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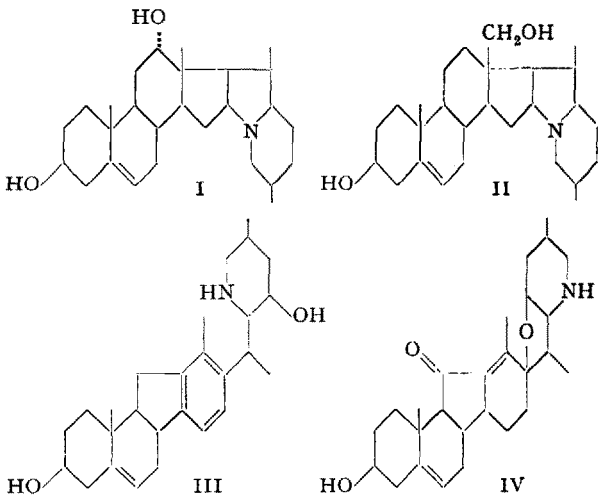
The Constitutions of Cevine and Some Related Alkaloids

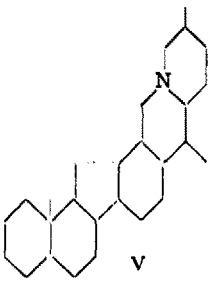
By D. H. R. BARTON[1], O. JEGER[2], V. PRELOG[2], and R. B. WOODWARD[3]

The characteristic alkaloids of *Veratrum* and related plant species are members of one or the other of two classes[4]. The first of these comprises a group of C_{27} bases, of relatively low oxygen content, which occur free, or in glycosidic combination. Two representatives, rubijervine (I) and isorubijervine (II) are simple steroidal alkaloids, while veratramine (III) and jervine (IV) are fashioned upon an interesting variant of the normal



steroid template. The second class embraces an array of highly oxygenated substances, designated *alkamines*, of the formulae $C_{27}H_{43}NO_n$ ($7 \leqslant n \leqslant 9$), which invariably occur in Nature as esters, containing one or more acyl functions derived from relatively simple organic acids (*vide infra*).

The structural problem presented by these ester alkaloids, already particularly fascinating in view of its intricacy, gains in importance from the established utility of the bases in medical practice in combatting hypertensive disorders. Experimental work with this class of compound offers also a special challenge since the multiplicity of hydrogen-bonding oxygen functions attached to a large alicyclic framework (*vide infra*) with hydrophobic properties may make crystallisation difficult even when the compounds are pure. Recent developments in Zürich, London, and Cambridge have led to a far-reaching clarification of the structural position. It is the purpose of this communication to summarize these advances.



It has been suggested recently[1] that these alkamines contain the basic skeleton (V), reminiscent of that of veratramine and jervine, but this framework has not hitherto been put to the test of accommodating the many oxygen atoms, whose disposition on this or another nucleus has been completely obscure.

Our point of departure was the alkamine *cevine*, $C_{27}H_{43}NO_8$. This base, which of its class had been the object of the most extensive prior degradative studies, is obtained by the *vigorous* alkaline hydrolysis of the naturally occurring ester alkaloids cevadine[2], veratridine[2], and cevacine[3]. More than a decade ago, JACOBS

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We wish to express our cordial appreciation to our collaborators: Messrs. C. J. W. BROOKS, J. S. FAWCETT, and P. DE MAYO (London), F. GAUTSCHI, E. KYBURZ, M. V. MIJOVIĆ, E. SUNDT, and CH. VOGEL (Zürich) and R. MIRZA (Cambridge) for their participation in the work summarized in this article. The experimental material, in so far as it has not already been published, will be presented in due course in papers in the Helv. chim. Acta and J. Chem. Soc.

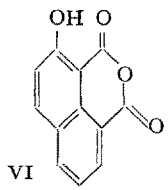
[4] T. A. HENRY, *The Plant Alkaloids*, 4th ed. (J. & A. Churchill, London, 1949), p. 700. – L. F. FIESER and M. FIESER, *Natural Products Related to Phenanthrene*, 3rd ed. (Reinhold Publishing Corp., New York, 1949), p. 600. – V. PRELOG and O. JEGER, *Solanum and Veratrum Alkaloids* in "The Alkaloids, Chemistry and Physiology", edited by R. H. F. MANSKE and H. L. HOLMES, Vol. III (Academic Press Inc., New York, 1953), p. 270. – J. MCKENNA, Quart. Rev. 7, 231 (1953).

[1] W. A. JACOBS and S. W. PELLETIER, J. Org. Chem. *18*, 765 (1953).

[2] T. A. HENRY, *The Plant Alkaloids*, 4th ed. (J. & A. Churchill, London, 1949), p. 700. – L. F. FIESER and M. FIESER, *Natural Products Related to Phenanthrene*, 3rd ed. (Reinhold Publishing Corp., New York, 1949), p. 600. – V. PRELOG and O. JEGER, *Solanum and Veratrum Alkaloids* in "The Alkaloids Chemistry and Physiology", edited by R. H. F. MANSKE and H. L. HOLMES, Vol. III (Academic Press Inc., New York, 1953), p. 270. – J. MCKENNA, Quart. Rev. 7, 231 (1953).

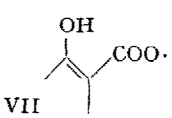
[3] S. M. KUPCHAN, D. LAVIE, C. V. DELIWALA, and B. Y. A. ANDOH, J. Amer. Chem. Soc. *75*, 5519 (1953).

and CRAIG[1] carried out a very careful study of the oxidation of cevine by chromic acid and sulfuric acid. Of the numerous products obtained, only succinic and methylsuccinic acids were identified, but many others were subjected to more or less extensive characterization. Of these, we should like to focus attention upon a *lactone tricarboxylic acid*, $C_{14}H_{18}O_8$[2]. When this substance was pyrolyzed, it was transformed smoothly into an *acid*, $C_{14}H_{14}O_6$, designated *decevinic acid*, in connection with which a veritable wealth of chemical detail was accumulated. Decevinic acid was found to consume exactly two moles of alkali on titration, and to give a dimethyl derivative, $C_{16}H_{18}O_6$, with diazomethane. Extensive hydrolytic and hydrogenation studies need not be treated here in extenso (*vide infra*), but special mention should be made of the key observation that decevinic acid is converted smoothly to *2-hydroxynaphthalic anhydride* (VI) on dehydrogenation with sulfur.

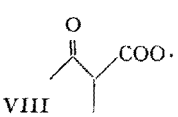


VI

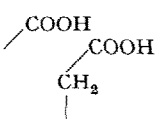
In attempting to deduce a satisfactory expression for decevinic acid, we made the tentative assumption that the acid, like its dehydrogenation product (VI), contained two carbon rings. By contrast, the precursor of decevinic acid–the saturated lactone tricarboxylic acid, $C_{14}H_{18}O_8$–must, from its elementary composition, contain no more than one alicyclic ring. It was therefore necessary to assume that the transformation of the precursor into decevinic acid must involve the formation of a new carbon-carbon bond, with closure of a second ring. Inspection of the structure of (VI) readily revealed a plausible framework for such a scheme. Thus the system (VII, or VIII), present in (VI), might well be present as well in decevinic acid, and contains a carbon-carbon bond of a type known



VII

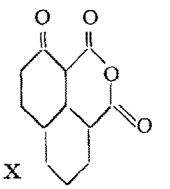


VIII

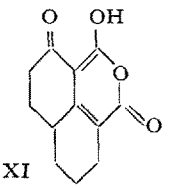


IX

to be formed in pyrolytic reactions from dibasic acids and their derivatives (IX). Now, if the presence in decevinic acid of the system (VII, or VIII) were accepted, it seemed not unlikely that further features of the structure of the dehydrogenation product (VI) devolved from closely allied groupings in the parent. In particular, it was tempting to assume the presence in the latter of an anhydride function, as in the part structure (X). At first, this supposition appeared to be doomed by the dibasic character of decevinic acid.

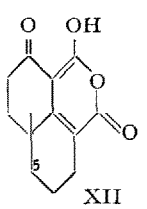


X

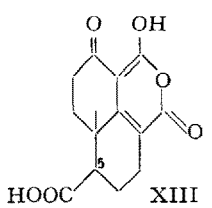


XI

Thus, since the congeries of oxygen atoms in (X) could not account for the consumption of more than one mole of diazomethane, the observed formation of a dimethyl derivative required that the remaining two oxygen atoms be incorporated in an acidic system. The functions of (X) must therefore be responsible for the smooth consumption of *one* mole of alkali—a most improbable state of affairs in view of the usual relatively low acidity of β-ketoesters, as well as the strong likelihood that the anhydride system would be susceptible to very ready cleavage. The dilemma was immediately resolved when it was realized that suitable incorporation of a double bond in (X) leads to the unique acyl glutaconic anhydride system shown in (XI). Such systems *behave as strong monobasic acids, and are relatively stable towards hydrolytic cleavage*[1]. Now the part structure (XI) contains the atoms $C_{12}H_{12}O_4$, while decevinic acid is $C_{14}H_{14}O_6$. The difference, $C_2H_2O_2 = CH_2 + CO_2$, suggests the presence in the latter of a methyl and a carboxyl group, both of which would be presumed to be lost in the dehydrogenation to (VI). This circumstance places the methyl group at the one available bridgehead, as in (XII), and only a carboxyl group remains to be placed. We may anticipate the argument in the sequel, and place this function at C.5, to give the full structure (XIII) for decevinic acid. In



XII



XIII

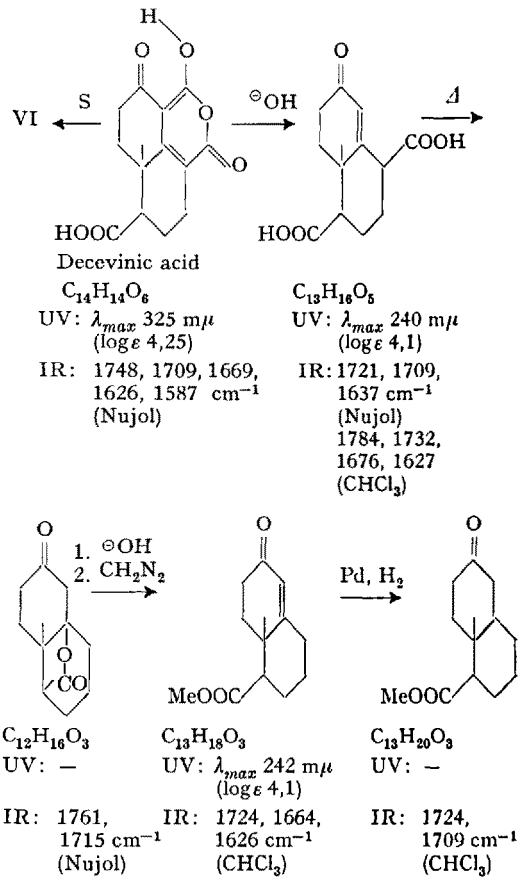
the light of this expression, the hitherto baffling chemistry of decevinic acid is virtually self-explanatory. Chart I summarizes the present position, and includes data, obtained in the course of new investigations in our laboratories, which have confirmed the structure (XIII) in every detail.

[1] L. C. CRAIG and W. A. JACOBS, J. Amer. Chem. Soc. *61*, 2252 (1939); J. Biol. Chem. *134*, 123 (1940); *141*, 253 (1941).
[2] L. C. CRAIG and W. A. JACOBS, J. Biol. Chem. *141*, 253 (1941).

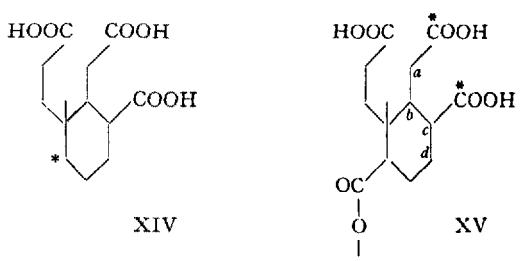
[1] N. BLAND and J. F. THORPE, J. Chem. Soc. *101*, 856 (1912). – *Cf.* also H. SCHMID and W. BENCZE, Helv. chim. Acta *36*, 1468 (1953).

Chart I[1]

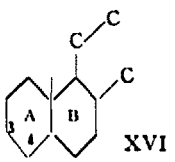
Degradation of Decevinic Acid



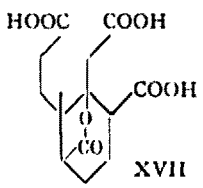
We turn now to the consideration of the structure of the lactone tricarboxylic acid from which decevinic acid is produced. On the basis of the preceding discussion, much of the structure may be written down at once, as in (XIV), and it remains only to interpolate a lactone group (–CO·O–). The placing of the carbonyl



terminus of this function at *, as in (XV), now confirmed by our new studies on decevinic acid, was first deduced from the probable origin of the skeleton of the degradation product in a steroid, or modified steroid, nucleus in cevine. *Only rings A and B of such a nucleus* (XVI) *are so constituted as to be precursal to* (XIV), and it is clear that cleavage of ring A of that system, between C.3 and C.4, leads simply and directly



to the left-hand portion of (XV). Now the ethereal oxygen atom of the lactone function must be attached to the carbon framework in the vicinity of the starred carboxyl groups of (XV), in order that its elimination may generate the double bond of the glutaconic anhydride system of decevinic acid (XIII). The vigor of the pyrolytic reaction perhaps bars a choice among the alternative sites—*a*, *b*, *c*, and *d* (in XV), but our new observations[1] that *the lactone ring of the precursor is five-membered* (infra-red band at 1782 cm⁻¹), *and that decevinic acid is formed by the action of base on the triester of the lactone tricarboxylic acid* narrow the possibilities to *d* and *b*, of which the latter is strongly favored. Thus, base-induced elimination of a lactone function under mild conditions is possible only if the acyloxy group is *β* to a carbomethoxyl group; further, attachment of the group at *d* requires a subsequent double-bond migration which must be initiated through removal of a substantially inactivated hydrogen atom (at *b*) as a proton. Further evidence, to be discussed in the sequel, is conclusive on the point at issue, and we may now write for the lactone tricarboxylic acid the full structure (XVII).



Among the other products isolated by JACOBS and CRAIG[2] from the chromic acid oxidation of cevine were a *hexane tetracarboxylic acid*, $C_{10}H_{14}O_8$, and a *heptane tetracarboxylic acid*, $C_{11}H_{16}O_8$. Previous attempts[3] to discern the structures of these acids have been unsuccessful. The clear implication[4] of the antecedent discussion is that the acids are (XVIII) and (XIX). The first of these deductions has now been confirmed

[1] F. GAUTSCHI, O. JEGER, V. PRELOG, and R. B. WOODWARD, Helv. chim. Acta *37* (1954), in preparation. – In this chart the stereochemistry of the compounds concerned is not indicated.

[1] F. GAUTSCHI, O. JEGER, V. PRELOG, and R. B. WOODWARD, Helv. chim. Acta *37* (1954), in preparation.

[2] L. C. CRAIG and W. A. JACOBS, J. Biol. Chem. *141*, 253 (1941).

[3] C. F. HUEBNER and W. A. JACOBS, J. Biol. Chem. *170*, 181 (1947). – L. F. FIESER and M. FIESER, *Natural Products Related to Phenanthrene*, 3rd ed. (Reinhold Publishing Corp., New York, 1949), p. 606. – W. Y. HUANG, H. L. HOLMES, and L. F. FIESER, J. Amer. Chem. Soc. *74*, 5920 (1952).

[4] *Cf.* N. ELMING, CH. VOGEL, O. JEGER, and V. PRELOG, Helv. chim. Acta *35*, 2541 (1952); *36*, 2022 (1953).

through the syntheses[1] (Chart II) of the *racemic* keto-anhydride (XX), whose infra-red spectrum is identical with that of the keto-anhydride, $C_9H_{10}O_4$, obtained from the cevine degradation product on pyrolysis.

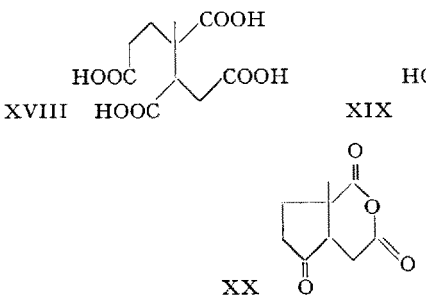
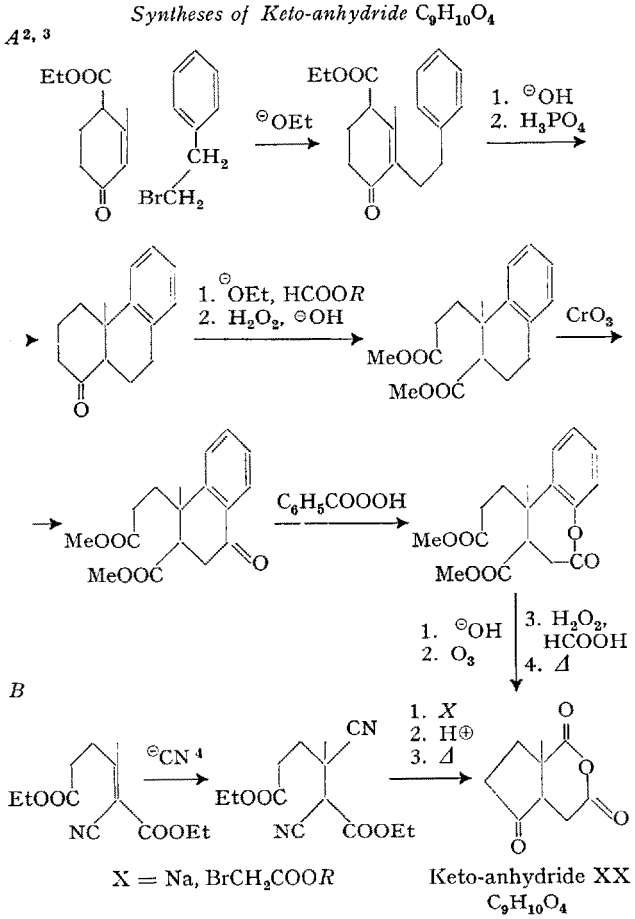


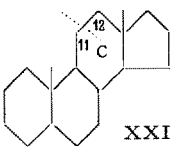
Chart II

Syntheses of Keto-anhydride $C_9H_{10}O_4$

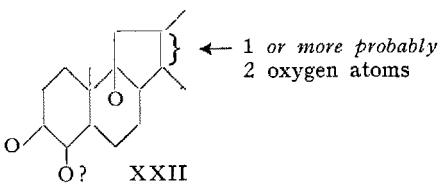


We are now in a position to assess the relevance of the new conclusions for the structure of cevine itself.

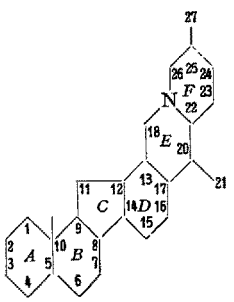
It is apparent that the oxidation studies demonstrate: (i) the presence of the normal *A-B* ring system of the steroids; (ii) the definite presence of oxygen at C.3 of ring *A*, and its probable presence at C.4; (iii) the presence of one, *and only one*, further oxygen atom in the *A-B* system, very probably at C.9. Beyond that, the appearance in the lactone tricarboxylic acid (XVII) of the chain $-CH_2COOH$ strongly suggests the presence in cevine of a five-membered ring C, since a normal steroid nucleus (XXI), however substituted, would al-



most certainly suffer cleavage between C.11 and C.12. All of these relationships are summarized in the expression (XXII), which includes one or two further oxygen atoms, attached to ring *C* in such wise as to facilitate oxidative cleavage in the observed sense.



In order to develop the structural position further, we must now adduce further evidence, of two sorts.



First, *we adopt for cevine the skeleton* (XXIII) *mentioned above* (see V), *suggested by* JACOBS *and* PELLETIER[1]. Their proposal was based on extensive dehydrogenation and correlative studies, which apart from certain special features (*vide infra*) need not be discussed here. The arguments of JACOBS and PELLETIER appear to us sound; further, it may be noted that our interpretation of the oxidation studies provides independent confirmation of the *A-B-C* portion of the skeleton, and that the ensuing discussion will include

[1] O. JEGER, R. MIRZA V. PRELOG, CH. VOGEL, and R. B. WOODWARD, Helv. chim. Acta *37* (1954), in preparation.

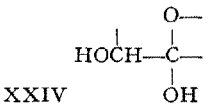
[2] This synthesis has the advantage that from a preparation starting with optically active analogs derived from dehydro-abietic acid, it will be possible to determine the absolute configuration of C.10 in cevine and germine.

[3] *Cf.* G. STORK und W. BURGSTHALER, J. Amer. Chem. Soc. *75*, 3544 (1951) and also J. KALVODA, D. ARIGONI, and O. JEGER, Helv. chim. Acta *37* (1954), in preparation.

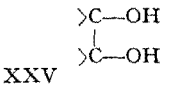
[4] D. K. BANERJEE, J. Ind. Chem. Soc. *17*, 424 (1940).

[1] W. A. JACOBS and S. W. PELLETIER, J. Org. Chem. *18*, 765 (1953).

new evidence which corroborates the six-membered character of ring *D*. Second, *we accept the presence in cevine of a masked secondary α-ketol system* (XXIV), *and an independent ditertiary* 1,2-*glycol system* (XXV), neither of whose hydroxyl groups is β to nitrogen. The first of these functions has been proposed in an earlier

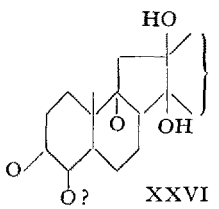


XXIV



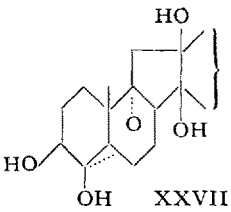
XXV

paper[1], and the detailed consequences of its presence will be discussed below. The ditertiary glycol system, and the restriction on its position, is deduced from these facts: (i) cevine forms a triacetate which is stable to chromic acid (and therefore cannot contain a secondary hydroxyl group) but readily consumes one mole of periodic acid and of lead tetraacetate[2]; (ii) our model experiments have shown that while β-dialkylamino-alcohols are not readily attacked[3] by lead tetraacetate, tertiary α-aminoketones consume one mole or more of this reagent at room temperature[4]. Consequently, were either of the hydroxyl groups of the glycol system β to nitrogen, consumption of lead tetraacetate by cevine triacetate would not stop at one mole. It is now clear that the glycol system can only be placed, on the skeleton (XXVI), at the *C-D* ring junction, as suggested earlier by our analysis of the oxidation results (cf. XXII). Further, the desirability of attaching oxy-



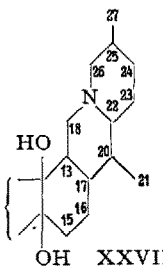
XXVI

gen atoms at both C.3 and C.4 of ring *A* suggests at once that the masked ketol system (XXIV) be so placed; indeed, there is scarcely an alternative, since (i) ring *D* is excluded by the prior placement of the glycol function, and (ii) except for the known oxygen atom at C.9, no further oxygen can be attached to the *A-B-C* system. These arguments lead to the expression (XXVII), which incorporates five of the eight oxygen atoms of cevine.

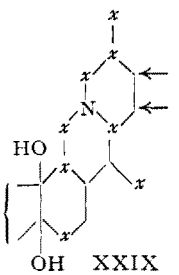


XXVII

We may now come to grips with the problem of assigning positions to the remaining three hydroxyl groups of cevine. It is clear that all of these groups must be placed on the *D-E-F* system (XXVIII). Further, all of the positions marked *x* in (XXIX) may be

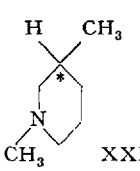


XXVIII



XXIX

rejected as possible points for attachment of hydroxyl groups on very simple grounds. Thus: (i) C.13 and C.15 are adjacent to the periodate sensitive *C-D* glycol system, and attachment of –OH at these sites would of necessity lead to the consumption of more than the observed amount of periodic acid by cevine; (ii) since *Kuhn-Roth* oxidation[1] of cevine reveals the presence of *at least three* C–Me *groups*, C.21 and C.27 cannot be substituted; this is confirmed by the oxidation of cevadine orthoacetate acetate to a ketone which is stable to chromic acid (*vide infra*)[2]; (iii) no oxygen is present at C.18, C.22, or C.26, since cevine shows none of the very characteristic properties of an α-carbinolamine; (iv) distillation of cevine with zinc dust and with soda lime and followed by hydrogenation of the resulting volatile bases and further processing gives a mixture from which *optically active*



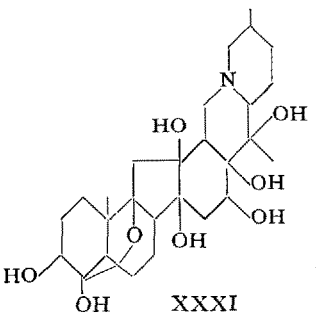
XXX

N-*methyl-β-pipecoline* (XXX) is isolable[3]; it is inconceivable that an hydroxyl group at C.25 could be replaced by hydrogen with maintenance of asymmetry

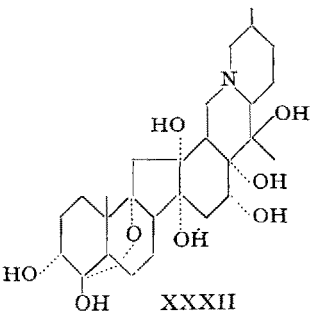
[1] D. H. R. Barton and J. F. Eastham, J. Chem. Soc. *1953*, 424
[2] D. H. R. Barton and C. J. W. Brooks, Chem. Ind. *1953*, 1366. – D. H. R. Barton, C. J. W. Brooks, and J. S. Fawcett, J. Chem. Soc. *1954*, in press.
[3] *Cf.* N. J. Leonard and M. A. Rebenstorf, J. Amer. Chem. Soc. *67*, 49 (1945).
[4] D. H. R. Barton, C. J. W. Brooks, and J. S. Fawcett, J. Chem. Soc. *1954*, in press. – V. Prelog and A. Kathriner, Helv. chim. Acta *31*, 505 (1948).

[1] D. H. R. Barton, C. J. W. Brooks, and J. S. Fawcett, J. Chem. Soc. *1954*, in press.
[2] D. H. R. Barton, C. J. W. Brooks, and P. de Mayo, J. Chem. Soc., in preparation.
[3] W. A. Jacobs and L. C. Craig, J. Biol. Chem. *120*, 447 (1937).

during the course of these brutal operations. Of the remaining available positions, we reject C.23 and C.24 (XXIX, *arrows*) for the perhaps somewhat less compelling reason that JACOBS and his collaborators, who isolated a long series of relatively simple pyridine and piperidine bases as products of drastic degradations of cevine, did not report the formation of presumably readily detectable 4-pyridones or phenolic 3-hydroxypyridines, which were easily found[1] among the products from alkaloids containing oxygen in ring *F* [*cf.* jervine (IV)]. Since only three sites are left, for three hydroxyl groups, we may now write for cevine the structure (XXXI) which is complete, apart from stereochemical relationships. The presence in (XXXI) of a new 1,2,3-



XXXI



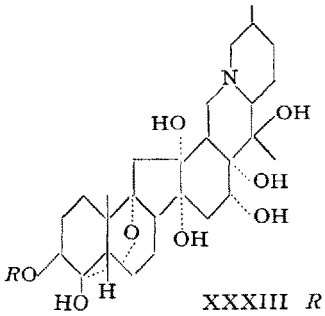
XXXII

triol system might present occasion for concern, in view of the consumption of only two moles of periodic acid by cevine, until it is recognized that pairs of adjacent hydroxyl groups in certain fixed geometric relationships, as in (XXXII)[2] are not susceptible to periodate cleavage[3].

Further, the extensive consumption[4] of lead tetraacetate by cevine, slow though it be after two moles, tends to lend support to the presence of adjacent hydroxyl groups other than those known to occupy the *C-D* bridgeheads. We may note further at this point that these same circumstances permit the unambiguous assignment of a *cis* relationship to the latter pair (*cf.* XXXII; for orientation of the hydroxyl groups at C.3, C.12, C.14, C.16, and C.17, *vide infra*).

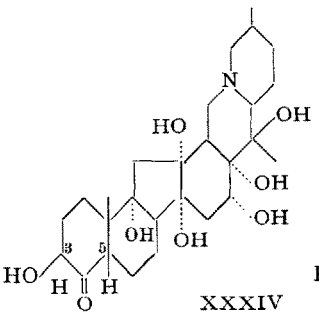
Abundant corroborative evidence for virtually all of the structural relationship embodied in the structure (XXXII) for cevine may now be adduced from several quarters. We shall discuss the several functions of the molecule, and their interactions, in turn.

The A-B system.—It is now well-known that cevine is not the true alkamine of the naturally occurring ester alkaloids from which it is derived. *Cevacine*[1], an acetate, *veratridine*[2], a veratrate, and *cevadine*[2], an angelate, all yield on mild methanolysis a new alkamine, *veracevine*, $C_{27}H_{43}NO_8$, isomeric with cevine. Veracevine is transformed[3] by gentle treatment with alkalies into cevagenine, also $C_{27}H_{43}NO_8$, and the latter in turn, under more strongly basic conditions, is isomerized[4] to cevine. Veracevine and cevine contain no carbonyl group, while cevagenine does contain such a function. Our structural proposals accomodate these remarkable relationships with ease. It may be noted first that the cooperation of a C.9 hydroxyl group and a ketol system in ring *A* in forming the masked ketol system discussed above *requires* a *cis* junction of rings *A* and *B*. We propose that veracevine is (XXXIII) in which the hydroxyl group at C.3 occupies the relatively unstable

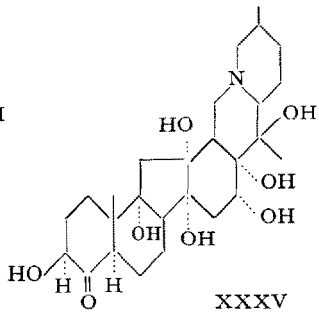


XXXIII $R = H$

axial β orientation; it is worthy of note here that hydroxyl groups at C.3 in naturally occurring C_{27} steroids have without exception been found to be β



XXXIV



XXXV

[1] W. A. JACOBS, L. C. CRAIG, and G. I. LAVIN, J. Biol. Chem. *141*, 51 (1941).

[2] We would emphasize that, whilst we regard the stereochemical configurations at C.3, C.4, C.5, C.9, and C.10 as in (XXXII) as established by the peculiar cage like structure of the molecule, the configurations allotted elsewhere in rings *C*, *D*, and *E*, although possibly correct, are used here only in an illustrative sense. The same qualification applies to all subsequent formulae in this article.

[3] *Cf.* O. WINTERSTEINER and M. MOORE, J. Amer. Chem. Soc. *72*, 1923 (1950). It is further worthy of note, in connection with the very ready cleavage of the C.12–C.14 glycol system, that *cis* cyclopentane-1,2-diol is cleaved by lead tetraacetate more then 8000 times as fast as *cis* cyclohexane-1,2 diol [R. CRIEGEE, L. KRAFT, and B. RANK, Lieb. Ann. *507*, 159 (1933), and R. CRIEGEE, E. BÜCHNER, and W. WALTER, Ber. *73*, 571 (1940)].

[4] D. H. R. BARTON and J. F. EASTHAM, J. Chem. Soc. *1953*, 424.

[1] S. M. KUPCHAN, D. LAVIE, C. V. DELIWALA, and B. Y. A. ANDOH, J. Amer. Chem. Soc. *75*, 5519 (1953).

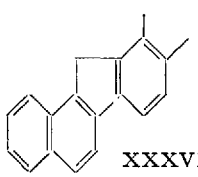
[2] T. A. HENRY, *The Plant Alkaloids*, 4th ed. (J. & A. Churchill, London, 1949), p. 700. – L. F. FIESER and M. FIESER, *Natural Products Related to Phenanthrene*, 3rd ed. (Reinhold Publishing Corp., New York, 1949), p. 600. – V. PRELOG and O. JEGER, *Solanum and Veratrum Alkaloids* in "The Alkaloids, Chemistry and Physiology", edited by R. H. F. MANSKE and H. L. HOLMES, Vol. III (Academic Press Inc., New York, 1953), p. 270. – J. MCKENNA, Quart. Rev. *7*, 231 (1953).

[3] S. M. KUPCHAN, D. LAVIE, C. V. DELIWALA, and B. Y. A. ANDOH, J. Amer. Chem. Soc. *75*, 5519 (1953). – S. W. PELLETIER and W. A. JACOBS, J. Amer. Chem. Soc. *75*, 3248 (1953).

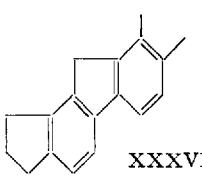
[4] A. STOLL and E. SEEBECK, Helv. chim. Acta *35*, 1270 (1952)

oriented. When veracevine is treated with base, it may be expected that the ring-chain tautomeric species (XXXIV) will suffer isomerization, through removal and re-addition of a proton at C.5, to the *trans* decalone isomer, cevagenine (XXXV)[1]. Three points of special interest may be cited in connection with these changes: (i) in the *trans* decalone system of cevagenine (XXXV), steric factors prevent the masking of the carbonyl group through interaction with the C.9 hydroxyl function; (ii) the C.3 hydroxyl group has now become *equatorial*, with no change in configuration at C.3; (iii) the more ready removal of the proton at C.5 than that at C.3, also activated by the carbonyl group, may well be a consequence of the axial orientation of the hydrogen at C.5, and the equatorial orientation of the hydrogen at C.3, in the intermediate (XXXIV). The formation of cevine (XXXII), the final member of the series, is now seen to involve inversion at C.3 and re-inversion at C.5, with reconstitution of the 4,9-oxide bridge. In sum the transformation of veracevine to cevine simply involves the inversion of the unstable axial C.3 hydroxyl group to the more stable equatorial orientation.

These views anent the ring *A* systems of cevine and its congeners are supported by several further lines of evidence. It may be noted first that the presence of the masked ketol system in ring *A*, with its consequent potentiality for ring contraction, accounts in a very satisfactory manner for the appearance, in the dehydrogenation studies of the JACOBS school, of parallel series of aromatic products, some containing the *benzfluorene* system (XXXVI), and others of the cyclopentanofluorene type (XXXVII). Second we may point to the oxidation of "anhydrocevine" (*vide infra*)

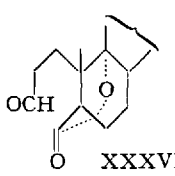


XXXVI

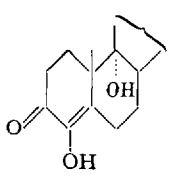


XXXVII

by periodic acid to an *aldehydo-γ-lactone* (XXXVIII)[2]. Third, the oxidation of cevagenine (XXXV) by bismuth oxide or by triphenyltetrazoliumchloride

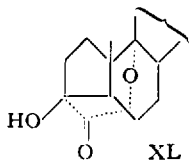


XXXVIII



XXXIX

gives a *diosphenol* (XXXIX)[1], whose relevant properties parallel exactly those of 3,4-diketocholestane (enol). Fourth, a second product of the bismuth oxide oxidation of cevagenine is an *hydroxy-δ-lactone*, clearly of the structure (XL); this substance is obtainable in like manner from veracevine and cevine, as well as from cevagenine[2].



XL

The placing of the ester groups in the natural alkaloids.—While veracevine[2], cevagenine and cevine[3] consume two moles of periodic acid, cevadine consumes only one mole of that reagent, and *gives a product which is not a γ-lactone*[4]. Consequently, the ester group must be at C.3 and we may formulate *cevadine* as (XLI = XXXIII, $R = CH_3CH{:}C(CH_3)CO-$ = Ang), *veratridine* as (XLI = XXXIII, $R = 3,4\text{-}(MeO)_2C_6H_3CO-$), and *cevacine* as (XLI = XXXIII, $R = CH_3CO-$).

The hydroxyl group at C.17.—Evidence suggesting the presence of an hydroxyl group at C.17 is now available from our studies of the *anhydro* compounds of the cevine series. These compounds have ordinarily been produced[5] in acetylation experiments under vigorous conditions, using perchloric acid as a catalyst. In this way, for example, cevine is converted into "*anhydrocevine tetraacetate*". "Anhydrocevine" itself may be obtained from its "tetraacetate" by vigorous hydrolysis[6]. Since lead tetraacetate titrations[6] show that the *C-D* glycol system is no longer present in the anhydro compounds, it has been assumed hitherto that their formation involved cooperation of the hydroxyl group at C.12 and or that at C.14 with another such function in formation of a cyclic ether. *We have now found that the presumed "anhydrocevine" is in fact cevine orthoacetate*[7]. It gives one mole of acetic acid on hydrolysis under *acidic* conditions, and its infra-red spectrum possesses a series of bands which is found in ethyl orthoacetate. On catalytic hydrogenation it is converted to a *dihydro derivative* which gives *acetaldehyde* on hydrolysis. The new formulation requires no less than *three*

[1] This formula for cevagenine, although very probably correct, is not established in every detail. Thus the ketonic oxygen could conceivably be attached at C.3 and the secondary hydroxyl of the α-ketol system at C.4.

[2] D. H. R. BARTON and C. J. W. BROOKS, Chem. Ind. *1953*, 1366. – D. H. R. BARTON, C. J. W. BROOKS, and J. S. FAWCETT, J. Chem. Soc. *1954*, in press.

[1] H. AUTERHOFF, Arch. Pharm. *286*, 319 (1953). – E. SUNDT, O. JEGER, and V. PRELOG, Chem. Ind. *1953*, 1365. – A. STOLL, D. STAUFFACHER, and E. SEEBECK, Helv. chim. Acta *36*, 2027 (1953).

[2] S. M. KUPCHAN and D. LAVIE, J. Amer. Chem. Soc. *76*, 314 (1954).

[3] D. H. R. BARTON and J. F. EASTHAM, J. Chem. Soc. *1953*, 424,

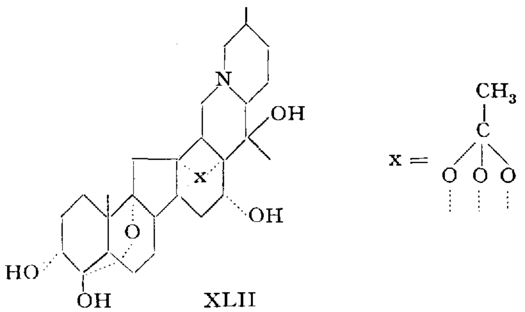
[4] D. H. R. BARTON, C. J. W. BROOKS, and P. DE MAYO, J. Chem. Soc., in preparation.

[5] A. STOLL and E. SEEBECK, Helv. chim. Acta *35*, 1270 (1952); *36*, 189 (1953).

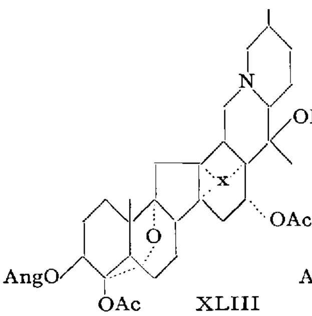
[6] A. STOLL and E. SEEBECK, Helv. chim. Acta *35*, 1943 (1952).

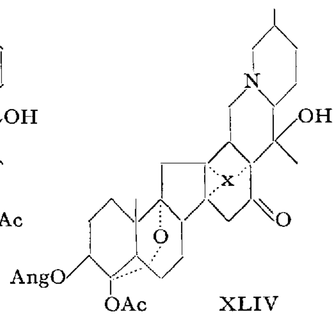
[7] D. H. R. BARTON, C. J. W. BROOKS, and J. S. FAWCETT, J. Chem. Soc. *1954*, in press. – D. H. R. BARTON, C. J. W. BROOKS, and P. DE MAYO, J. Chem. Soc. *1954*, in preparation.

tertiary hydroxyl groups so disposed in space as to permit orthoester formation. Since one of these must be that at C.12 or C.14, steric considerations, and the exclusions discussed above in connection with our initial placement of the *D-E-F* oxygen atoms, require a hydroxyl group at C.17, and the formulation of cevine orthoacetate as (XLII)[1].


XLII

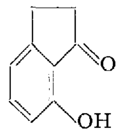
The hydroxyl group at C.16.—Conclusive evidence for the hydroxyl group at C.16 is available from two new lines of experiment. When cevadine orthoacetate diacetate (XLIII) is methanolized, it loses one acetyl group.


XLIII

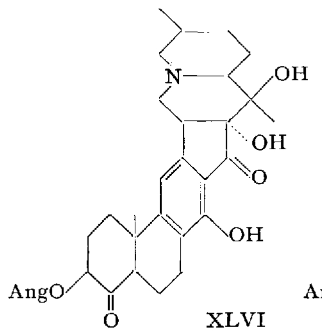

XLIV

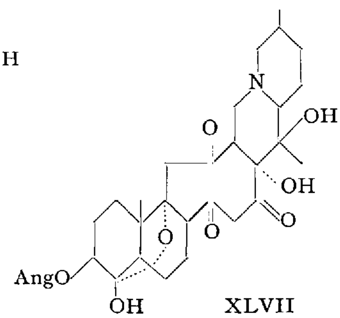
That the hydroxyl group freed is secondary is shown by oxidation to a ketone (XLIV), which is stable to chromic acid[2].

More striking evidence has been obtained through mild oxidation of cevadine itself (XLI, R = Ang) with chromic acid in the presence of sulfuric acid[3]. The product of this oxidation is a *substance*, $C_{32}H_{41}NO_7$, in which the groups RCOO–, >C=O, and the 7-hydroxy-indanone system (XLV) have been identified unequivocally by physical data and chemical reactions. Thus,

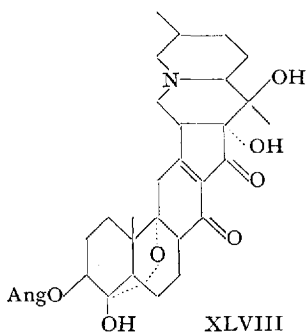
XLV


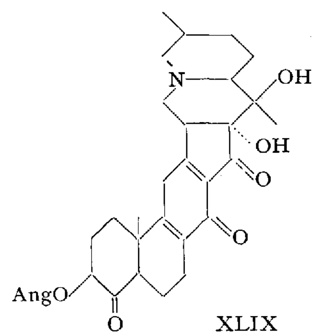
the infra-red spectrum of the compound possesses bands at 1730 cm^{-1} (RCOO)–, 1715 cm^{-1} (C=O), 1695 cm^{-1} (C=O of 7-hydroxyindanone), 1639 and 1597 cm^{-1} (aromatic ring of 7-hydroxyindanone); its ultraviolet absorption in neutral solution possesses maxima at 273 mμ and 325 mμ, and in alkaline media at 240 mμ, 282 mμ, and 374 mμ. It gives a strong positive ferric reaction, forms a *monomethyl ether* with diazomethane, and is reduced by lithium aluminium hydride to a *substance*, $C_{27}H_{39}NO_6$, which *no longer contains the indanone carbonyl group*, and shows simple *phenolic* properties. It is clear that the oxidation product possesses the structure (XLVI). Its formation from cevadine


XLVI


XLVII

(XLI, R = Ang) is readily formulable in terms of the sequence (XLI) → (XLVII) → (XLVIII) → (XLIX) → (XLVI), which is possible only with oxygen at C.16.


XLVIII


XLIX

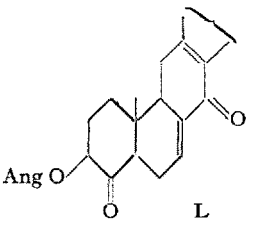
It may be noted further that these changes (i) confirm the identification of ring D as six-membered, (ii) substantiate the presence of –OH at C.17, since in its absence β-elimination of the C.20 hydroxyl group would probably follow generation of >C=O at C.16, and (iii) dispose once and for all of the remote alternative, implied above in connection with the discussion of

[1] It should be pointed out that on geometric grounds one end of the orthoacetate system might possibly terminate at C.20 (seven-membered ring!), *or at C.13*. Oxygen at C.13 in these alkaloids is presumably excluded by our periodate and lead tetraacetate oxidation studies *(vide supra)*; nevertheless, it is not entirely out of the question that special circumstances might render a ketol of the type –CO–C(12)–C(13)(–CH)< non-cleavable, and in the absence, as yet, of *direct* evidence for oxygen at C.17, the possibility that the hydroxyl group attached at that position in the above formulae should be moved to C.13 should not be dismissed.

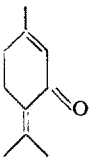
[2] D. H. R. BARTON, C. J. W. BROOKS, and P. DE MAYO, J. Chem. Soc., in preparation.

[3] M. V. MIJOVIĆ, E. SUNDT, E. KYBURZ, O. JEGER, and V. PRELOG, Helv. chim. Acta *37* (1954), in preparation.

constitution of the precursor of decevinic acid, that the ether bridge might terminate at C.7, rather than C.9; for in that case, the intermediate in the above series would have the part structure (L), and it is well-known



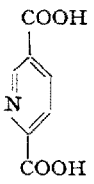
L



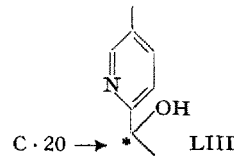
LI

that such systems do not undergo ready change to phenolic isomers [*cf.* piperitenone (LI)][1]. The equatorial orientation of C.16 hydroxyl group is suggested by the readiness by which acetylation and deacetylation reactions take place at that centre.

The hydroxyl group at C.20.—No new evidence is as yet available which confirms the placing of an hydroxyl group at C.20. On the other hand, the early observation of the formation of a *base*, $C_8H_{11}NO$, on selenium dehydrogenation of cevine clearly tends to validate the placement. The base was oxidized by permanganate to the *acid* (LII)[2], and must therefore be a side-chain



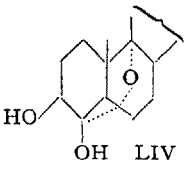
LII



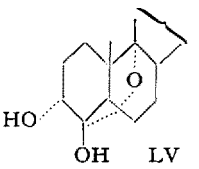
LIII

hydroxylated 2-ethyl-5-methylpyridine. The absence of primary hydroxyl groups in cevine renders most unlikely the presence of such groups in the degradation product; hence we conclude that the base is oxygenated at * (LIII), which corresponds to C.20 in cevine.

Other alkamines and ester alkaloids.—The behavior of the alkamines from the other ester alkaloids of *Veratrum* species parallels exactly that of the cevine group. *Germine*[3], $C_{27}H_{43}NO_8$, an isomer of cevine, and the alkamine of the natural alkaloids *protoveratridine, germerine, germidine, neogermitrine,* and *germitrine,* is successively isomerizable to a ketonic isomer, *isogermine*[3], and a non-ketonic isomer, *pseudogermine*[4]. In the light of the above discussion, these observations alone suggest strongly that germine and pseudogermine possess the part structures (LIV) and (LV). Proof of this relationship is now available in the observation that the

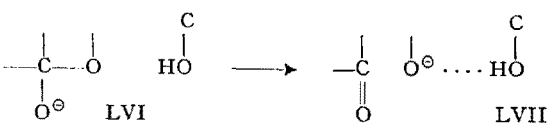


LIV



LV

acetonides of the two alkamines are converted to the same aldehydo-γ-lactone (characterized as the oxime) by periodic acid[1]. When the similarity of the dehydrogenation products from the two alkamines, and the formation from both of the same hexane tetracarboxylic acid (XVIII) are considered[2], it is apparent that germine differs from veracevine only in the placing of one or more hydroxyl groups in the *C-D-E-F* system. Little evidence is available which permits assessment of the possible differences, but the apparent greater difficulty of the change germine → isogermine, as compared with veracevine → cevagenine may possibly indicate the absence in germine of the C.14 hydroxyl group of veracevine; in the presence of such a function, the opening of the C.4–C.9 ether bridge is undoubtedly facilitated



LVI LVII

by internal solvation[3] (LVI → LVII). *Pari passu,* these circumstances provide the basis for the α-orientation of this group in cevine (*cf.* XXXII, *et seq.*).

Very little is known concerning the remaining alkamines of the *Veratrum* groups—*zygadenine*[4], $C_{27}H_{43}NO_7$, and *protoverine*[4], $C_{27}H_{43}NO_9$—but their ready isomerization provides a basis for confidence that they too contain the unique 3,4-dihydroxy-4,9-oxido system of veracevine.

Zusammenfassung

Die sauerstoffreichen Veratrum-Alkaloide gewinnen in letzter Zeit als blutdrucksenkende Arzneimittel immer mehr an Bedeutung. Darüber hinaus erwecken sie ein

[1] *Cf.* W. KUHN and H. SCHINZ, Helv. chim. Acta *36*, 161 (1953).

[2] L. C. CRAIG and W. A. JACOBS, J. Biol. Chem. *139*, 263 (1941).

[3] T. A. HENRY, *The Plant Alkaloids*, 4th ed. (J. & A. Churchill, London, 1949), p. 700. – L. F. FIESER and M. FIESER, *Natural Products Related to Phenanthrene*, 3rd ed. (Reinhold Publishing Corp., New York, 1949), p. 600. – V. PRELOG and O. JEGER, *Solanum and Veratrum Alkaloids* in "The Alkaloids, Chemistry and Physiology" edited by R. H. F. MANSKE and H. L. HOLMES, Vol. III (Academic Press Inc., New York, 1953), p. 270. – J. MCKENNA, Quart. Rev. *7*, 231 (1953).

[4] S. M. KUPCHAN, M. FIESER, C. R. NARAYANAN, L. F. FIESER, and J. FRIED, J. Amer. Chem. Soc. *76* (1954), in press.

[1] S. M. KUPCHAN, M. FIESER, C. R. NARAYANAN, L. F. FIESER, and J. FRIED, J. Amer. Chem. Soc. *76* (1954), in press.

[2] L. C. CRAIG and W. A. JACOBS, J. Biol. Chem. *148*, 57 (1943).

[3] *Cf.* the differential ease of elimination of glycolic acid from strychninolic and dihydrostrychninonic acids: H. L. HOLMES in *The Alkaloids, Chemistry and Physiology*, edited by R. H. F. MANSKE and H. L. HOLMES, Vol. II (Academic Press Inc., New York, 1952), p. 517.

[4] T. A. HENRY, *The Plant Alkaloids*, 4th ed. (J. & A. Churchill, London, 1949), p. 709. – L. F. FIESER and M. FIESER, *Natural Products Related to Phenanthrene*, 3rd ed. (Reinhold Publishing Corp., New York, 1949), p. 607. – V. PRELOG and O. JEGER, *Solanum and Veratrum Alkaloids* in "The Alkaloids, Chemistry and Physiology", edited by R. H. F. MANSKE and H. L. HOLMES, Vol. III (Academic Press Inc., New York, 1953), p. 308. – J. MCKENNA, Quart. Rev. *7*, 231 (1953).

grosses Interesse vom Standpunkt des organischen Chemikers, da sie zu den kompliziertest gebauten niedrig molekularen Naturstoffen gehören.

Bei der Konstitutionsaufklärung des Alkamins Cevin (XXXII), das eine Schlüsselstellung in dieser Reihe einnimmt, wurden unter anderem die folgenden neuen Ergebnisse erhalten:

a) Die Konstitution zweier Abbauprodukte des Cevins – der Decevinsäure (XIII) und der «Hexan-tetracarbonsäure» (XVIII) – konnte bestimmt werden.

b) Das sogenannte Anhydrocevin wurde als ein Orthoazetat XLII erkannt.

c) Das Cevadin [XLI, $R = CH_3CH{=}C(CH_3)CO$], aus dem das Cevin durch alkalische Hydrolyse entsteht, gab bei milder Oxydation mit Chromsäure durch spontane Zyklisation des entstandenen Zwischenproduktes XLVII ein 7-Oxy-hydrindanon-(1)-Derivat (XLVI).

Die Interpretation dieser und bereits bekannter Tatsachen an Hand des von JACOBS und PELLETIER vorgeschlagenen Kohlenstoff-Stickstoff-Gerüstes erlaubte erstmals, die Konstitution eines Naturstoffes mit einem hydrophoben polyzyklischen Ringsystem und zahlreichen hydrophilen Sauerstoffunktionen weitgehend aufzuklären und dessen Konfiguration teilweise zu bestimmen.