[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

THE VERATRINE ALKALOIDS. XXXVI. A POSSIBLE SKELETAL STRUCTURE FOR VERACEVINE,[1] CEVINE, GERMINE, AND PROTOVERINE

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Received February 6, 1953

In earlier work from this laboratory certain data were obtained which suggested that cevine and therefore the related veratrine bases could possess modified steroidal structures in which ring B is five-membered (2). However, later data accumulated, such as the direct correlation of rubijervine (3) and isorubijervine (4) with solanidine and the experience with jervine (5) and veratramine (6), which were inconsistent with a B ring of five carbon atoms. Although the possibility had been considered that ring C instead of B could be of cyclopentano-character, it was discarded at the time for lack of evidence. Later work showed the apparent benzenoid character of ring D in veratramine. While this conclusion at first appeared compatible with a perhydrochrysene structure, it has since been abandoned in favor of a perhydrobenzofluorene structure such as recently proposed by Wintersteiner, *et al.* (7) for jervine and veratramine (X and XIV).

Such a modified structure with some additions we now believe will explain more satisfactorily the data which were previously obtained, especially those from the dehydrogenation of cevine, germine, and protoverine. A review of these data and an attempt at their reinterpretation and correlation with more recent work are presented in this paper. A discussion of oxidation products, such as the hexane- and heptane-tetracarboxylic acids and decevinic acid, we hope to present at a later time.

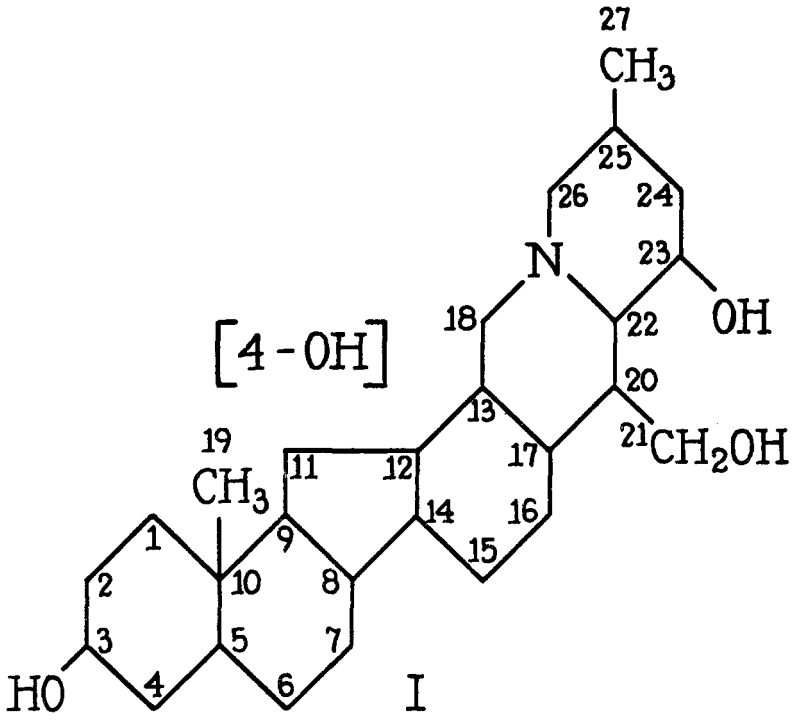
In formula I a general structure[2] which is now favored for veracevine (1), the precursor of cevine, is shown in which the positions of a few of the hydroxyl groups are suggested. Both germine and protoverine must possess similar structures which differ only by the number and positions of the hydroxyl groups and perhaps also in a configurational way.

From the selenium dehydrogenation of cevine (Plate I), except for 4,5-benzohydrindene (VI), apparently only one type (VII) of related hydrocarbons was obtained, *viz.*, $C_{17}H_{16}$, $C_{18}H_{18}$, $C_{19}H_{20}$, and $C_{24}H_{30}$ (8). The similarity of the ultraviolet absorption spectra of these hydrocarbons, their formulations, and a positive Vanscheidt color test indicated at the time their tetracyclic cyclopentenofluorene character. A still larger characteristic basic fragment was the cevanthridine (V) discovered by Blount (9). The formulation of this base was re-

[1] In a paper in press (1) veracevine has been shown to be the original alkanolamine present in cevadine and veratridine whereas cevagenine and cevine are isomerization products of veracevine.

[2] The eighth oxygen atom, which is not shown in formula I, may not exist as a hydroxyl group but as an oxide linkage as recently suggested by Barton and Eastham [*J. Chem. Soc.*, 424 (1953).

vised by Craig and Jacobs (10) to $C_{25}H_{27}N$ and a definite relationship to the above hydrocarbons was derived from a study of the ultraviolet absorption of its hydrogenation product, tetrahydrocevanthridine (IX).



I

The curves in Fig. 1 taken from the earlier papers show the marked difference between the ultraviolet absorption of cevanthridine itself and the $C_{24}H_{30}$ hydrocarbon chosen for comparison from the above $C_{17}H_{16}$ series. On the other hand, the absorption of tetrahydrocevanthridine, in which the nitrogen-containing ring is hydrogenated, has become strikingly similar. This similarity may best be explained by assuming a pentacyclic cyclopentenofluorene-*isoquinoline* structure for cevanthridine (V), for with a quinoline structure, the absorption of its tetrahydro-derivative should differ more markedly from that of the $C_{24}H_{30}$ hydrocarbon owing to the stronger influence of a nitrogen atom adjacent to the aromatic ring. It appears most likely that no synthesis of smaller fragments is responsible for the production of cevanthridine but that it is formed directly from cevine with accompanying cleavage of the C_{26}-N bond and loss of two carbon atoms from the molecule.

If it is accepted that cevanthridine has this partial isoquinoline structure, a new arrangement of the nitrogen-containing rings in cevine as shown in II appears to be more in accord with the formation of cevanthridine. An octahydropyrrocoline structure, such as found in solanidine and therefore in rubijervine and isorubijervine, is difficult to reconcile with the production of a substituted isoquinoline such as cevanthridine without the assumption of considerable

rearrangement involving the opening and closing of the nitrogen rings. The octahydropyridocoline structure (II) readily accounts for the formation of cevanthridine by cleavage of the C_{26}-N bond and the production not only of 2-

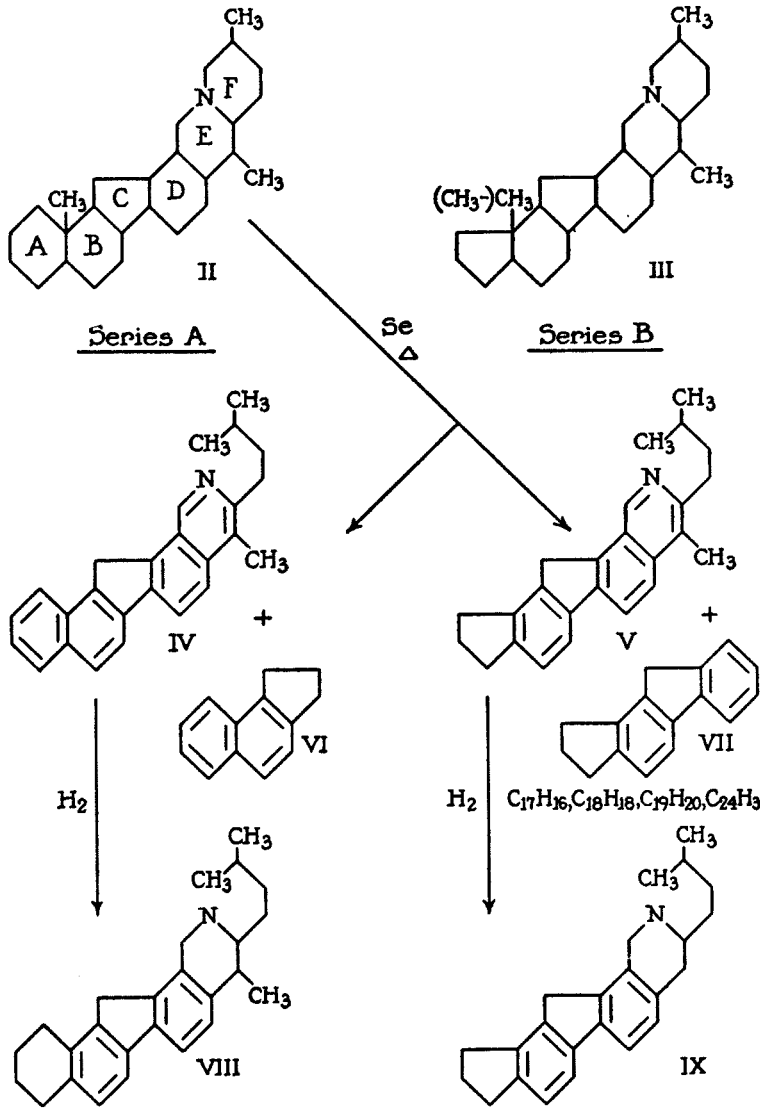


PLATE I. DEGRADATION AND TRANSFORMATION PRODUCTS FROM THE SELENIUM DEHYDROGENATION OF CEVINE.

ethyl-5-methylpyridine on selenium dehydrogenation, but also of the N-methyl-β-pipecoline which was obtained from cevine on zinc dust distillation (11). Structure II is also compatible with the direct formation of the other dicyclic

nitrogenous bases (octahydropyridocolines?) which were isolated from the mixture obtained by pyrolysis with soda lime (12).

The formation of the cyclopentenofluorene hydrocarbons and the presumed cyclopenteno-fluorene portion of cevanthridine is not readily explained without assuming that the usual steroid cyclohexane A ring suffers contraction to a five carbon ring during dehydrogenation or that the five carbon ring is formed from the steroid side chain. Otherwise such a ring system as shown in III would be required in the original structure.

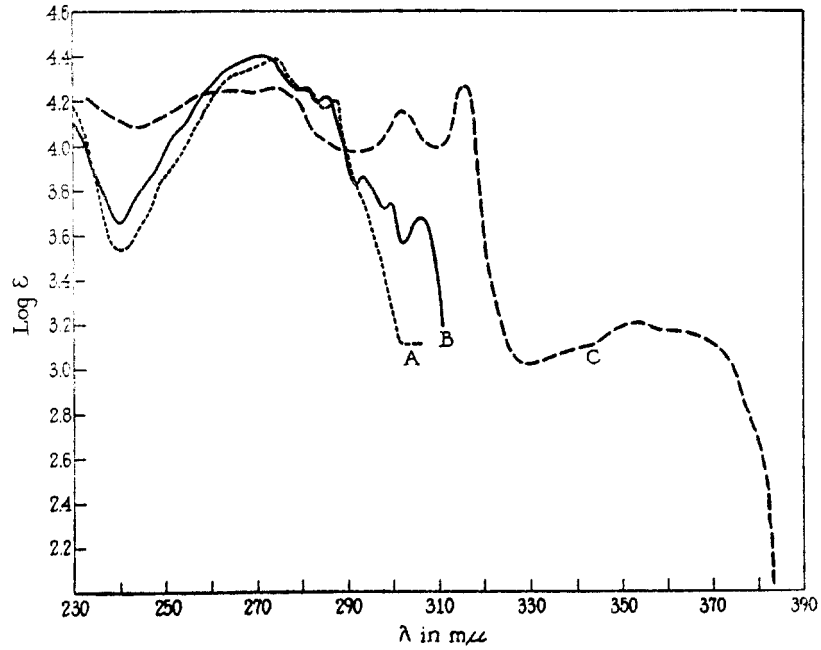


FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA. A = tetrahydrocevanthridine; B = the cyclopentenofluorene, $C_{24}H_{30}$, from cevine; C = cevanthridine; all in ethanol.

In the case of jervine (X) and veratramine (XIV) (Plate II), a normal steroid structure for rings A and B was indicated by their behavior as Δ^5-3-hydroxy derivatives. However, when dehydrogenated, jervine yielded two groups of hydrocarbons (series A and B) (13). The ultraviolet absorption data and the formulations indicated a cyclopentenofluorene character (XIII) for series B hydrocarbons, *viz.*, $C_{20}H_{22}$ and $C_{24}H_{30}$, and a close relationship to the $C_{17}H_{16}$ series obtained from cevine. On the other hand, the hydrocarbons of series A, *viz.*, $C_{20}H_{16}$ and $C_{22}H_{20}$ (the latter obtained also from veratramine), gave ultraviolet spectra characteristic of 1,2-benzofluorenes. Since the formulations of of these series A hydrocarbons indicate an additional saturated presumably cyclopentane ring, they must be pentacyclic, *i.e.*, cyclopentenobenzofluorenes with the extra ring apparently formed from the side chain as shown in formula XI. The direct production of the latter could be expected from the revised per-

hydrobenzofluorene skeletal structures of both cevine and jervine. The fact that jervine yields cyclopentenofluorenes (Series B) as well requires that at least one series must result from partial rearrangement. The production of series B hydrocarbons by contraction of the A ring of an original perhydrobenzo-

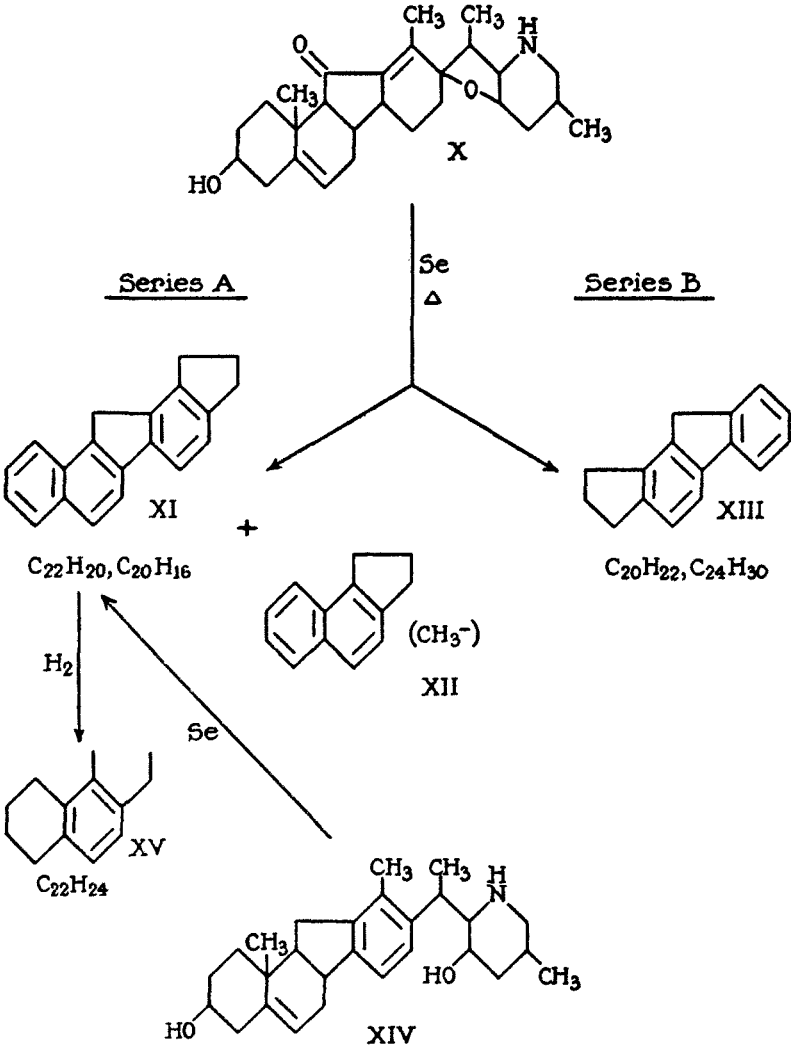


PLATE II. DEGRADATION AND TRANSFORMATION PRODUCTS FROM THE SELENIUM DEHYDROGENATION OF JERVINE AND VERATRAMINE.

fluorene structure is possible though the mechanism is not clear. The formation of such cyclopentenofluorenes from cevine is therefore not inconsistent with the perhydrobenzofluorene structure of II.

More recent evidence for the hydrogenated benzofluorene character of cevine has been obtained by a study of the $C_{26}H_{25}N$ tertiary base previously obtained

from it by dehydrogenation (8). If this base results by a direct cleavage of cevine it is the largest fragment isolated thus far, and presumably the loss of an angular methyl group is involved in its formation. Its formulation suggests that it differs from cevanthridine (V) in having the benzofluorene-isoquinoline structure of IV. An attempt has been made to check this possibility by a study of the ultraviolet spectrum of IV before and after hydrogenation. These curves appear in Fig. 2 together with the previously reported curve for the $C_{22}H_{20}$ cyclopenteno-

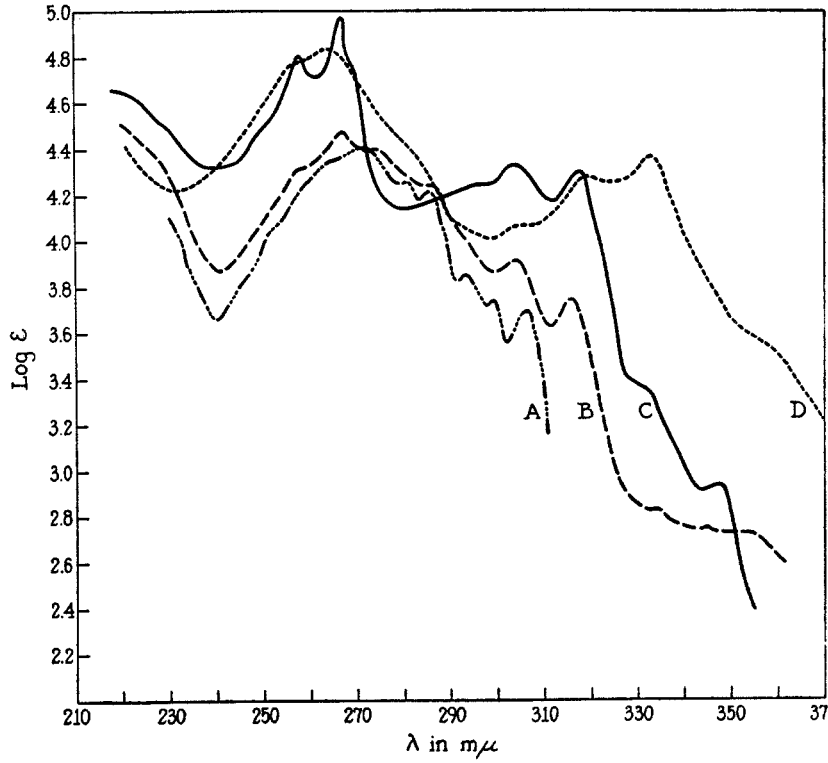


FIG. 2. ULTRAVIOLET ABSORPTION SPECTRA. A = the $C_{24}H_{30}$ hydrocarbon from cevine B = the octahydro base, $C_{26}H_{33}N$, from D; C = the cyclopentenobenzofluorene, $C_{22}H_{20}$ from jervine; D = the $C_{26}H_{25}N$ base from cevine; all in ethanol.

benzofluorene hydrocarbon obtained from jervine. During hydrogenation IV absorbed beyond the two mole stage experienced with cevanthridine, and behaved as would be expected of a benzofluorene-isoquinoline derivative. When hydrogenation had progressed somewhat beyond the four mole stage it was interrupted. The crystalline product, m.p. 145–146°, gave analytical data in fair agreement with those of the expected octahydrobase $C_{26}H_{33}N$ (VIII). The ultraviolet absorption curve of VIII (Fig. 2) appears to be consistent with that of a cyclohexenofluorene-tetrahydroisoquinoline derivative since the curve of the latter should approach that of a cyclopentenofluorene hydrocarbon. This is suggested by a comparison of the curve of VIII with that of the above mentioned $C_{24}H_{30}$ cyclopentenofluorene from cevine (Curves B and A, Fig. 2). The observed

effects of hydrogenation thus appear to be in the general direction expected for a cyclopentenobenzofluorene such as shown in IV.

Strong support for this conclusion has been obtained in a recent study of the effect of hydrogenation on the cyclopentenobenzofluorene $C_{22}H_{20}$ (XI) obtained from jervine and veratramine. The resulting tetrahydro derivative $C_{22}H_{24}$ (m.p. 156.8–160.5°), (XV) showed absorption in the ultraviolet strikingly similar to that of the above hydrogenated base $C_{26}H_{33}N$ (VIII) as shown in Fig. 3. It is

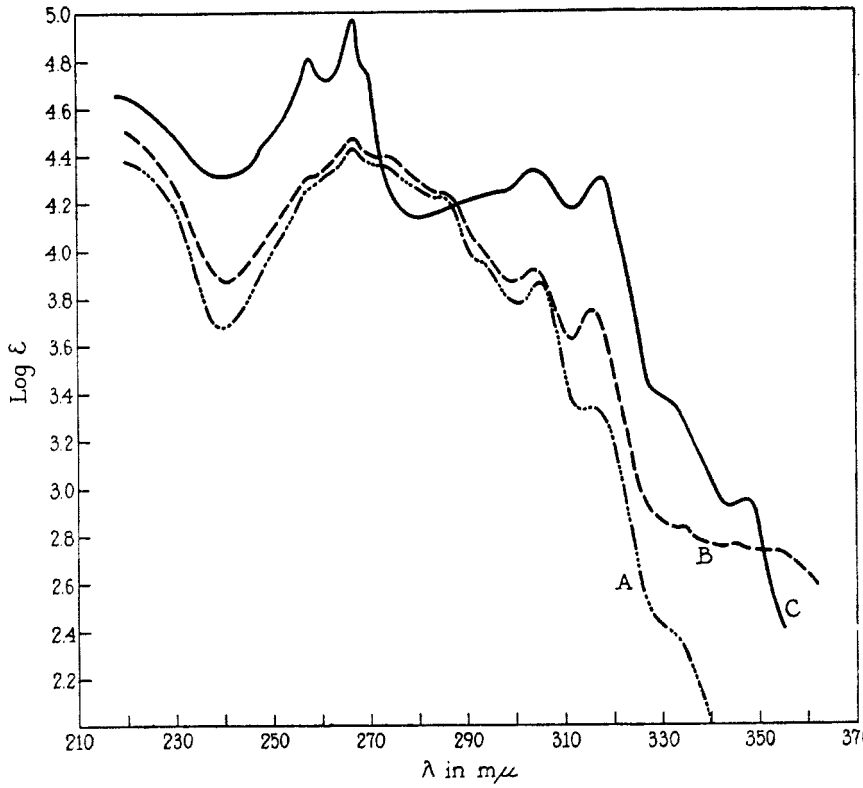


FIG. 3. ULTRAVIOLET ABSORPTION SPECTRA. A = the tetrahydro derivative, $C_{22}H_{24}$ B = the octahydro base, $C_{26}H_{33}N$, from cevine; C = the $C_{22}H_{20}$ hydrocarbon from jervine; all in ethanol.

apparent that the absorption of the parent $C_{22}H_{20}$ hydrocarbon has been markedly changed by hydrogenation. The similarity of the absorption curves of VIII and XV (Curves B and A, Fig. 3) is a strong argument for the close relationship of these hydrogenated products and therefore of the substances XI and IV. It is probable that not only is a 1,2-benzofluorene moiety common to the latter substances, but also that the position of the cyclopentane ring (E) in XI is analogous to that of the nitrogen ring in IV. The extra five-membered ring may be formed during dehydrogenation by a cyclization involving carbon atoms 18 and 21 (or 22) coincident with nitrogen bond cleavage.

In the earlier work there was also obtained from cevine a smaller hydro-

carbon fragment identified as 4,5-benzohydrindene (VI) and another from jervine identified as a methyl-4,5-benzohydrindene (XII). The production of such products is in accord with a direct cleavage of the ABC rings from a perhydrobenzofluorene structure. The fact that jervine and cevine have yielded several types of hydrocarbons requires explanation and perhaps makes less certain the size of ring A. On the basis of the above correlations a perhydrobenzofluorene structure is to be preferred. Both types of structures shown in II and III can be constructed with Fisher-Taylor-Hirschfelder models. It should be noted, however, that the observed molecular rotation differences for jervine and its derivatives are definitely of a magnitude characteristic of a normal steroid structure for rings A and B (14).

EXPERIMENTAL

The octahydro derivative (VIII) *of the $C_{26}H_{25}N$ base.* The base $C_{26}H_{25}N$ (40 mg.) which was previously obtained from cevine (8) by selenium dehydrogenation was hydrogenated in acetic acid solution with 25 mg. of the platinum oxide catalyst of Adams and Schreiner. The absorption proceeded gradually but progressively decreased in rate. After a total of about 11.9 ml. (4 moles are *ca* 10.8 ml.) had been absorbed (three hours) the process was interrupted. The original brown yellow color of the solution had practically disappeared.

The filtered solution which contained some colloidal metal was concentrated to dryness *in vacuo* and redissolved in benzene. The latter was cleared with Norit and on concentration showed signs of crystallization but was again brought to dryness. When dissolved in about one ml. of 95% ethanol the material gradually crystallized. After 24 hours at 0° it was collected with cold solvent (21 mg.) and was recrystallized by solution in ether, addition of 95% ethanol, and subsequent concentration to one ml. At 0° it crystallized largely as clusters of thin hexagonal leaflets. The product sintered at 139° and melted at 145–146° corr.

Anal. Calc'd for $C_{26}H_{33}N$: C, 86.85; H, 9.25.
Found: C, 87.30, 86.97; H, 9.02, 8.96.

Its ultraviolet absorption spectrum is shown in Fig. 2.

The tetrahydro derivative (XV) *of the $C_{22}H_{20}$ hydrocarbon.* A suspension in absolute ethanol of 35 mg. of the cyclopentenobenzofluorene hydrocarbon obtained from the dehydrogenation of jervine was hydrogenated with 25 mg. of platinum oxide catalyst. After reduction of the catalyst the absorption occurred very gradually and the substance was progressively replaced by the colorless hydrogenation product. After about 25 hours the apparent hydrogen absorption was roughly 6 ml. beyond catalyst requirement or about 2 moles. However, the operation was continued overnight when an apparent additional absorption of 1 ml. occurred. Although the absorption appeared to be continuing very slowly the operation was interrupted. On warming, the product redissolved and the solution was filtered from the catalyst with the aid of benzene. After concentration the substance separated again from the ethanol as lustrous thin mostly six-sided micro leaflets; yield 25 mg.; m.p. 155.8–159.8° corr. The mother liquor yielded an additional crop. After recrystallization from ethanol the product melted at 156.8–160.5° corr.

Anal. Calc'd for $C_{22}H_{24}$: C, 91.61; H, 8.39.
Found: C, 91.50, 91.22; H, 8.10, 8.23.

All analytical data have been obtained by Mr. D. Rigakos of this laboratory.

SUMMARY

A reinterpretation and correlation of older data with recent new data have suggested a modified steroidal structure (II) for the polyhydroxy tertiary vera-

trine bases, veracevine (precursor of cevine), germine, and protoverine. The favored structure is similar to the recently adopted structures for jervine and veratramine in which rings A, B, and D are six-membered and ring C is five-membered. In structure II rings E and F are formed by a union of the steroidal isooctyl side chain with the nitrogen atom to give an octahydropyridocoline moiety attached to ring D. This structure differs from the octahydropyrrocoline structure of the steroidal tertiary bases solanidine, rubijervine, and isorubijervine.

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