the ether solution left in the ice-box for 24 hours. A dilute solution of sodium hydroxide then was added until all the sodium sulfate dissolved; the ether layer was separated after thorough shaking and dried again with sodium sulfate. The resulting product was obtained in a yield of 794 mg. and was converted into a picrolonate.

This compound melted at 70° and gave no depression on admixture with the previous product. The free bases liberated from both picrolonates had identical ultraviolet spectra in neutral, alkaline and acidic alcohol.

Reduction of the Compound XXIX (X = Br) with Sodium Borohydride.—The free base of XXIX was converted into the bromide by treatment with an equivalent of hydrobromic acid in methanol and evaporating to dryness. The bromide proved to be gummy. It was (16 g.) dissolved in 200 ml. of methanol and treated with 15 g. of sodium borohydride. The mixture was refluxed for 2 hours. Most of the solvent was removed *in vacuo;* dilute sodium hydroxide was added and the basic product extracted with ether. The yield was 10.3 g. of a light yellow oil. The product was characterized as a picrate. It melted at 158° after crystallization from methanol and was assigned structure XXXI.

Anal. Calcd. for $C_{23}H_{26}N_4O_9$: C, 54.97; H, 5.22; N, 11.15. Found: C, 54.98; H, 5.18; N, 11.01.

Oxidation of Compound XXXI with Potassium Permanganate.—Compound XXXI (1.03 g.) was dissolved in 100 ml. of acetone and a solution of potassium permanganate (2.98 g.) in 200 ml. of acetone was added dropwise with cooling to 0° and stirring. After the addition was complete the solution was stirred overnight at room temperature. The precipitated manganese dioxide was filtered off and the filtrate evaporated to dryness. The residue was dissolved in chloroform and washed with dilute acid and water. The yield was 265 mg. of an amorphous foam (fraction A). The manganese dioxide was suspended in water and chloroform, and cooled with ice, when sulfur dioxide was introduced until a clear solution resulted. The chloroform layer was separated and the aqueous layer repeatedly extracted. The combined chloroform extracts yielded 559 mg. of an amorphous foam (fraction B). The two fractions A and B were combined and separated into acidic and neutral portions in the standard way.

The acidic fraction (546 mg.) crystallized. It was recrystallized from ethyl acetate to a melting point of 174–175°. The structure XXXV was assigned to it.

Anal. Calcd. for $C_{14}H_{17}NO_5$: C, 60.20; H, 6.14; N, 5.02. Found: C, 60.26; H, 6.45; N, 5.06.

The acid was further characterized by esterification with diazomethane and reduction of the ester with lithium aluminum hydride. The aminoalcohol XXXVII was thus obtained in an 87% yield and characterized as a picrate. It melted at 174–175° after crystallization from methanol.

Anal. Calcd. for $C_{20}H_{24}N_4O_7$: C, 50.00; H, 5.04; N, 11.66. Found: C, 49.86; H, 4.96; N, 11.89.

The neutral material (260 mg.) was purified by chromatography on alumina. The bulk of the product was eluted with 0.5% methanol in chloroform and recrystallized for analysis from ethyl acetate to a melting point of 175°. Structure XXXVI was assigned to it.

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.29; H, 6.27; N, 6.87.

Oxidation of Compound XXX with Permanganate.—The compound XXX (1.00 g.) was oxidized and worked up exactly as in the previous experiment. The amount of permanganate used was 5 g. The only difference in the working up was that owing to the great water solubility of the resulting acid all extractions of aqueous layers were performed continuously with ether. The desired dicarboxylic acid was purified conveniently by extracting the acidified aqueous layer with ether in a separatory funnel, discarding the ether extract and extracting the dicarboxylic acid continuously from the aqueous layer. It was obtained as 310 mg. of a foam. The acid was esterified in methanolic solution by ethereal diazomethane and the ester was chromatographed on 14.4 g. of neutral alumina. The purified ester XXXIII was eluted by benzene–ether (1:1) as 130 mg. of a slowly crystallizing oil. It was recrystallized from ether to a melting point of 123°.

Anal. Calcd. for $C_{20}H_{25}NO_7$: C, 61.37; H, 6.44; N, 3.57. Found: C, 61.73; H, 6.55; N, 3.86.

The neutral material (251 mg.) was chromatographed on 10 g. of alumina. The lactam XXXII was eluted with ether as 143 mg. of crystalline material. It was recrystallized from ether to a melting point of 109–110°.

Anal. Calcd. for $C_{20}H_{25}NO_3$: C, 73.36; H, 7.70; N, 4.28. Found: C, 73.22; H, 7.49; N, 3.96.

FREDERICTON, NEW BRUNSWICK
CANADA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, HARVARD UNIVERSITY]

Schoenocaulon Alkaloids. III. The Bismuth Oxide Oxidation of Veracevine, Cevagenine and Cevine[1a]

BY S. MORRIS KUPCHAN AND DAVID LAVIE[1b]

RECEIVED JULY 30, 1954

Oxidation of cevine with bismuth oxide in acetic acid yields cevinilic acid δ-lactone, $C_{27}H_{41}O_8N$. Similar oxidations of veracevine and cevagenine afford the same product. Veracevine consumes two moles of periodic acid; veracevine triacetate consumes one mole of periodic acid and is stable to chromic acid in acetic acid. These facts are most satisfactorily explained on the basis of the recently-advanced structures I, II and III for veracevine, cevagenine and cevine, respectively.

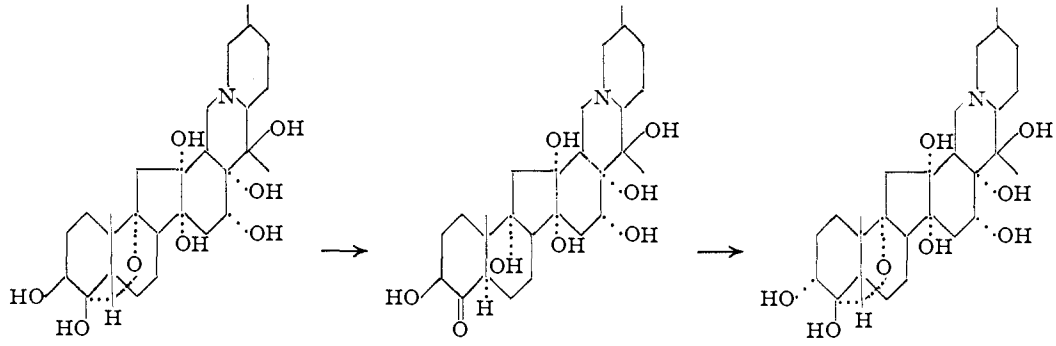
The view that veracevine and cevine contain the same α-ketol-5-membered hemiketal system and differ only in the configuration of the hydroxyl group of the α-ketol system was entertained in a recent communication.[2] These partial structures were supported by the facts: (1) bismuth oxide oxidation of veracevine, cevagenine and cevine yields the same crystalline hydroxy-δ-lactone, (2) veracevine, like cevine, consumes two moles of periodic acid and (3) veracevine triacetate, like cevine triacetate, is stable to chromic acid in acetic acid, and consumes one mole of periodic acid.

Subsequent rapid developments in several laboratories have led to elaboration of substantially complete formulations for veracevine, cevagenine and cevine (I, II, III).[3] The present paper presents details of our experience with the bismuth oxide oxidation of the schoenocaulon alkamines. The results are interpreted in the light of the above structures.

(1) (a) This investigation was supported by grants from the National Institutes of Health (RG-2553(C2)), Research Corporation, and the Plymouth County Chapter of the Massachusetts Heart Association. (b) Weizmann Institute of Science, Rehovot, Israel.

(2) Paper II, S. M. Kupchan and D. Lavie, THIS JOURNAL, **76**, 314 (1954).

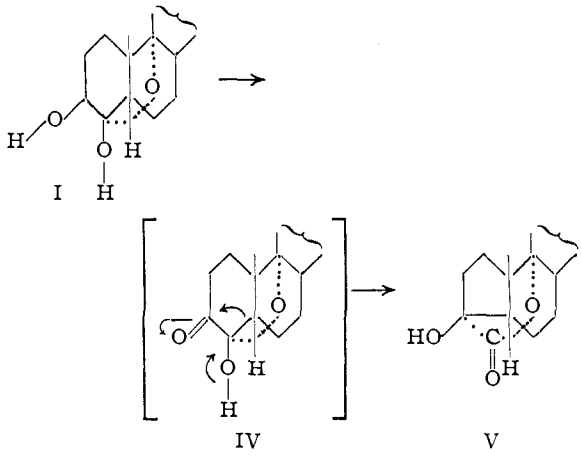
(3) We thank Professor R. B. Woodward for kindly communicating his deduction of the major aspects of these structures to us prior to publication; *cf.* D. H. R. Barton, O. Jeger, V. Prelog and R. B. Woodward, *Experientia*, **10**, 81 (1954).



Veracevine (I) Cevagenine (II) Cevine (III)

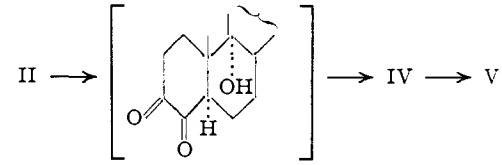
The key product in this investigation is an oxidation product of cevine, $C_{27}H_{41}O_8N$, to which structure V has been assigned on the basis of infrared spectral evidence and degradation results. This product (m.p. 252–253° dec., $[\alpha]^{22}D$ − 33° (*c* 1.07 chf.)) was obtained first by oxidation of cevine with bismuth oxide in acetic acid[4] and chromatography of the crude product on sulfuric acid-washed alumina. In subsequent experiments, chromatography was dispensed with, since the product could be obtained in 40% yield by crystallization of the crude product from acetone–ether. Similar oxidation of veracevine and cevagenine afforded the same product.[5]

The infrared spectrum of V in chloroform showed a strong band at 5.74 μ[6] indicative of a δ-lactone. Hence we were led to consider from the start that the product is a hydroxy-δ-lactone formed by rearrangement of the α-diketone hemiketal formed by initial oxidation of the α-ketol hemiketal system of I and III.[3] According to the new formulas, these changes can best be represented as



I IV V

The formation of V from cevagenine can be assumed to involve prior oxidation to the expected α-diketone VI followed by epimerization at C_5 and closure to the hemiketal IV. Analogy for the formation of V to the benzilic acid rearrangement leads us to propose the name **cevinilic acid δ-lactone** for V.



VI

Inherent in the interpretation of the above reaction is the contraction of ring A to a 5-membered ring. Evidence for such a ring contraction has been secured through the following reactions. Reduction of cevinilic acid δ-lactone V with lithium aluminum hydride led to the octahydroxy compound, **cevinilol (VII)**, $C_{27}H_{45}O_8N$, m.p. 268–270° dec., $[\alpha]^{26}D$ −70° (*c* 1.66, MeOH). The infrared spectrum of this product in tetrahydrofuran showed no absorption in the carbonyl region. Acetylation of VII with acetic anhydride–pyridine at steam-bath temperature gave an amorphous product which resisted crystallization. The infrared spectrum of this product showed acetate ester absorption at 5.79 μ and bands at 7.12, 8.85 and 11.22 μ characteristic of the C-orthoacetate grouping.[7] We therefore have assigned to this compound the tentative formulation (VIII) of **cevinilol C-orthoacetate diacetate.** Alkaline hydrolysis of VIII gave an amorphous product whose infrared spectrum showed no carbonyl absorption but did show the C-orthoacetate bands at 7.12, 8.85 and 11.22 μ. This product therefore was assigned the tentative formulation (IX) of **cevinilol C-orthoacetate.** Oxidation of IX with periodic acid gave X, $C_{28}H_{41}O_7N$, m.p. 235–237° dec., $[\alpha]^{24}D$ +23° (*c* 1.66 alc.). The infrared spectrum of X showed a carbonyl band at 5.76 μ (five-membered ring ketone) and the C-orthoacetate bands discussed above. Acetyl determination showed that one mole of acetic acid was liberated during acid hydrolysis. Hence the product was assigned formula X, and we designate the compound as **norcevinone C-orthoacetate.**

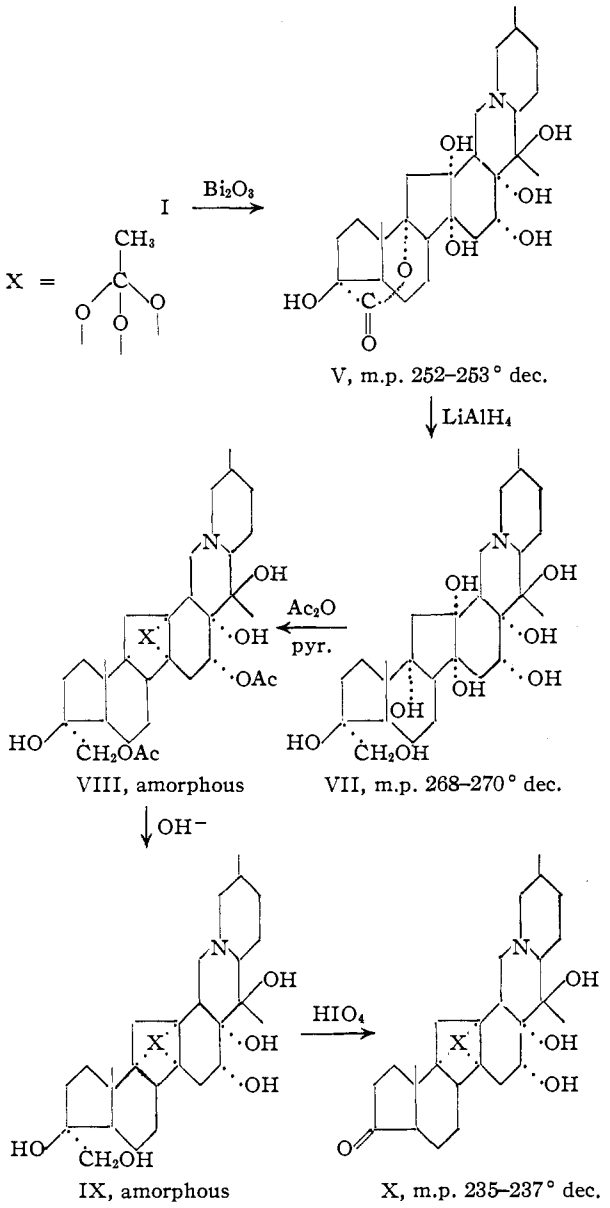
Incidentally, we should like to report at this time a correction to the literature. It was reported that room temperature acetylation of cevagenine with acetic anhydride–pyridine yields

(4) W. Rigby, *J. Chem. Soc.*, 793 (1951).

(5) E. Sundt, O. Jeger and V. Prelog (*Chem. and Ind.*, 1365 (1953)) have reported recently the isolation of a diosphenol from the product of bismuth oxide oxidation of cevagenine.

(6) Corrected value. The lower value reported earlier (5.72μ)[2] was incorrect because of faulty calibration of the infrared spectrophotometer.

(7) S. M. Kupchan, THIS JOURNAL, **77**, 686 (1955).



cevagenine triacetate.[8] Last year, we reported that this reaction affords a mixture of cevagenine orthoacetate diacetate ("anhydrocevagenine triacetate") and a second compound (m.p. 242–243.5° dec., $[\alpha]^{22}D$ −62° (*c* 1.33 alc.)), which we assumed to be the same triacetate.[9] On the basis of formula II, it would be expected that mild acetylation of cevagenine should affect only the hydroxyl groups at C_3 and C_{16}, and the reaction in question has been re-examined. Analysis of the compound melting at 242–243.5° dec. has now revealed that it is in fact cevagenine diacetate, as required by formulation II for cevagenine.

Acknowledgment.—We take pleasure in expressing our appreciation to Mrs. Mary Fieser and Professor R. B. Woodward for stimulating discussions and suggestions.

(8) A. Stoll and E. Seebeck, *Helv. Chim. Acta*, **35**, 1270 (1952).

(9) S. M. Kupchan, D. Lavie, C. V. Deliwala and B. Y. A. Andoh, THIS JOURNAL, **75**, 5519 (1953).

Experimental

Oxidation of Cevine (III) with Bismuth Oxide, Cevinilic Acid δ-Lactone (V).—Cevine (10 g.) was dissolved in acetic acid (100 ml.) and the solution was added to a solution of bismuth oxide (10 g.) in acetic acid (100 ml.). The mixture was heated under reflux for six hours. After cooling, the black precipitate (3 g.) was filtered and the filtrate was evaporated to dryness *in vacuo*. The brown oily residue was taken up in chloroform (50 ml.) and shaken with aqueous ammonia (5 ml.). The inorganic precipitate was filtered, and the chloroform solution was washed with dilute ammonia (10 ml.) and twice with water (10 ml.). The chloroform solution was dried over anhydrous sodium sulfate and evaporated to dryness *in vacuo*. The residue crystallized from acetone–ether; yield 4.6 g. of needles, m.p. 249–252° dec. Recrystallization from the same solvents afforded pure cevinilic acid δ-lactone (3.9 g.), m.p. 252–253° dec., $[\alpha]^{22}D$ −33° (*c* 1.07 chf.). Oxidation of veracevine and cevagenine by the same procedure afforded the same product.

Anal. Calcd. for $C_{27}H_{41}O_6N$: C, 63.88; H, 8.14. Found: C, 63.55; H, 8.17.

Reduction of Cevinilic Acid δ-Lactone with Lithium Aluminum Hydride. Cevinilol (VII).—A solution of cevinilic acid δ-lactone (4 g.) in dry tetrahydrofuran (50 ml.) was added dropwise to a solution of lithium aluminum hydride (4 g.) in the same solvent (150 ml.), and the mixture was heated under reflux for four hours. After cooling in ice-water, chips of ice were added carefully until the hydrolysis reaction subsided. Addition of a saturated solution of sodium potassium tartrate (10 ml.) caused coagulation of a mass of inorganic salts, and this was filtered with slight suction and washed with tetrahydrofuran. The filtrate was dried over anhydrous sodium sulfate and concentrated to a small volume (about 10 ml.). Addition of ether led to crystallization of needles (2 g.). Two recrystallizations from methanol–ether afforded pure cevinilol (1.4 g.), m.p. 268–270° dec., $[\alpha]^{26}D$ −70° (*c* 1.66, methanol).

Anal. Calcd. for $C_{27}H_{45}O_6N$: C, 63.38; H, 8.87. Found: C, 63.61; H, 8.74.

Acetylation of Cevinilol. Cevinilol C-Orthoacetate Diacetate (VIII).—Cevinilol (2 g.) was acetylated with acetic anhydride (15 ml.) and pyridine (30 ml.) at steam-bath temperature for two hours. After evaporation of the solvents *in vacuo* at room temperature, the residue was treated with dilute aqueous ammonia (10 ml.) and extracted with chloroform (three 35-ml. portions). The chloroform was washed with water (10 ml.), dried over anhydrous sodium sulfate and evaporated to dryness *in vacuo;* residue, 2.30 g. This material resisted all attempts at crystallization, and was characterized by its infrared spectrum (*cf.* Discussion).

Alkaline Hydrolysis of Cevinilol C-Orthoacetate Diacetate. Cevinilol C-Orthoacetate (IX).—Cevinilol C-orthoacetate diacetate (2.30 g.) was treated with methanol (150 ml.) and 4% sodium hydroxide solution (30 ml.) and the solution was allowed to stand at room temperature overnight. The methanol was distilled *in vacuo* and the residual aqueous suspension was extracted with chloroform (four 30-ml. portions). The chloroform was washed and dried as usual and evaporated to dryness *in vacuo*. The residue (1.8 g.) resisted crystallization and was characterized by its infrared spectrum (*cf.* Discussion).

Oxidation of Cevinilol C-Orthoacetate with Periodic Acid. Norcevinone C-Orthoacetate (X).—Cevinilol C-orthoacetate (0.53 g.) was treated with ethanol (25 ml.) and a solution of periodic acid (0.51 g.) in water (5 ml.), and the mixture was allowed to stand at room temperature for one hour. The alcohol was removed *in vacuo;* the aqueous solution was made alkaline with sodium bicarbonate and extracted with chloroform (three 30-ml. portions). The chloroform was washed and dried and evaporated to dryness *in vacuo*. The residue (0.47 g.) was dissolved in warm ether (40 ml.) and the solution was concentrated to a small volume (8 ml.). After 15 minutes, a yellow amorphous precipitate (50 mg.) was collected and rejected. From the filtrate, a crystalline product separated on standing (120 mg., m.p. 224–228° dec.). Recrystallization from ether gave pure norcevinone C-orthoacetate in the form of colorless needles (50 mg.), m.p. 235–237° dec., $[\alpha]^{24}D$ +23° (*c* 1.66, alc.).

Anal. Calcd. for $C_{28}H_{41}O_7N$: C, 66.77; H, 8.21; acetyl, 8.55. Found: C, 66.75; H, 8.10; acetyl, 8.42.[10]

Oxidation of Veracevine with Periodic Acid.—Veracevine (201 mg., 254 mg.) was oxidized with periodic acid in 50% aqueous methanol by the procedure of Barton and Eastham.[11] The periodic acid uptake after 24 hours corresponded to 1.81, 1.96 moles for the respective runs.

Oxidation of Veracevine Triacetate with Periodic Acid and Chromic Acid.—Veracevine triacetate (320 mg., 352 mg.) was oxidized with periodic acid as above. The periodic acid uptake after 24 hours corresponded to 1.16, 1.05 moles for the respective runs.

Veracevine triacetate (400 mg., 0.63 mmole) was treated with chromium trioxide (400 mg.) in 50% aqueous acetic acid at 5°. With the aid of an appropriate blank, the consumption of chromic acid after 24 hours was found to be 0.157, 0.123 meq. in successive runs (theor. for one oxygen, 1.26 meq.).

Cevagenine Diacetate.—The following results have been obtained upon analysis of the second compound isolated from the product of room temperature acetylation of cevagenine (m.p. 242–243.5° dec., $[\alpha]^{22}D$ −62° (*c* 1.33, alc.).[10]

Anal. Calcd. for $C_{31}H_{47}O_{10}N$: C, 62.71; H, 7.98; acetyl, 14.50. Found: C, 62.48; H, 8.09; acetyl, 14.70.

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(10) Hydrolysis in the acetyl determination was done with *p*-toluenesulfonic acid; *cf.* J. B. Niederl and V. Niederl, "Micromethods of Quantitative Organic Analysis," John Wiley and Sons, Inc., New York, N. Y., pp. 257–262. This determination and the other microanalyses were carried out by Dr. S. M. Nagy and associates at the Massachusetts Institute of Technology. All samples were dried *in vacuo* at 110°.

(11) D. H. R. Barton and J. G. Eastham, *J. Chem. Soc.*, 424 (1953).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, HARVARD UNIVERSITY]

Schoenocaulon Alkaloids. IV. The Isomeric Cevagenine Orthoacetates[1]

BY S. MORRIS KUPCHAN

RECEIVED JULY 30, 1954

Hydrolysis of cevadine orthoacetate diacetate with 5% methanolic potassium hydroxide affords cevagenine D-orthoacetate. $[\alpha]D$ +20°. Treatment of cevagenine D-orthoacetate with mineral acid yields cevagenine C-orthoacetate, $[\alpha]D$ −35°. Acetylation of cevagenine D-orthoacetate with acetic anhydride–pyridine at steam-bath temperature gives cevagenine C-orthoacetate diacetate. Hydrolysis of cevagenine C-orthoacetate diacetate with 20% alcoholic potassium hydroxide gives cevagenine C-orthoacetate. Treatment of cevagenine D-orthoacetate with 20% alcoholic potassium hydroxide gives cevine orthoacetate. The structures of cevagenine C- and D-orthoacetates and the stereochemical implications of these structures are discussed.

No explanation has been advanced for the fact that cevagenine forms an orthoacetate under milder conditions than its isomers (*i.e.*, upon treatment with acetic anhydride–pyridine at steam-bath temperature, cevagenine yields cevagenine orthoacetate diacetate, whereas veracevine and cevine yield triacetates).[2]

It now appears that two isomeric orthoacetates of cevagenine exist. One of these, levorotatory, was first reported by Stoll and Seebeck[3] who obtained it by mild alkaline hydrolysis of cevadine orthoacetate diacetate, followed by extraction with mineral acid. On repetition of their hydrolysis without subsequent treatment with mineral acid, a dextrorotatory isomer has been obtained. Since these isomers are both cevagenine orthoacetates, I propose to distinguish them by the prefixes D- and C-, the former prefix for the dextrorotatory isomer and the latter for the levorotatory isomer.

The levorotatory or C-isomer, $C_{29}H_{43}O_8N$, m.p. 180–190°, $[\alpha]^{24}D$ −35° (*c* 1.58, alc.) was first obtained in this Laboratory by alkaline hydrolysis of cevagenine orthoacetate diacetate with 20% alcoholic potassium hydroxide. This result differs from that of Stoll and Seebeck,[4] who reported the isolation of cevine orthoacetate from the reaction. The assignment of a cevagenine orthoacetate formulation to the product was made on the bases: (1) The infrared spectrum shows carbonyl absorption characteristic of a 6-membered ring ketone (5.84 μ) and the displaced methyl band (7.12 μ) and ether bands (near 8.85 μ) characteristic of orthoacetates.[5] (2) The compound yields one mole of acetic acid upon acid hydrolysis, though the infrared spectrum shows no ester carbonyl absorption.

The physical constants of cevagenine C-orthoacetate showed certain anomalies with respect to the physical constants of the other orthoacetates in the series. The infrared spectrum of cevagenine C-orthoacetate closely resembles that of cevagenine orthoacetate diacetate in the region from 8.50 to 11.50 μ (*cf.* Fig. 1) but differs from the spectra of cevine orthoacetate[3,5] and cevadine orthoacetate diacetate ("anhydrocevadine triacetate"[2c]) (*cf.* Fig. 2). Particularly noteworthy is the presence of a medium intensity band near 11.20 μ in the former pair of compounds, which is absent in the latter pair. Furthermore, the molecular rotation change from cevagenine to cevagenine C-orthoacetate (+57°) approximates the change from cevagenine diacetate[6] to cevagenine orthoacetate diacetate (+77°), but differs markedly from the change from cevine to cevine orthoacetate (+441°). Hence it appeared that the site of the orthoacetate grouping in cevagenine C-orthoacetate is the same as in cevagenine (C-) orthoacetate diacetate but differs from its location in cevine orthoacetate and cevadine orthoacetate diacetate; and that a second cevagenine orthoacetate, related to the

(1) This investigation was supported by a research grant (H-1563 (C3)) from the National Health Institute, of the National Institutes of Health, Public Health Service.

(2) (a) A. Stoll and E. Seebeck, *Helv. Chim. Acta*, **35**, 1142 (1952); (b) D. H. R. Barton and C. J. W. Brooks, *Chem. and Ind.*, 1366 (1953); (c) S. M. Kupchan, D. Lavie, C. V. Deliwala and B. Y. A. Andoh, THIS JOURNAL, **75**, 5519 (1953).

(3) A. Stoll and E. Seebeck, *Helv. Chim. Acta*, **37**, 824 (1954).

(4) A. Stoll and E. Seebeck, *ibid.*, **36**, 189 (1953).

(5) D. H. R. Barton, C. J. W. Brooks and J. S. Fawcett, *J. Chem. Soc.*, 2137 (1954). I thank Professor Barton for kindly communicating these results to me prior to publication.

(6) Paper III, S. M. Kupchan and D. Lavie, THIS JOURNAL, **77**, 683 (1955).