GARRYA ALKALOIDS

I. THE STRUCTURE OF GARRYINE AND VEATCHINE[1]

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ABSTRACT

By means of hydrogenation, oxidation, and isomerization experiments it has been established that the chemistry of veatchine and garryine parallels the chemistry of atisine and isoatisine. Dehydrogenation of the *Garrya* alkaloids yields a base $C_{16}H_{15}N$, which, on the basis of comparison of ultraviolet spectra, might be a substituted phenanthridine. 1-Methyl-7-ethyl phenanthrene has also been obtained. The chemistry and structure of the aconite and *Garrya* alkaloids is discussed in the light of the present work.

Oneto (11) has described the isolation of the two alkaloids, veatchine and garryine, from the bark of *Garrya veatchii* Kellogg. They have both been given the empirical formula $C_{22}H_{32}O_2N$. Garryine crystallized as a monohydrate, m.p. ca. 96°C. Veatchine crystallized without water of crystallization and melted at 122-123°C. The separation of these two alkaloids was achieved by fractional precipitation with alkali; the material precipitating first was richer in garryine.

We have achieved a quantitative separation of these alkaloids by a nine-funnel countercurrent distribution between chloroform and an aqueous buffer of pH = 7. In this system veatchine remains in the first three funnels and garryine travels to the last two; in between lies a deep "valley". The properties of both compounds are in fair agreement with those described by Oneto (11) with the exception that both compounds and their derivatives check perfectly to the formula $C_{22}H_{33}O_2N$. Both compounds show approximately one active hydrogen in the Zerevitinoff determination and both have one N-alkyl group.

Potentiometric microtitration in 80% methyl cellosolve shows veatchine to have a pK of 11.5 and garryine a pK of 8.7.

The infrared spectra of the two alkaloids are almost indistinguishable. There is an — OH band at 3300 cm.$^{-1}$ At 1665 cm.$^{-1}$ there is a band which is too weak for a carbonyl group and is likely to be due to a carbon–carbon double bond. A band at 1440 cm.$^{-1}$, which disappears on hydrogenation, is due to a terminal methylene group; the overtone for this group appears at 1800 cm.$^{-1}$ The band at 1400 cm.$^{-1}$ is probably due to — CH_2 bending. One other band, which can be definitely assigned, is that at 1375 cm.$^{-1}$, which is characteristic of a C-methyl group.

Infrared spectra are given in Figs. 1-8.

On hydrogenation with Adams catalyst in glacial acetic acid, both alkaloids absorb two moles of hydrogen and give the same tetrahydro compound $C_{22}H_{37}O_2N$ (m.p. 147-149°C.), characterized also by the picrate. The pK value of tetrahydroveatchine is 6.85. Kuhn-Roth oxidation of tetrahydroveatchine indicates

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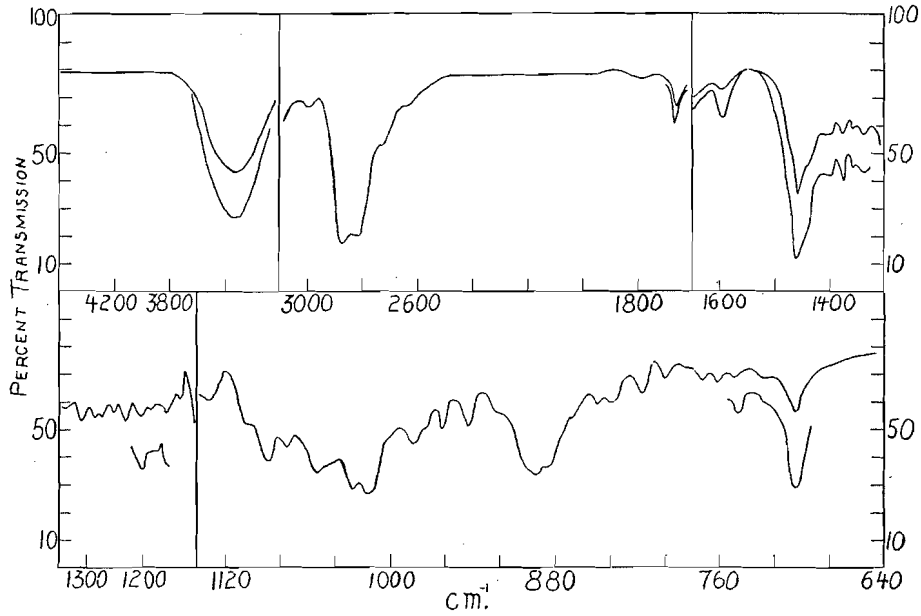


FIG. 1. Infrared spectrum of veatchine.

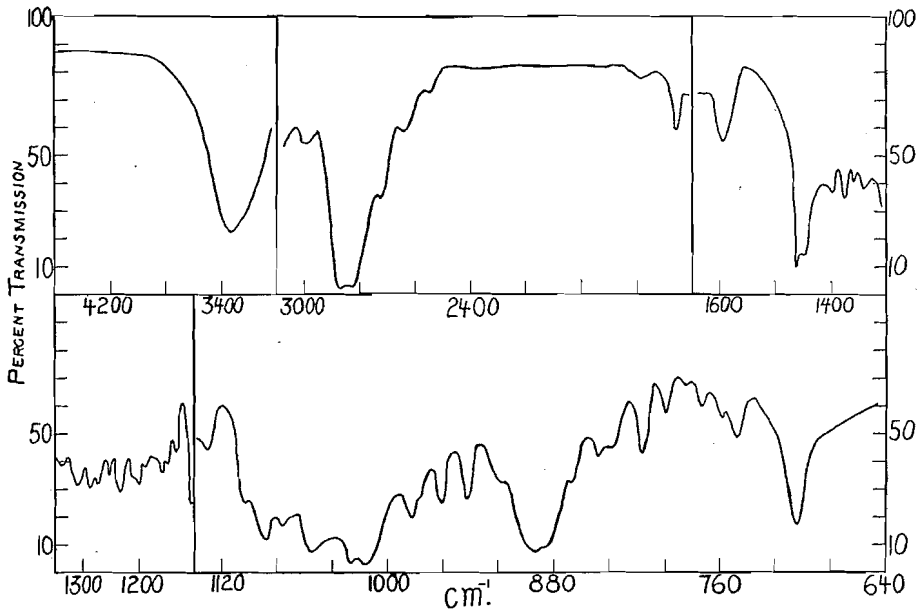


FIG. 2. Infrared spectrum of garryine.

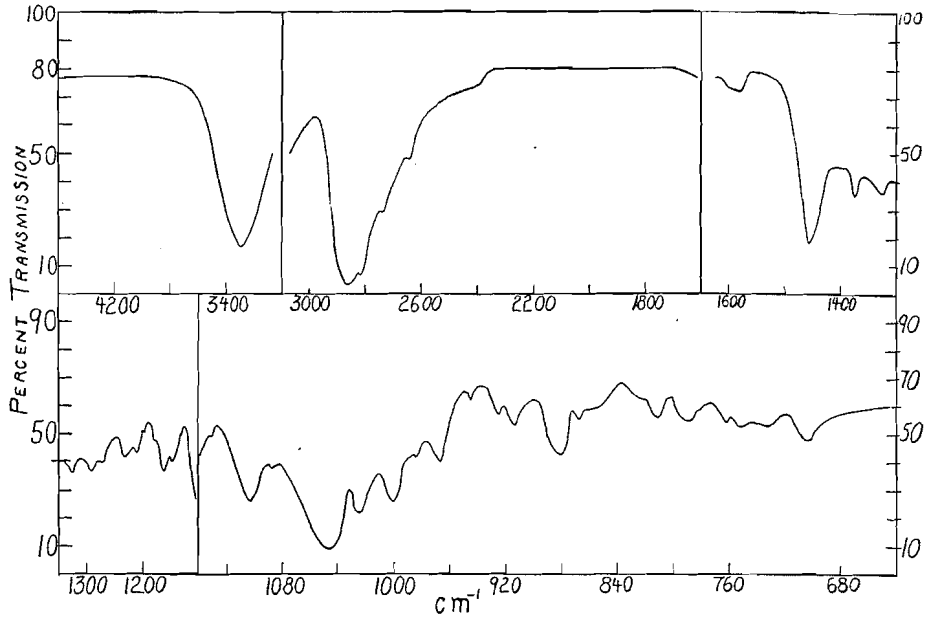


FIG. 3. Infrared spectrum of tetrahydrogarryine.

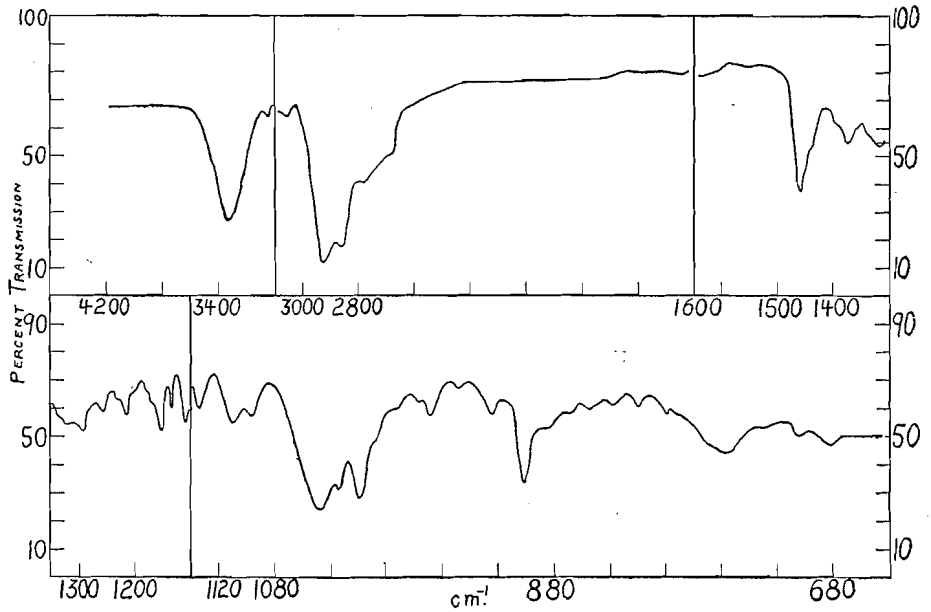


FIG. 4. Infrared spectrum of $LiAlH_4$ reduced veatchine.

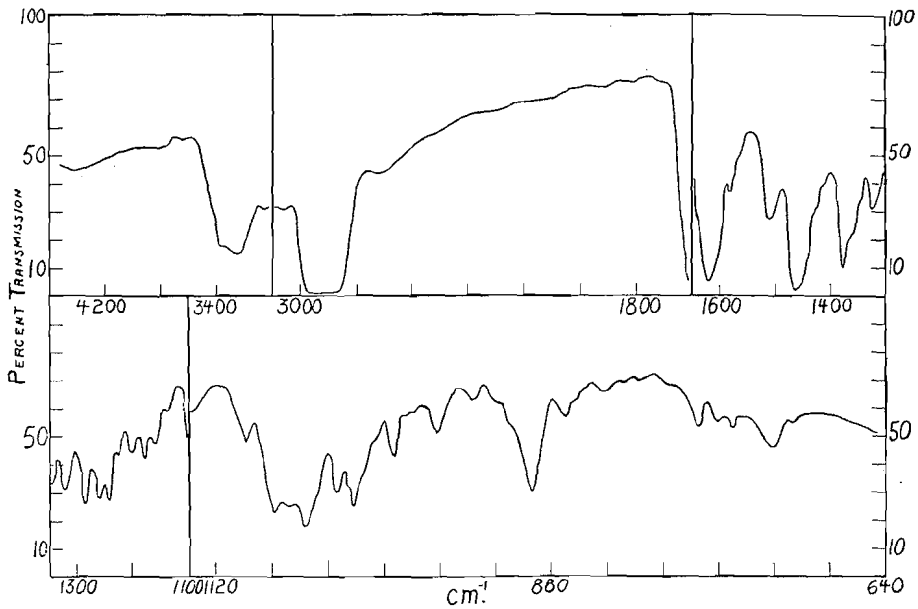


FIG. 5. Infrared spectrum of oxogarryine.

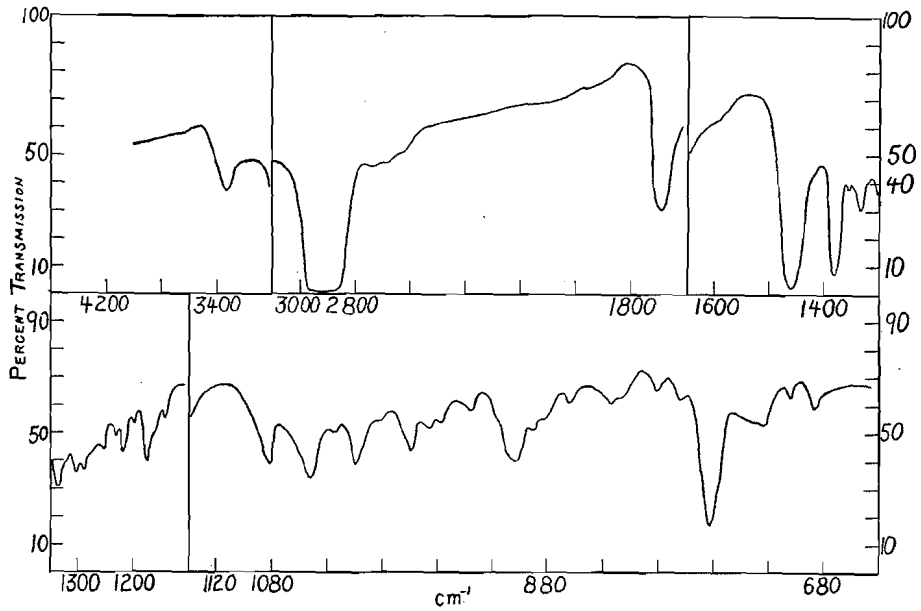


FIG. 6. Infrared spectrum of oxoveatchine *A*.

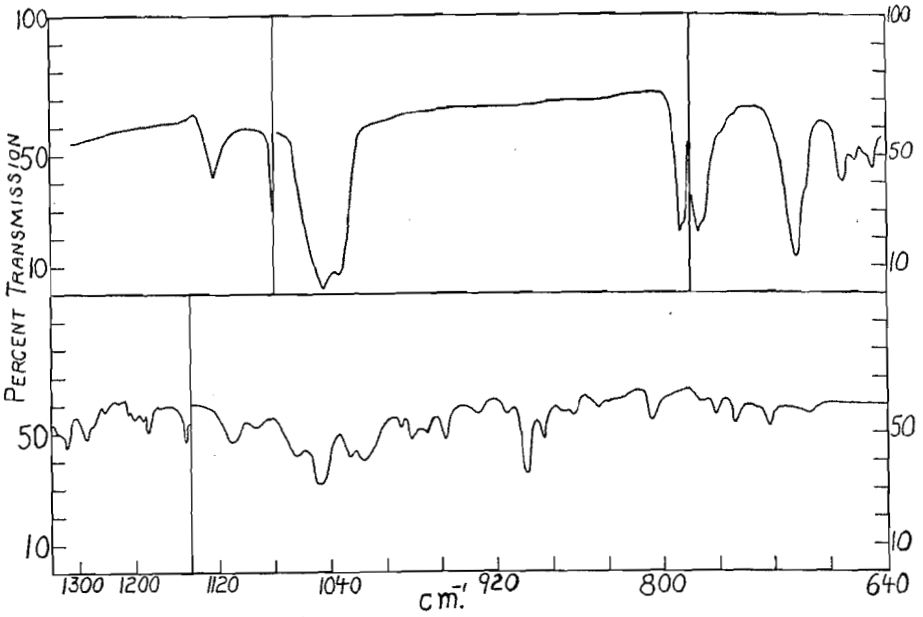


FIG. 7. Infrared spectrum of oxoveatchine *B*.

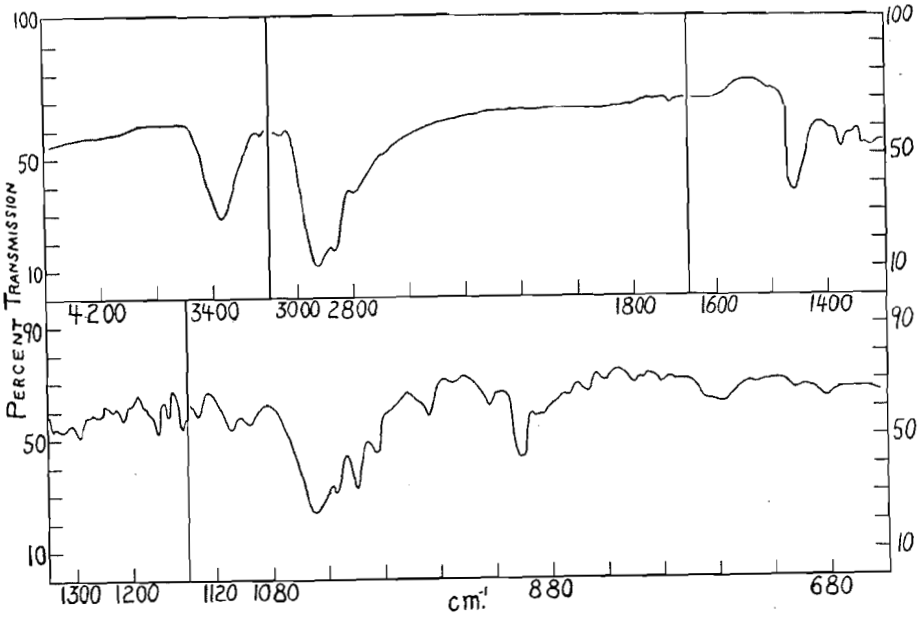


FIG. 8. Infrared spectrum of $LiAlH_4$ reduced oxogarryine.

a content of two C-methyl groups, whereas both veatchine and garryine analyze for only one such group; this result is in agreement with the interpretation of the infrared spectra. The presence of a terminal methylene group in veatchine and garryine was further corroborated by the isolation of formaldehyde as the dimedone complex in ozonolysis experiments.

Veatchine can be quantitatively isomerized to garryine by the action of boiling alcoholic sodium hydroxide.

These results indicate that the difference between garryine and veatchine is just in the position of one carbon–carbon double bond, and this bond must be associated with the nitrogen. It is well established (1) that tertiary bases of the type $> N - \underset{|}{C} = C <$ are unusually strong, because they form salts having the characteristics of quaternary ammonium salts.

Neither garryine nor veatchine contains a carbonyl group, as is seen from the infrared spectra and from the failure to obtain carbonyl derivatives.

Acetylation of veatchine yielded a basic acetyl hydrochloride, which consistently gave analytical values between a mono- and a di-acetyl compound. The free acetylated base analyzed well for a monoacetyl compound.

Tetrahydroveatchine yielded a basic diacetyl derivative on acetylation.

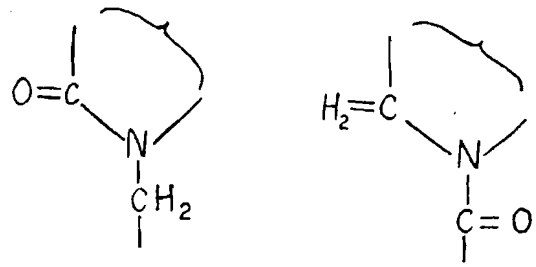
From these results it would seem that the hydrogenation consisted in the reduction of the terminal methylene group and the transformation of the second oxygen of veatchine to an hydroxyl group. As this second oxygen was not a carbonyl group, it was assumed that it might be present in the form of an ether or oxide bridge. However, all attempts to cleave such a group resulted in the recovery of starting material.

Reduction of veatchine with lithium aluminum hydride yielded a dihydro compound, in which the carbon–carbon double bond associated with the nitrogen was reduced, as evidenced by the change in the pK value of this derivative from 11.5 to 6.85 (that of tetrahydroveatchine). The dihydro derivative, however, still exhibited the presence of a terminal methylene group in the infrared spectrum, and gave formaldehyde on ozonolysis. These facts prove that there is a methylene group present, which is not associated with the nitrogen, and, therefore, a total of two carbon–carbon double bonds in veatchine and garryine.

The oxidation of veatchine with potassium permanganate under mild conditions yielded two neutral products (Compound *A* and Compound *B*), both analyzing for $C_{22}H_{31}O_3N$. A difference was apparent not only in their melting points, but also in their infrared spectra. Both compounds are thought to be amides derived from veatchine by the abstraction of two hydrogens and the addition of one oxygen atom. The nature of these compounds becomes obvious upon comparison of their carbonyl frequencies in the infrared region. Compound *A* (m.p. 210°C.) has a carbonyl peak at 1690 cm.$^{-1}$ and in more dilute solution at 1700 cm.$^{-1}$, whereas Compound *B* (m.p. 233°C.) has a carbonyl peak at 1630 cm.$^{-1}$

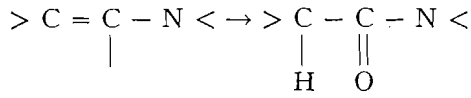
The wave length of the carbonyl peak of Compound *A* indicates an amide

group in a ring, possibly a six-membered ring condensed with several other rings or a five-membered ring which is not a part of a highly condensed system. The carbonyl group of Compound *B*, on the other hand, is likely to belong to a disubstituted amide, which is not in a ring. The ultraviolet spectra of both compounds show end absorption. It seems, therefore, that the relationship of the two compounds can be represented by the following structures:

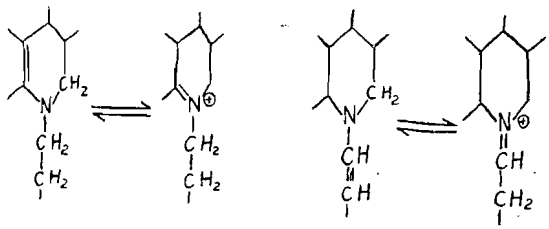


Compound A Compound B

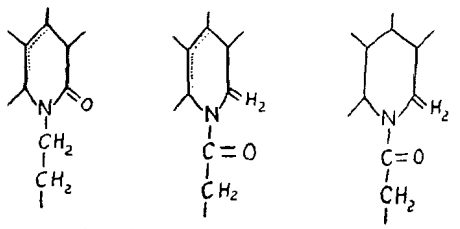
The oxidation of garryine with permanganate gives a high yield of a neutral crystalline product $C_{22}H_{33}O_3N$. The empirical formula of this compound shows that only one oxygen has been added to garryine. This fact can be explained in the following manner:



The infrared spectrum of oxogarryine shows a strong band at 1618 cm.$^{-1}$ with a shoulder at 1637 cm.$^{-1}$ This is a wave length comparable with that of oxoveatchine *B*, and very different from that of oxoveatchine *A*, in which the amide group seems to be in a ring. The carbonyl group in oxogarryine can, therefore, be best explained as that of a disubstituted amide, which is not a part of a ring. If we accept that the amide group in oxogarryine is formed from the carbon–carbon double bond, and assume for the present that the ring containing the nitrogen is six-membered, we obtain the following tentative scheme for all the compounds involved:



Veatchine Garryine



This scheme is in agreement with basicities of the compounds involved. It is well known from the work of Adams and Mahan (1) that the basifying influence of a carbon–carbon double bond in vinyl tertiary amines is stronger if the double bond is in a ring than if it is in an open chain.

There is, however, one difficulty which necessitates caution in the interpretation of these reactions. In view of the parallelism of the chemistry of atisine and veatchine (*vide infra*), this scheme, which is based on the infrared carbonyl frequencies of the oxoveatchines and oxogarryine, seems to be in contradiction to the properties and further reactions of the tricarboxylic acid, IV, derived from isoatisine. However, as no infrared spectrum of oxoisoatisine has been published and the corresponding experimental data on acids derived from garryine are not at present available, further development will have to be awaited. A comprehensive study of the infrared spectroscopy of six-membered lactams is also required.

The carbonyl frequency of 1,3-dimethylhexahydrooxindole has been observed at 1690 cm.$^{-1}$, which is identical with that of oxoveatchine *A*. It is also possible that condensation with other rings, in the case of a six-membered lactam, could produce a similar frequency.

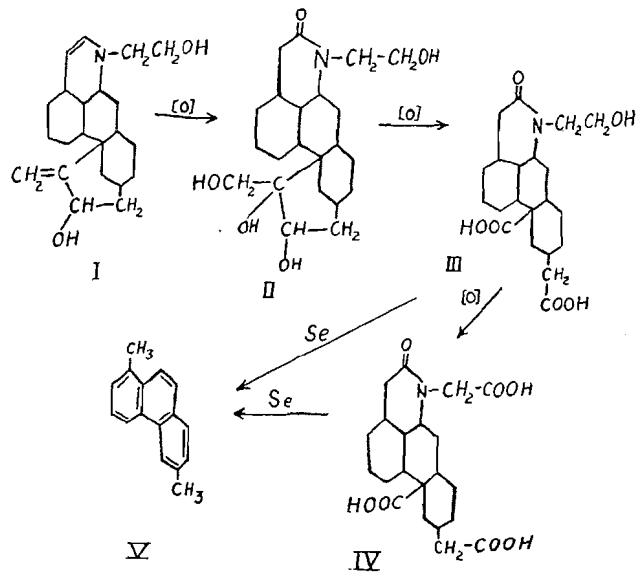
The infrared spectrum of oxogarryine contains two features which are not found in the spectrum of oxoveatchine *B*: one is a band at 1508 cm.$^{-1}$; the other is a double band at 3245 cm.$^{-1}$ and 3368 cm.$^{-1}$ The 1508 cm.$^{-1}$ and 3245 cm.$^{-1}$ bands could, perhaps, be ascribed to N–H bending and N–H stretching of a monosubstituted amide, which is not a part of a ring. However, unless more evidence is produced to support such a view, this appears unlikely.

Finally, we have reduced oxogarryine with lithium aluminum hydride to obtain dihydroveatchine, which is identical, as shown by infrared spectra, with the dihydroveatchine obtained by the action of the same reagent on veatchine. This evidence is, of course, difficult to reconcile with the assumption that oxogarryine is a monosubstituted amide, but it is fully in agreement with the assumption that the amide group originated from the carbon–carbon double bond without any change in the skeleton.

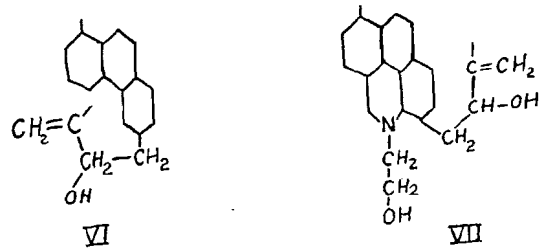
All the reactions of veatchine and garryine are strongly reminiscent of the relationship of atisine and isoatisine, which has been reported in a series of papers by Jacobs and his collaborators (5, 6, 7, 8, 9, 10). The methylenic nature of the double bond in atisine, although assumed, has not been proved. Permanganate

oxidation of atisine did not yield neutral substances analogous to our oxoveatchines *A* and *B*, but acids which were derived from an oxoatisine $C_{22}H_{31}O_3N$.

In his most recent paper, Jacobs proposed the tentative structure I for isoatisine. This structure was based mainly on the isolation of 1-methyl-6-ethyl phenanthrene from the selenium dehydrogenation of atisine and the series of degradations as indicated by the formulae I-V:



From these reactions it is evident that three of the four carbocyclic rings form a perhydrophenanthrene skeleton. The fourth carbocyclic ring can be opened with the formation of a dicarboxylic acid. From the dehydrogenation of this diacid to 1,6-dimethylphenanthrene, one point of attachment of this fourth ring can be located at carbon 6. The second point of attachment is likely to be a tertiary carbon atom. This follows from the properties of one of the carboxyl groups of the dicarboxylic acid. However, the point of attachment in formula I is not the only posssible one. The isolation of the tricarboxylic acid represented by formula IV indicates the primary character of one of the hydroxyl groups in I. The mode of attachment of the nitrogen ring in I is tentative.



In summary, we have, therefore, a partial structure VI fairly well established (although variations in the order of the carbon–carbon double bond and the hydroxyl group in the ring attached to carbon 6 appear possible), and to complete the structure we have only to add, in addition to the N-alkyl group, one carbon and one nitrogen atom to form the nitrogen ring. Finally, one carbon–carbon bond has to be located between the end of the side-chain at carbon 6 and one tertiary carbon of the perhydrophenanthrene skeleton.

The manner in which the nitrogen ring is completed in formula I seems to us to be in contradiction to the results of the Kuhn-Roth determination, which indicates one C-methyl group for both atisine and veatchine.

Another purely tentative way to complete the partial structure is depicted by formula VII. This formula would explain the C-methyl group, and it would be in better agreement with the basic dehydrogenation product.

We have preliminarily reported (3) a base $C_{16}H_{15}N$, which was obtained from veatchine by selenium dehydrogenation just as a similar base was obtained by Jacobs (9) from atisine. Our base has no active hydrogen, no N-alkyl group, and a pK value (80% methyl cellosolve) of 4.0. The ultraviolet spectrum of this base is given in Fig. 9 (Curve 1).

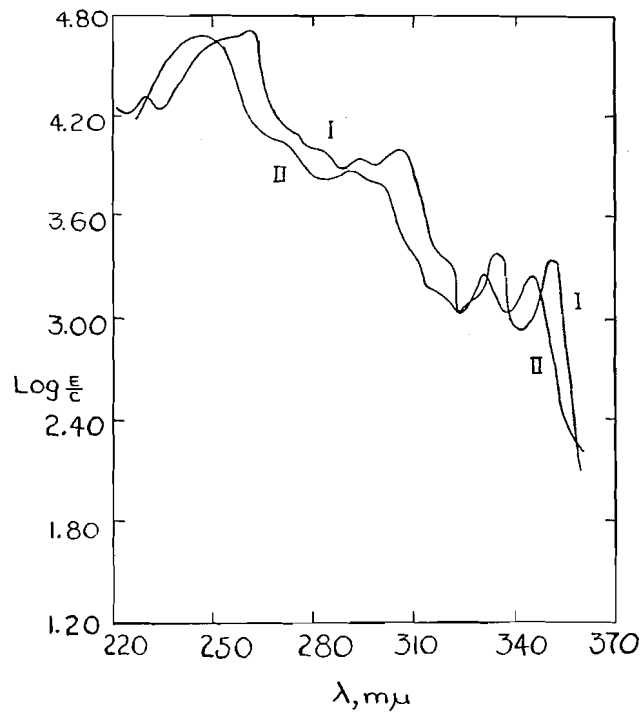


FIG. 9. Ultraviolet spectra. I. $C_{16}H_{15}N$ base. II. Phenanthridine.

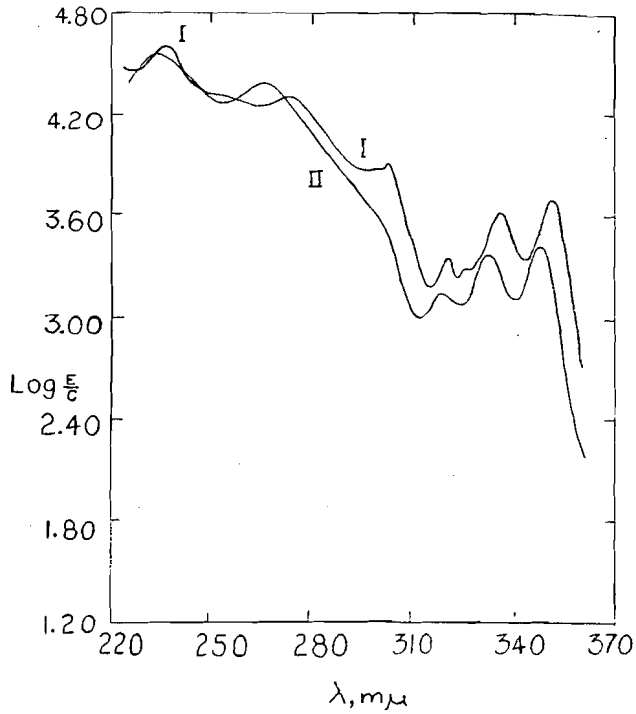


FIG. 10. Ultraviolet spectra. I. Azaretene. II. α-Naphthoquinoline.

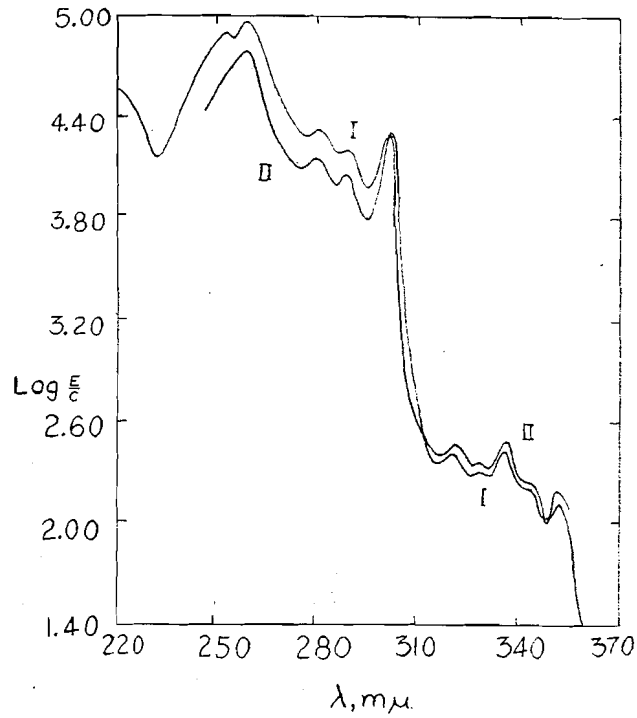


FIG. 11. Ultraviolet spectra. I. $C_{17}H_{16}$ hydrocarbon. II. Pimanthrene.

This spectrum (Fig. 9, Curve 1) is obviously that of an azaphenanthrene. The spectra of different azaphenanthrenes are similar to spectra of phenanthrenes and very different from those of acridines or other heterocycles (2). If we compare, however, the spectrum of our base with that of α-naphthoquinoline (Fig. 10, Curve 2) or azaretene (Fig. 10, Curve 1), we see that, although they are of the same general type, there are undoubtedly differences which cannot be ascribed to substitution. On the other hand, the spectrum of phenanthridine (Fig. 9, Curve 2) is similar in its entirety to that of our base, except that the latter is shifted to a higher wave length. Such a shift to higher wave length is the result of substitution, as can readily be shown by comparing the spectra of substituted and unsubstituted phenanthrenes or those of azaretene and β-naphthoquinoline (4).

We believe that elucidation of the structure of the $C_{16}H_{15}N$ base will clarify considerably the structure around the nitrogen atom; appropriate synthetic and degradative studies are in progress.

From the neutral material produced in the dehydrogenation of veatchine, a phenanthrene hydrocarbon $C_{17}H_{16}$ (m.p. 91.5°C.; m.p. of trinitrobenzene complex 135-136°C.) was isolated. The spectrum of this compound (Fig. 11, Curve 1) is identical with that of retene or pimanthrene (Fig. 11, Curve 2).

The reported melting point (12) of 1-methyl-7-ethyl phenanthrene is 87.5°C. and that of its trinitrobenzene complex is 134°C. We are at present undertaking the synthesis of this compound.* Thus it would seem that the point of attachment of the fourth carbocyclic ring is one of the main differences between the structure of atisine and that of veatchine.

EXPERIMENTAL PART

Isolation of Alkaloids

The crude alkaloid mixture was isolated by a modification of Oneto's method (11). The ground bark was percolated with alcohol, and the percolate was evaporated to a small volume. The residue was dissolved in water, and the solution was filtered. The filtrate was made strongly alkaline with sodium hydroxide and extracted three times with chloroform. The volume of the chloroform extract was reduced *in vacuo*, and the bases were separated by shaking with 5% sulphuric acid. The acidic extract was then made alkaline, and the precipitated bases were extracted with chloroform. The yield of crude bases was 1.1%.

From the mixture of crude bases veatchine and garryine were separated by countercurrent distribution. The crude bases were first distributed between a phosphate–citrate buffer of pH = 7 and chloroform using nine funnels (200 ml. of each phase). A typical experiment employing 23 gm. of the crude mixture gave the following result:

**Note added to proof: This has now been completed and the identity of our phenanthrene with 1-methyl-7-ethyl phenanthrene has been established by mixed melting points and infrared spectra.*

Funnel No.	Wt. of substance (gm.)
1	4.188
2	4.228
3	4.457
4	4.278
5	3.200
6	0.571
7	0.229
8	0.596
9	1.811

Recrystallization of the contents of the first three funnels from acetone–water yielded pure veatchine, which melted at 119-120°C. after six recrystallizations. It was sublimed for analysis in high vacuum at 140°C. Another sample was dried in high vacuum at 80°C.

Calc. for $C_{22}H_{33}O_2N$: C, 76.92; H, 9.68; N, 4.08; act.H, 0.29; (N)–CH_3, 4.37; (C)–CH_3, 4.37%.

Found: C, 76.97, 76.75, 76.75; H, 9.73, 9.84, 9.80; N, 4.19, 4.31, 4.22; act.H, 0.31; (N)–CH_3, 4.17; (C)–CH_3, 2.89%.

Microtitration in methyl cellosolve: pK = 11.5.

The last two funnels of the countercurrent distribution contained garryine, and the contents were redistributed between a phosphate–citrate buffer of pH = 5.5 and chloroform (100 ml. of each phase).

The result was as follows:

Funnel No.	Wt. of substance (gm.)
1	0.146
2	0.154
3	0.220
4	0.243
5	0.297
6	0.191
7	0.093
8	0.120
9	0.718

The material from funnels 3, 4, and 5 yielded 768 mgm. of pure garryine upon recrystallization from acetone–water. After eight recrystallizations the hydrate melted over the range 74-82°C. On warming or drying *in vacuo*, the hydrate lost water and was transformed into the oily anhydrous compound. For analysis it was distilled in a sublimation tube at 140°C. in high vacuum.

Calc. for $C_{22}H_{33}O_2N$: C, 76.92; H, 9.68; N, 4.08; act.H, 0.29; (N)–CH_3, 4.37; (C)–CH_3, 4.37%.

Found: C, 76.92, 76.64, 76.51; H, 9.78, 9.79, 9.53; N, 4.09, 4.41; act. H, 0.27; (N)–CH_3, 2.13; (C)–CH_3, 1.94%.

Microtitration in methyl cellosolve: pK = 8.7.

Veatchine Hydrochloride

This material was recrystallized eight times from absolute alcohol – ether. It melted at 267-271°C. Potentiometric microtitration showed pK = 11.5.

Calc. for $C_{22}H_{33}O_2N.HCl$: C, 69.55; H, 9.02; N, 3.69; Cl, 9.33%.

Found: C, 69.12; H, 9.32; N, 3.46; Cl, 9.48%.

Garryine Hydrochloride

This compound, when recrystallized eight times from absolute alcohol – ether, melted at 263-268°C. Potentiometric microtitration showed pK = 8.7.

Calc. for $C_{22}H_{33}O_2N.HCl$: C, 69.55; H, 9.02; N, 3.69; Cl, 9.33%.

Found: C, 69.44; H, 9.05; N, 3.78; Cl, 9.26%.

Acetyl Veatchine

Veatchine (100 mgm.) was dissolved in 1 ml. of dry pyridine and 2 ml. of acetic anhydride and allowed to react at room temperature for 60 hr. At the end of this period the solution was evaporated to dryness *in vacuo*, dissolved in chloroform, and washed several times with 10% hydrochloric acid. Upon evaporation of the chloroform, crystalline acetyl veatchine hydrochloride remained. It was recrystallized to a constant melting point of 258-259°C. The free base was liberated and recrystallized from acetone–water. The latter compound melted at 152-153°C., and was sublimed for analysis.

Calc. for $C_{24}H_{35}O_3N$: C, 74.77; H, 9.15; acetyl, 11.16%.

Found: C, 75.15, 74.51; H, 8.71, 9.24; acetyl. 9.55%.

Microtitration: pK = 11.5.

Hydrogenation of Veatchine

Veatchine (500 mgm.) was hydrogenated in 20 ml. of glacial acetic acid with 100 mgm. of platinum oxide. The uptake of hydrogen (2 moles) was completed in two-three hours. The reaction mixture yielded tetrahydroveatchine, which was recrystallized six times from acetone–water to a melting point of 147-149°C. It was sublimed for analysis at 120°C. in high vacuum.

Calc. for $C_{22}H_{37}O_2N$: C, 76.00; H, 10.73; N, 4.03; 2 act.H, 0.58; 1 (C)–CH_3, 4.32%.

Found: C, 76.05; H, 10.77; N, 4.11; act.H, 0.55; (C)–CH_3, 6.08, 5.87%.

Microtitration in methyl cellosolve: pK = 6.8.

The picrate of the compound melted at 206-207°C.

Hydrogenation of Garryine

Garryine showed an uptake of 2 moles of hydrogen under the same conditions as were used in the case of veatchine. The resulting tetrahydrogarryine melted at 148-150°C. (acetone–water), and gave no depression upon admixture with tetrahydroveatchine. It was sublimed for analysis.

Calc. for $C_{22}H_{37}O_2N$: C, 76.00; H, 10.73; N, 4.03; 2 act.H, 0.58; (N)–CH_3, 4.32%.

Found: C, 76.02; H, 10.79; N, 4.25; act.H, 0.59; (N)–CH_3, 4.41%.

Tetrahydrogarryine picrate melted at 205-207°C. (alcohol), and did not depress the melting point of tetrahydroveatchine picrate. The former picrate was dried at 80°C. for 24 hr. in high vacuum and then analyzed.
Calc. for $C_{22}H_{37}O_2N.C_6H_3O_7N_3$: C, 58.24; H, 7.04; N, 9.71%.
Found: C, 58.41; H, 6.92; N, 9.94%.

Diacetyl Tetrahydroveatchine

Tetrahydroveatchine (500 mgm.) was acetylated in the usual way with pyridine and acetic anhydride at room temperature. The reaction mixture was evaporated to dryness and the residue dissolved in chloroform. The chloroform solution was then washed with 5% hydrochloric acid and water and evaporated to dryness. The residue contained the crude gummy hydrochloride of diacetyl tetrahydroveatchine. This was again dissolved in chloroform, and the free base was liberated by washing the solution with dilute alkali. Purification of this compound was achieved by chromatography on neutral alumina in absolute benzene, followed by distillation in a sublimation tube at 140°C. in high vacuum. Potentiometric microtitration in methyl cellosolve showed pK = 5.6.
Calc. for $C_{26}H_{41}O_4N$: C, 72.35; H, 9.58; acetyl, 20.00%.
Found: C, 72.37; H, 9.72; acetyl, 21.65%.

Ozonolyses

Veatchine, garryine, dihydroveatchine, and tetrahydroveatchine (200 mgm. of each) were ozonized in absolute chloroform at 0°C. for three hours. The chloroform was evaporated from each *in vacuo* at room temperature, and 5 ml. of 5% sulphuric acid was added. The mixtures were then steam-distilled, and 2 ml. of 5% ethanolic dimedone solution was added to each distillate. Garryine, veatchine, and dihydroveatchine gave a positive result; approximately 0.5 mole of crystalline dimedone–formaldehyde complex was obtained in each case (m.p. 183-186°C. and no depression upon admixture with an authentic specimen). Tetrahydroveatchine gave only traces of precipitate.

Conversion of Veatchine to Garryine

Veatchine (1 gm.) was refluxed for three hours with 50 ml. of 5% methanolic potassium hydroxide. The alcohol was distilled *in vacuo* and water was added. The resulting precipitate was extracted with chloroform, and this solution was evaporated to dryness. The residue was distributed in nine funnels between a phosphate–citrate buffer of pH = 7 and chloroform (50 ml. of each phase). The result was as follows:

Funnel No.	Wt. of substance (gm.)
1	0.08
2	0
3	0
4	0
5	0.005
6	0.038
7	0.158
8	0.386
9	0.360

The contents of funnels 6, 7, 8, and 9 were garryine. It was recrystallized several times from acetone–water and melted at 75-82°C. It was then sublimed for analysis.

Calc. for $C_{22}H_{33}O_2N$: C, 76.92; H, 9.68%.
Found: C, 77.03; H, 9.69%.
Microtitration in methyl cellosolve: pK = 8.7.

Dihydroveatchine

Veatchine (200 mgm.) was placed in a Soxhlet and extracted overnight with 30 ml. of absolute ether containing 1 gm. of lithium aluminum hydride. The excess hydride was destroyed with water, and the mixture was worked up in the usual manner. The product crystallized from acetone–water and melted at 141-143°C. No depression of melting point was evidenced in admixture with tetrahydroveatchine. However, the infrared spectrum distinctly showed several differences, one of these being the presence of a band assigned to a $C = CH_2$ group in veatchine; this band is absent in the spectrum of tetrahydroveatchine.

Calc. for $C_{22}H_{35}O_2N$: C, 76.47; H, 10.21%.
Found: C, 76.47; H, 10.24%.
Microtitration in methyl cellosolve: pK = 6.9.

The picrate of this compound melted at 193-195°C. (methanol).

Permanganate Oxidation of Veatchine

Veatchine (5 gm.) was dissolved in 335 ml. of acetone and 6 gm. of potassium permanganate in 260 ml. of acetone was added dropwise at 10-15°C. The reaction was allowed to proceed at this temperature for four and one-half hours. Manganese dioxide was removed by filtration, and evaporation of the acetone yielded 2.49 gm. of product. This was separated into a neutral fraction (493 mgm.) and a basic fraction (unchanged veatchine).

The manganese dioxide was suspended in a mixture of water and chloroform (200 ml. of each), and the whole was cooled to 5°C. Sulphur dioxide was then passed into the mixture until all the manganese dioxide was reduced. The chloroform layer was separated, and the aqueous layer was extracted several more times with chloroform. The combined chloroform layers yielded 1.08 gm. of white foam. This was combined with the neutral material obtained previously (493 mgm.), and the whole was separated into a neutral fraction (698 mgm.) and an acidic fraction.

Chromatography of the neutral material on alumina yielded two main substances: *Compound A*, 133 mgm. of crystalline material eluted with absolute benzene, and *Compound B*, 162 mgm. of white foam eluted with absolute ether. Compound *A* melted at 211-213°C. and Compound *B* at 234-237°C.; both were recrystallized from absolute methanol – ether. A mixture of the two compounds melted at 160-200°C. That the two compounds were distinctly different was further shown by the differences in their infrared spectra, especially in the carbonyl region.

Calc. for $C_{22}H_{31}O_3N$: C, 73.91; H, 8.76; N, 3.92%.
Found for Compound *A*: C, 73.88, 73.82; H, 8.45, 8.65; N, 3.85%.
Found for Compound *B*: C, 74.19, 74.20; H, 8.85, 8.63; N, 3.60%.

Permanganate Oxidation of Garryine

Garryine (500 mgm.) was dissolved in 50 ml. of acetone and 0.5 ml. of glacial acetic acid. To this solution 300 mgm. of finely powdered potassium permanganate was added over a period of 30 min. The stirring was continued for a further 20 min. The residue upon separation yielded 268 mgm. of neutral material and a small amount of unchanged garryine. The neutral material was recrystallized from ethyl acetate to a constant melting point of 187-188°C.

Calc. for $C_{22}H_{33}O_3N$: C, 73.48; H, 9.26; N, 3.90%.
Found: C, 73.60, 73.38; H, 9.32, 9.11; N, 3.71%.

Conversion of Oxogarryine to Dihydroveatchine

Oxogarryine (500 mgm.) was reduced with 1.5 gm. of lithium aluminum hydride in 50 ml. of absolute ether using a Soxhlet extractor. After being worked up in the usual manner, the product was recrystallized from acetone–water (m.p. 148°C.). This substance did not depress the melting point of dihydroveatchine, and its infrared spectrum was identical with that of dihydroveatchine. A sample was sublimed for analysis in high vacuum.

Calc. for $C_{22}H_{35}O_2N$: C, 76.47; H, 10.21%.
Found: C, 76.43; H, 10.20%.

Dehydrogenation of Veatchine

Veatchine (20 gm.) was mixed with 40 gm. of red selenium, and the whole was heated in an atmosphere of nitrogen at 340°C. for 12 hr. The selenium "cake" was pulverized and extracted overnight in a Soxhlet with ether. The total amount of a brown-colored viscous oil thus obtained was 15.12 gm. This was separated into four fractions by extracting in the usual manner with hydrochloric acid, sodium bicarbonate, and sodium hydroxide. The fractions were:

1. Neutral, ether soluble; 9.38 gm.
2. Neutral, chloroform soluble; 1.87 gm.
3. Basic; 3.75 gm.
4. Phenolic; 0.124 gm.

Chromotography of the Basic Fraction

The basic material was chromatographed on 150 gm. of untreated Fisher alumina, 250 ml. fractions being taken. The result was as follows:

1. Fractions 1-8 eluted with absolute benzene yielded 0.409 gm. of colorless oil.

2. Fractions 9-26 eluted with absolute benzene yielded 1.047 gm. of crystals, m.p. 65-95°C.

3. Fractions 27-36 eluted with absolute benzene–ether (1:1) yielded 0.927 gm. of crystalline material.

4. Further fractions eluted with absolute ether – chloroform and absolute methanol – chloroform were dark and resinous and have not yet been investigated.

The crystalline material was recrystallized to a constant melting point of 115°C. (absolute ether). This compound was then sublimed at 90°C. in high vacuum for analysis.

Calc. for $C_{16}H_{15}N$: C, 86.83; H, 6.84; N, 6.33%.
Found: C, 87.20, 87.33; H, 6.83, 7.01; N, 6.07, 5.99; (N)–CH_3, 0.0; act.H, 0.0%.
Microtitration in methyl cellosolve: pK = 4.0.

The picrate of this base melted at 243°C. It was dried at 80°C. for 24 hr.
Calc. for $C_{16}H_{15}N.C_6H_3O_7N_3$: C, 58.64; H, 4.03; N, 12.44%.
Found: C, 58.98, 58.93; H, 4.02, 3.80; N, 12.83%.

Chromatography of the Neutral Fractions

The neutral material was chromatographed on 500 gm. of untreated Fisher alumina, 500 ml. fractions being taken. The result was as follows:

1. Fractions 1-6 eluted with absolute petroleum ether yielded 1.261 gm. of an oily liquid.

2. Fractions 7-19 eluted with absolute petroleum ether yielded 2.48 gm. of crystalline material.

3. Further fractions eluted successively with benzene, ether, and methanol–chloroform were oily and have not yet been investigated.

Several samples of the crystalline material were prepared by successive recrystallization from petroleum ether, ether, and finally methanol. All samples melted at 91.0-91.5°C., and they were sublimed at 80°C. in high vacuum.
Calc. for $C_{17}H_{16}$: C, 92.68; H, 7.32%.
Found: C, 92.38, 92.59, 92.55, 92.62; H, 7.33, 7.36, 7.31, 7.23%.

The trinitrobenzene complex melted at 135-136°C. (alcohol). A sample was dried for analysis at 40°C. in high vacuum for 48 hr.
Calc. for $C_{17}H_{16}.C_6H_3N_3O_6$: C, 63.71; H, 4.42; N, 9.73%.
Found: C, 64.17; H, 4.23; N, 9.71, 9.80%.

The microanalyses were performed partly by Dr. Robert Dietrich of Zurich and partly in the microanalytical laboratory of the University of Pittsburgh.

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