52–56% yield, is 106–109° at 13 mm.

[1] N-Alkyl determination by Mr. D. Rigakos, Rockefeller Institute.

Benzaldehyde α-ethyl-α-phenylhydrazone was prepared from fraction (b) and pure benzaldehyde, and after two recrystallizations from water-alcohol, the compound melted at 49°. Michaelis and Phillips (16) report the melting point 49° for the α-ethyl-α-phenylhydrazone of benzaldehyde. Fraction (b) was used in subsequent reactions.

Diethylacetal of γ-aminobutyraldehyde. This compound was prepared in good yield according to the method of Manske (8), starting with acrolein, hydrobrominating this to give the diethylacetal of β-bromopropionaldehyde, then replacing the bromine with the cyano group, and finally reducing the diethylacetal of β-cyanopropionaldehyde (n_D^{25} 1.4162) with sodium and alcohol to yield the diethylacetal of γ-aminobutyraldehyde, boiling at 85° at 11 mm., n_D^{25} 1.4266. Manske reports the boiling point 84° at 11 mm.

1-Ethyltryptamine. This was made according to the method employed by Manske for the preparation of tryptamine. A mixture of 40 g. (0.25 mole) of the above acetal and 35 g. (0.26 mole) of α-ethyl-α-phenylhydrazine contained in a 500-cc. round-bottom flask, was treated with 34 g. (0.25 mole) of finely powdered, freshly fused zinc chloride. The mixture was heated together, finally under reflux, until the end of the vigorous exothermic reaction. The product, upon cooling, was dissolved in acetic acid (30 g. of glacial acetic acid and 50 g. of water). Three hundred cubic centimeters of water was added and the zinc was precipitated by a stream of hydrogen sulfide. After filtration, the filtrate was made alkaline with sodium hydroxide and extracted with ether. The ethereal solution was dried, the solvent removed, and the residue distilled *in vacuo*, with fractionation, giving the following fractions: fraction (a) 9.1 g. boiling below 165° at 2 mm.; fraction (b) 18.0 g. (38% yield) boiling at 165–175° and 2 mm. Fraction (b), on redistillation, boiled at 170–171° and 2 mm., giving a pale yellow liquid; n_D^{26} 1.5821.

Anal. Calc'd for $C_{12}H_{16}N_2$: C, 76.5; H, 8.6; N, 14.9.
Found: C, 76.5; H, 8.6; N, 14.9.

The *phthalimide* was prepared according to the method of Manske for the same derivative of 1-methyltryptamine. It formed long, monoclinic needles from absolute alcohol and melted at 149–150°.

Anal. Calc'd for $C_{20}H_{18}N_2O_2$: C, 75.5; H, 5.7.
Found: C, 75.3; H, 5.8.

The *picrate* of 1-ethyltryptamine was made in alcohol solution and recrystallized from absolute alcohol as stout, orange, monoclinic prisms, melting at 178.5–180.5°.

Anal. Calc'd for $C_{18}H_{19}N_5O_7$: C, 51.8; H, 4.6.
Found: C, 52.0; H, 4.7.

1-Ethyl-2,3,4,5-tetrahydro-β-carboline. The method of preparation was analogous to that used by Späth and Lederer (6) for the preparation of the 1-methyl compound. A solution of 4 g. of 1-ethyltryptamine in 250 cc. of dilute sulfuric acid (2 cc. of conc'd sulfuric acid in 250 cc.), after addition of 5 cc. of 40% formalin, was warmed at 70° for 1 min. The solution was cooled, made alkaline, and extracted with ether, the ether evaporated, and the residue refluxed 45 min. with 2 liters of sulfuric acid (2:250). The resulting solution was cooled, made alkaline, and extracted with ether. The residual yellow oil, after removal of the ether, was dissolved in alcohol. To the alcoholic solution was added picric acid in alcohol solution and the orange picrate thus obtained was recrystallized from alcohol, with decolorizing carbon. The total yield of *1-ethyl-2,3,4,5-tetrahydro-β-carboline picrate* was 7.5 g. or 82%. The orange monoclinic prisms melted at 224–225°.

Anal. Calc'd for $C_{19}H_{19}N_5O_7$: C, 53.2; H, 4.5.
Found: C, 53.6; H, 4.7.

Two grams of the picrate was decomposed by the addition of strong hydrochloric acid to a water suspension which was stirred with benzene on a steam-bath. The benzene layer was removed and a fresh portion of benzene added, this process being repeated until the extraction of picric acid was complete. The acidic solution was then made alkaline with sodium hydroxide and extracted with ether. The ethereal solution was dried and the ether removed, leaving a clear yellow oil which was distilled *in vacuo* at 140–170° bath temperature and 0.2 mm. pressure. The free base could not be obtained crystalline and an analysis was not attempted on the light yellow oil.

The p-*nitrobenzamide* of the secondary amine was made by refluxing 100 mg. of the oil and 100 mg. of pure *p*-nitrobenzoyl chloride for 1 hr. in benzene solution. Benzene and unreacted acid chloride and acid were removed, and the residual crystalline material was recrystallized three times from alcohol, from which the *p*-nitrobenzamide separated as pale yellow, diamond-shaped crystals, melting at 146–148°.

Anal. Calc'd for $C_{20}H_{19}N_3O_3$: C, 68.8; H, 5.5.
Found: C, 68.9; H, 5.6.

1-Ethyl-β-carboline (*IV*). This was prepared by dehydrogenation of the tetrahydrocarboline according to the method employed by Späth and Lederer (6) for making 1-methyl-β-carboline. Six hundred seventy milligrams of 1-ethyl-2,3,4,5-tetrahydro-β-carboline was heated at 160–170°for 45 min. with 1.5 g. of palladium black (one-third of this quantity also gives a good yield). On distillation at 130–160° bath temperature and redistillation at 130–140° bath temperature and 0.2 mm. pressure, a straw-yellow oil was obtained. When this oil was taken up in petroleum ether (Skellysolve B) and the minimum quantity of benzene necessary for solution, crystals formed very slowly on long standing. The colorless regular prisms melted at 41–42° after two slow recrystallizations from benzene-petroleum ether.

Anal. Calc'd for $C_{13}H_{12}N_2$: C, 79.6; H, 6.2; N, 14.3.
Found: C, 79.2; H, 6.2; N, 14.4.

The *picrate* of 1-ethyl-β-carboline was made in alcohol solution and recrystallized three times from alcohol, in which it is but slightly soluble, giving long, golden-yellow needles, melting at 227–228°.

Anal. Calc'd for $C_{19}H_{15}N_5O_7$: C, 53.7; H, 3.6.
Found: C, 54.0; H, 3.8.

The *methiodide* was made by refluxing the free base with excess methyl iodide in benzene. It separated from absolute alcohol as pale yellow needles, melting at 293–295°.

Anal. Calc'd for $C_{14}H_{15}IN_2$: C, 49.7; H, 4.5.
Found: C, 49.9; H, 4.8.

1-Ethyl-β-carboline (IV) is not, therefore, identical with Base F, since the melting points of the free bases, picrates, and methiodides are not the same.

In addition, the other possible N-ethyl-β-carboline, namely *3-ethyl-β-isocarboline* (*VI*), was synthesized for comparison with Base F.

Norharman ethiodide was prepared by refluxing 400 mg. of norharman in dry benzene with excess ethyl iodide. The insoluble ethiodide was recrystallized from absolute alcohol, from which it separated as pale yellow needles melting at 198–199°.

3-Ethyl-β-isocarboline (*VI*). This was prepared according to the method of Fischer (19) and Perkin and Robinson (20) for making methylharmine and methylnorharmine. A water solution of 600 mg. of norharman ethiodide was treated with excess sodium hydroxide solution. The yellow crystalline precipitate was recrystallized twice from water, from which it separated slowly as yellow plates; these softened and bubbled on slow heating, with final melting taking place at 176.5–178.5°. The material was dried *in vacuo* over phosphorus pentoxide for 12 hrs. at room temperature, then for 5 hrs. at 100°. The partially dehydrated sample was taken up in boiling toluene and boiled down to small volume. A further portion of dry toluene was added and the solution boiled down again. This process was repeated several times. Upon cooling of the conc'd toluene solution, flocculent yellow needles separated which were recrystallized once from dry toluene and twice from dry benzene. The yellow, hygroscopic needles melted at 176.5–178.5° (VI).

Anal. Calc'd for $C_{13}H_{12}N_2$: C, 79.6; H, 6.2.
Found: C, 79.6; H, 6.3.

3-Ethyl-β-isocarboline ethiodide (*VII*). The ethiodide was prepared by refluxing 3-ethyl-β-isocarboline in dry benzene with excess ethyl iodide. The precipitated ethiodide crystallized from absolute alcohol as very pale yellow needles which melted at 213.5–215°.

Anal. Calc'd for $C_{13}H_{12}N_2 \cdot C_2H_5I$: C, 51.1; H, 4.9.
Found: C, 50.9; H, 5.0.

The *ethiodide* of *1-ethyl-β-carboline* (*IV*), which was prepared in a similar manner, like-

wise separated from absolute alcohol as very pale yellow needles melting at 213.5–215°. As would be expected (21), this ethiodide proved identical in every way with VII, and mixed melting points of the ethiodides prepared by the two methods showed no depression.

2-Ethyl-β-carboline was prepared by heating 500 mg. of tryptophan in dilute sulfuric acid with 15 cc. of 12% propionaldehyde solution, followed by oxidation with potassium dichromate; the method was exactly like that employed by Kermack, Perkin, and Robinson (11) for the preparation of the next lower homolog, 2-methyl-β-carboline, or harman. The compound separated from benzene as prisms and melted at 193–195°, as reported by Späth and Lederer (6) for the same compound prepared by a different method.

Zinc dust distillation of alstonine. This reaction was carried out both in an atmosphere of hydrogen and under normal atmospheric conditions, with no appreciable difference in the final result. For the distillation in a stream of hydrogen, the apparatus used was similar to that described by Jacobs and Craig (17); for distillation in air, a wide knee-tube was used. A mixture of 2 g. of alstonine and 50 g. of zinc dust was heated in a sand-bath for 1 hr. at 300-350°, after raising the temperature rapidly to this region. The distillate was dissolved in ether, extracted with 10% hydrochloric acid, and then the ethereal solution was washed with water. The neutral material obtained on evaporation of the ether gave a blue color with Ehrlich's reagent. The color was similar to that shown by β-alkyl indoles. However, no chemical individual could be isolated from this fraction. The hydrochloric acid solution was made alkaline and extracted with ether. The ether was removed and the residue was twice distilled *in vacuo* at 140–180° bath temperature and 0.2 mm. The distillate was dissolved in benzene (300 mg. in 50 cc.) and chromatographed on 6 g. of aluminum oxide (Brockmann). Three main rings were obtained, which were developed and eluted with benzene. No pure chemical individual could be obtained from the first and third zones, nor could any crystalline picrate be obtained from their solutions. The benzene eluate of the second zone was treated with dry picric acid in benzene, and a crystalline picrate was obtained. This was filtered off and recrystallized many times from alcohol, from which it finally separated as clusters of fine yellow needles, melting with decomposition at 261–263°. A mixed melting-decomposition point with the picrate of Base F showed no depression.

Reduction of tetrahydroalstonine with sodium and butyl alcohol. Hexahydroalstonol. To 100 cc. of boiling *n*-butyl alcohol was added 2 g. of tetrahydroalstonine; when solution was complete 8 g. of sodium was added quickly in small portions. The solution became slightly yellow, and when all the sodium had dissolved, the solution was cooled rapidly and poured quickly into 5% hydrochloric acid. If allowed to cool slowly, the solution turned red, but this color change, with the subsequent difficulty in obtaining a pure, colorless product, could be circumvented by rapid cooling. The resulting acidic mixture was steam-distilled to free it from butyl alcohol. The yellow solution remaining in the distilling flask was made strongly basic with sodium hydroxide solution and extracted with chloroform. The total chloroform extract was dried over anhydrous magnesium sulfate and the solvent was removed *in vacuo*. The yellow crystalline residue was recrystallized three times from 90% alcohol, and yielded 800 mg. of material; this was recrystallized from absoute alcohol, from which it separated as tiny, well-formed prisms which melted at 282–284° with decomposition. It showed $[\alpha]_D^{27}$ −78° ± 3° (c = 0.338 in pyridine) as compared with $[\alpha]_D^{27}$ −88° ± 2° for tetrahydroalstonine in pyridine.

Anal. Calc'd for $C_{20}H_{26}N_2O_2$: C, 73.6; H, 8.0; N, 8.6.
Found: C, 73.3, 73.5; H, 8.0, 8.1; N, 8.8.

The *picrate* was prepared in alcohol and after three recrystallizations from alcohol, formed small, stout yellow prisms which melted at 237–238° with decomposition.

Anal. Calc'd for $C_{20}H_{26}N_2O_2 \cdot C_6H_3N_3O_7$: C, 56.2; H, 5.3; N, 12.6.
Found: C, 55.9; H, 5.2; N, 12.5.

The above $C_{20}H_{26}N_2O_2$ compound could not be obtained from the reduction of alstonine itself with sodium and butyl alcohol; as a matter of fact, no crystalline product could be obtained from this reaction.

The acetate was prepared by refluxing the free base with acetic anhydride for 1 hr. and

also by warming it with pyridine and acetic anhydride; however, the optimum conditions were the following: 50 mg. of base was dissolved in 5 cc. of anhydrous pyridine and 0.4 cc. of redistilled acetic anhydride was added. The solution was allowed to stand 5 days at 25°, well-stoppered and in the absence of light. To the straw-yellow solution was added 3 cc. of methyl alcohol and the solution was evaporated to dryness *in vacuo*. This process was repeated several times with methyl alcohol and finally with water. The crystalline residue was decolorized with charcoal in alcoholic solution and recrystallized five times from absolute alcohol, yielding colorless crystals, mainly in the form of tetragonal bipyramids, which melted at 95–96°.

Anal. Calc'd for $C_{24}H_{30}N_2O_4$: C, 70.2; H, 7.4; N, 6.8.
Calc'd for $C_{22}H_{28}N_2O_3$: C, 71.7; H, 7.7; N, 7.6.
Found: C, 71.4; H, 7.6; N, 7.6.

The *picrate of acetylhexahydroalstonol* was prepared in alcohol solution, from which it separated after boiling and long standing. It formed small yellow plates after five recrystallizations from alcohol, and melted, with decomposition, at 223–224.5°.

Anal. Calc'd for $C_{24}H_{30}N_2O_4 \cdot C_6H_3N_3O_7$: N, 10.9.
Calc'd for $C_{22}H_{28}N_2O_3 \cdot C_6H_3N_3O_7$: N, 11.7.
Found: N, 11.9.

The Zerewitinoff determinations were carried out in dry pyridine in an atmosphere of dry nitrogen (18).

TABLE I

ZEREWITINOFF ACTIVE HYDROGEN DETERMINATION

SUBSTANCE	MOLES CH_4 PER MOLECULE
Yohimbine hydrochloride	3.2
Tetrahydroalstonine	1.28
Alstonine hydrochloride	2.3
Alstonine acid sulfate	3.2

The ultra violet absorption spectra measurements were done with a Hilger rotating sector quartz spectrophotometer using Eastman Process plates.

The microanalyses here reported were performed by Mr. Saul Gottlieb of these laboratories.

SUMMARY

1. The formula of alstonine has been definitely checked as $C_{21}H_{20}N_2O_3$.

2. From the products of alkali fusion of alstonine and tetrahydroalstonine, harman, norharman, indole-α-carboxylic acid, and three bases of undetermined structure, probably β-carboline derivatives, have been obtained.

3. Thermal decomposition of alstonine leads to the formation of three bases of undetermined structure, but which are apparently β-carboline derivatives.

4. Reduction of tetrahydroalstonine with sodium and butyl alcohol leads to a new base, hexahydroalstonol, $C_{20}H_{26}N_2O_2$, the absorption curve for which is identical with that of yohimbine and α,β-dimethylindole.

5. 1-Ethyl-β-carboline and 3-ethyl-β-isocarboline have been prepared.

6. A partial structure for alstonine is discussed.

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