

**N-n-Butylpyrrolidone-2.**—This substance was prepared by the general method of Späth and Lintner.<sup>16</sup> A mixture of 50 g. (0.58 mole) of butyrolactone and 46 g. (0.64 mole) of *n*-butylamine was heated at 280° for four hours. After cooling, the reaction mixture was dissolved in 50 cc. of 6 *N* hydrochloric acid and the aqueous solution continuously extracted with ether for fifteen hours to remove the *N*-*n*-butylpyrrolidone-2, which is exceedingly soluble in water. After drying and removal of the ether the product was distilled; b. p. 121° (16 mm.);  $n_{D}^{20}$  1.4650;  $d_{4}^{20}$  0.964; yield 78 g. (95%).

*Anal.* Calcd. for  $C_8H_{15}ON$ : C, 68.04; H, 10.71; N, 9.92. Found: C, 68.03; H, 10.75; N, 10.18.

### Summary

1. A variety of cyclic and straight chained vinyl tertiary amines have been synthesized as well as the corresponding saturated molecules.

2. Comparative basicity studies demonstrated that the vinyl tertiary amines were in all cases more basic than the corresponding saturated compounds.

3. This is explained by assuming hydration and rearrangement to a quaternary ammonium base.

URBANA, ILLINOIS

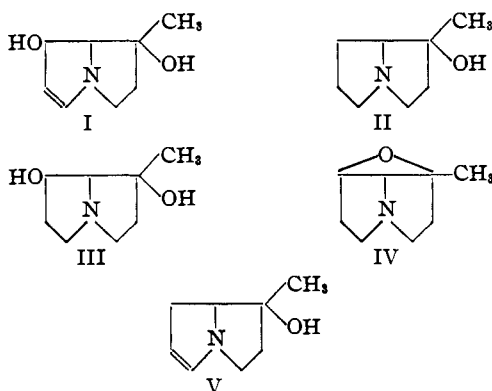
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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

## Structure of Monocrotaline. VII.<sup>1</sup> Structure of Retronecine and Related Bases

BY ROGER ADAMS, MARVIN CARMACK AND J. E. MAHAN

Structure I, previously suggested for retronecine, was deduced on the basis of (a) the validity of structure II for oxyheliotridane, a stereoisomer<sup>2</sup> of retronecanol, as proposed by Menshikov,<sup>3</sup> and (b) the reduction characteristics of retronecine and the reactivity of the hydroxyls in retronecine and related molecules. No structure other than I will explain as satisfactorily all the available experimental facts. The formulation of platynecine as III, anhydroplatynecine as IV, and desoxyretronecine as V will then result.



The most objectionable feature to structure I for retronecine, as pointed out in a previous paper, lies in the results obtained upon esterification. One hydroxyl in retronecine esterifies very readily, more readily than would be anticipated from the usual secondary alcohol, and the other esterifies

(1) VI, Adams and Rogers, *THIS JOURNAL*, **68**, 537 (1941).

(2) Konovalova and Orekhov, *Bull. soc. chim.*, [5] **4**, 1285 (1937); *Ber.*, **69B**, 1908 (1936).

(3) Menshikov, *Bull. acad. sci. U. S. S. R., Classe sci. math.*, Ser. chim., **978** (1936).

with difficulty, but with more facility than is observed with any ordinary tertiary alcohol. Moreover, retronecanol (II) dehydrates more sluggishly than would be expected on the basis of a tertiary hydroxyl group.

Direct chemical proof for the positions of the hydroxyls and double bond in retronecine (I) was undertaken. The evidence for a pyrrolidine nucleus and for a methyl group in the 1-position is indisputable. A complete assembly of the facts concerning known vinyl tertiary amines revealed that in no instance where the vinyl amine structure was established unequivocally was the molecule stable both to alkali and acid; hydrolysis occurs with one or the other especially when warmed with the reagent. Retronecine is stable to both even on boiling. Further evidence that the presence of a vinyl amine structure is unlikely was obtained through basicity studies. The following table gives the  $pK_H$  values for retronecine and its related compounds.

TABLE I

BASICITY OF RETRONECINE AND RELATED COMPOUNDS			
Name	$pK_H$	$T, ^\circ C.$	$pK_H (25^\circ)$
Retronecine	8.92	26	8.94
Platynecine	10.24	24	10.22
Desoxyretronecine	9.55	25	9.55
Retronecanol	10.92	24.5	10.91
Anhydroplatynecine	9.44	24	9.42
Heliotridane	11.44	27	11.48
Heliotridene	10.59	25.5	10.60
Isoretronecanol <sup>b</sup>	10.87	25.5	10.88

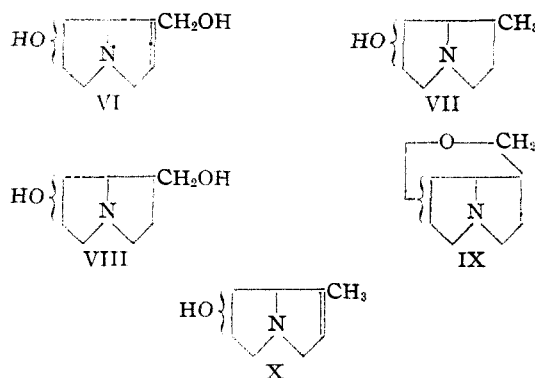
It is to be noted that the saturated molecules on the basis of the postulated structures (I-V)

are more basic than the unsaturated—platynecine (III) is more basic than retronecine (I) and retronecanol (II) is more basic than desoxyretronecine (V). These results are in direct contradiction to what would be expected. Vinyl tertiary amines are more basic than the corresponding saturated molecules.<sup>4</sup>

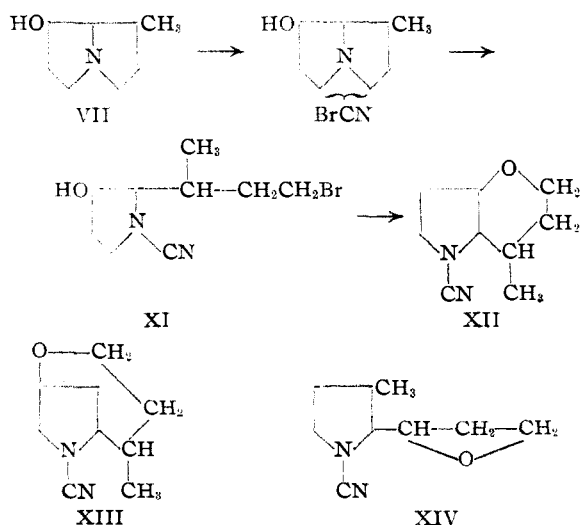
The weight of this evidence and that derived from the stability experiments was sufficient to warrant the assumption that the vinyl amine structures for retronecine and desoxyretronecine were very probably incorrect. Assignment of the double bond in retronecine to any other non-vinyl position and retention at the same time of the positions shown in formula I for the hydroxyls gives molecular structures which will explain almost none of the important reactions of the molecule. It was thus obvious that a complete revision of the orientation of the double bond and hydroxyl groups in retronecine was necessary.

The experiments of Menshikov on oxyheliotridane, from which he deduced structure II, leave much to be desired. He performed a series of exhaustive methylations and reductions until a nitrogen-free compound was obtained. The final product was described<sup>3</sup> as a tertiary octanol. However, in this degradation no intermediates were isolated or purified, the characterization of the tertiary octanol was doubtful and no detailed description of his procedure was published. In view of this, the oxyheliotridane (stereoisomeric with retronecanol) structure reported by Menshikov was disregarded and a new set of structures for retronecine and its related compounds was formulated. The two hydroxyls and the double bond were introduced into the 1-methylpyrrolizidine nucleus in such a way that the following established experimental facts were satisfied: (a) difference in the rate of esterification of the two hydroxyls, which would more nearly agree with one secondary and one primary hydroxyl than with one secondary and one tertiary; (b) the ease of hydrogenolysis of one hydroxyl under very mild conditions; (c) the relative difficulty in dehydration of retronecanol which resembles more a secondary than a tertiary hydroxyl; (d) the resistance to hydrogenolysis of either hydroxyl in platynecine; (e) the ease of dehydration of platynecine to anhydroplatynecine; and (f) the absence of a vinyl amine linkage. The postulation of a primary hydroxyl limits its position to a sub-

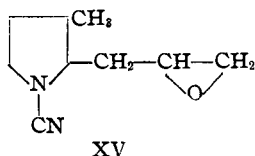
stitution of a hydrogen atom on the methyl group of the 1-methylpyrrolizidine nucleus and this automatically, when the other conditions are fulfilled, establishes retronecine as having one of two structures (VI). Retronecanol would then be assigned structures VII, platynecine VIII, anhydroplatynecine IX, and desoxyretronecine X.



The readily hydrogenolyzed hydroxyl, the primary one, is shown as an allylic type. Construction of models indicates the structures represented by IX to involve very little strain whether the secondary hydroxyl is in the 6- or 7-position. The 7-position is favored on the basis of experiments involving the degradation of retronecanol (VII) by bromocyanogen. An addition compound is formed with this reagent which on rearrangement and treatment with alkali yields a halogen-free compound postulated as an ether (XII). Only the cyanide group is removed on hydrolysis with hot sulfuric acid; there is no cleavage of the cyclic ether. The mechanism of formation is postulated as follows



(4) Adams and Mahan, *THIS JOURNAL*, **64**, 2588 (1942).



The cleavage is believed to take place in the ring containing the methyl group; assuming the 7-position for the hydroxyl group a six-membered ether (XII) is produced, or assuming the 6-position a much less likely structure (XIII) would result. Cleavage of the unmethylated ring in VII would yield an ether of structure XIV or XV, depending on the position of the hydroxyl group. Either of these would be expected to hydrolyze upon treatment with hot sulfuric acid.

The changes in basicity of retronecine and related compounds, as influenced by the presence or absence of an hydroxyl group or double bond, are surprisingly parallel. These are shown in Table II. The structure of heliotridane is XVI, and the structure of isoretronecanol is XVII.

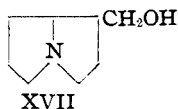
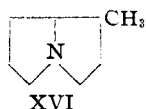


TABLE II

BASICITY COMPARISONS OF RETRONECINE AND RELATED COMPOUNDS;  $pK_H$  VALUES

(a) Effect of removal of primary hydroxyl	
Desoxyretronecine (X)	9.6
Retronecine (VI)	8.9
	-----
	0.7
Retronecanol (VII)	10.9
Platynecine (VIII)	10.2
	-----
	0.7
Heliotridane (XVI)	11.5
Isoretronecanol (XVII) <sup>5</sup>	10.9
	-----
	0.6
(b) Effect of removal of secondary hydroxyl	
Heliotridane (XVI)	11.5
Retronecanol (VII)	10.9
	-----
	0.6
(c) Effect of removal of double bond	
Platynecine (VIII)	10.2
Retronecine (VI)	8.9
	-----
	1.3
Retronecanol (VII)	10.9
Desoxyretronecine (X)	9.6
	-----
	1.3

(5) Adams and Hamlin, *THIS JOURNAL*, **64**, 2597 (1942).

As shown in Table II, the removal of the primary or secondary hydroxyl results in an increase in basicity of about 0.7  $pK_H$  unit; the removal of the double bond in an increase in basicity of 1.3  $pK_H$  unit.

Experiments to establish whether the structures in series VI-X are correct are now under way and the first results are reported in this communication. A comparison of structures I-V and VI-X reveals that I-V all contain C-CH<sub>3</sub> groups, whereas such groups exist in the series VI-X only in structures VII and X. The determination of C-CH<sub>3</sub> in each of these molecules was undertaken and none could be found in retronecine (VI), platynecine (VIII), or anhydroplatynecine (X), but one was present in both retronecanol (VII) and desoxyretronecine (IX). As observed by those who have studied extensively this quantitative method, the amount of acetic acid produced upon oxidation of a molecule with a C-CH<sub>3</sub> group is never quantitative but varies in degree with the character of the molecule as a whole and especially on the substituents present on the carbon holding the methyl groups. The results are shown in Table III.

TABLE III

ACETIC ACID BY OXIDATION OF RETRONECINE AND RELATED BASES

Substance	Moles HOAc per mole of substance
Retronecine	None
Platynecine	None
Anhydroplatynecine	None
Retronecanol	0.69
Desoxyretronecine	.66
Heliotridane	.58
Heliotridene	.40
Isoretronecanol	None

These analytical data conform to the new structures VI-X which may be accepted provisionally in place of those previously proposed (I-V). None of the known experimental facts are in disagreement with present postulated formulas.

### Experimental

**Determination of Basic Strength Constants.**—The procedure employed for the determination of the  $pK_H$  values was that previously described.<sup>3</sup> All solid amines were recrystallized to constant melting point, and the three liquid amines were freshly distilled in a carbon dioxide-free atmosphere immediately before use. The basicity measurements were taken at temperatures within the range 23 to 27° and the observed constant corrected to 25° employing the value of the negative temperature coefficient of the constant as given by Hall and Sprinkle.<sup>6</sup> Duplicate meas-

(6) Hall and Sprinkle, *ibid.*, **54**, 3469 (1932).

urements were made on all of the substances listed in Tables I and II.

**Carbon-Methyl Analysis.**—The procedure used for carbon-methyl determinations was a macro modification adapted from the micro procedure of Kuhn and Roth,<sup>7</sup> and the macro method of Kuhn and L'Orsa.<sup>8</sup> That the acidity of the distillate after chromic acid oxidation was due to acetic acid was shown by conversion of the acid component to its *p*-bromophenacyl ester, m. p. 85°. The reported melting point of *p*-bromophenacyl acetate is 85°.<sup>9</sup>

Thymol was used as a control and gave 1.31 moles of acetic acid per mole of substance. Kuhn and L'Orsa<sup>8</sup> reported a value of 1.40.

**Conversion of Retronecanol to the Cyanamide Ether (XII).**—A solution of 8 g. of cyanogen bromide in 60 cc. of dry ether was cooled in a dry-ice-acetone mixture. To this was added slowly and with constant swirling a solution of 10 g. of retronecanol in 140 cc. of dry ether. A voluminous white precipitate separated instantly. The reaction mixture was allowed to warm up gradually (constant swirling) and at a point just below room temperature the white solid changed into a viscous oil. When the mixture had reached room temperature, 15 cc. of water was added to dissolve the sirup, the ether layer was then separated and washed once with very dilute hydrochloric acid to remove any unreacted retronecanol. The aqueous layer and acid washings were both extracted with ether and the ether washings combined with the ether layer from the original reaction mixture. The ethereal solution was dried over anhydrous magnesium sulfate and the solvent removed by distillation. The pale yellow viscous oil which remained was heated on the water-bath under reduced pressure to remove remaining solvent and any excess of cyanogen bromide; yield 11.3 g. All attempts to crystallize the sirup failed. It is probable that this product consisted of a mixture of bromocyanamides.

A sample of the bromocyanamide oil which had stood at 2° for several days deposited a small amount of crystalline material. A further quantity of this substance was obtained by dissolving the viscous residue in methanol, cooling in a dry-ice-acetone bath, seeding, and filtering rapidly through a precooled funnel. Pure material was obtained by recrystallization from water; m. p. 94.5–95° (cor.). Qualitative tests showed the absence of halogen. A solution in carbon tetrachloride did not decolorize bromine, and a solution in acetone-water did not decolorize 1% potassium permanganate solution.

*Anal.* Calcd. for C<sub>8</sub>H<sub>14</sub>ON<sub>2</sub>: C, 65.03; H, 8.49; N, 16.86. Found: C, 65.14; H, 8.37; N, 16.89.

*Rotation.* 53.7 mg. made up to 2.50 cc. with absolute ethanol at 28° gave α<sup>31</sup>D –4.63°; *l*, 2; [α]<sup>31</sup>D –107.6°.

This substance was obtained in better yields as follows. A sample of 5.8 g. of the crude liquid bromocyanamide dissolved in 20 cc. of dry pyridine was refluxed for thirty minutes. The solution, which had turned deep red in color, was cooled, diluted with an equal volume of water, treated with Norite, and the solvent removed by distilla-

tion *in vacuo*. The residual brown viscous oil was diluted with a little water and on seeding crystallization ensued. Thus in two crops 1.08 g. was obtained; m. p. 92–94° (18% from retronecanol, or 28% from the crude bromocyanamide). Refluxing in pyridine for longer periods of time than thirty minutes did not increase the yield. The cyanamide ether could also be formed in approximately the same yield by warming the crude bromocyanamide with methanolic potassium hydroxide.

**Hydrolysis of the Cyanamide Ether to a Secondary Amine.**—A mixture of 0.88 g. of the cyanamide ether and 15 cc. of 15% sulfuric acid was refluxed for fifty-five hours. The solution was decolorized with Norite, cooled, made strongly alkaline with potassium hydroxide and the precipitated salts removed by filtration through glass wool. The filtrate was extracted thoroughly with ether and the ether extract dried over sodium carbonate. After removal of solvent the residue was distilled at 20 mm. and a bath temperature of 110–120°; yield 0.64 g. of colorless liquid. Although this product was not analyzed as such its identity as a secondary amine was shown by conversion to the following three analyzed derivatives.

**Reconversion to Cyanamide Ether.**—A sample of 68 mg. of the liquid amine was warmed with excess cyanogen bromide in ether for ten minutes. After evaporation of the solvent the residue was taken up in warm water and the solution seeded; yield 20 mg.; m. p. 92–93°, mixed melting point with an authentic sample of cyanamide ether produced no depression.

**Picrate.**—A sample of 68 mg. of liquid amine from the acid hydrolysis of the cyanamide ether was treated with 130 mg. of picric acid containing 15% water dissolved in 1 cc. of hot ethanol. After cooling in the ice-bath for fifteen minutes, 141 mg. of picrate was filtered; glistening yellow plates, m. p. 121.5–122.5° (cor.). Further recrystallization did not raise the melting point.

*Anal.* Calcd. for C<sub>8</sub>H<sub>13</sub>ON·C<sub>6</sub>H<sub>3</sub>O<sub>7</sub>N<sub>3</sub>: C, 45.41; H, 4.90; N, 15.13. Found: C, 45.36; H, 5.01; N, 15.07.

**N-Methyl Hydroiodide.**—To a solution of 0.64 g. of the liquid amine in a mixture of 1 cc. of dry acetone and 1 cc. of dry ether was added gradually 1 cc. of methyl iodide. After the original vigorous reaction had subsided the mixture was refluxed on the steam-bath for ten minutes. On cooling crystallization occurred; yield 0.44 g. (in two crops). Two recrystallizations from acetone yielded pure material; long fine prisms, m. p. 195–196° (cor.).

*Anal.* Calcd. for C<sub>9</sub>H<sub>15</sub>ONI: C, 38.17; H, 6.41; N, 4.95. Found: C, 38.29; H, 6.54; N, 4.69.

*Rotation.* 15.7 mg. made up to 0.500 cc. with absolute ethanol at 33° gave α<sup>33</sup>D –0.54°; *l*, 1; [α]<sup>33</sup>D –17.2°.

Although this substance has the same molecular formula as retronecanol methiodide (m. p. 193°) a mixed melting point between the two gave a depression to 145–148°.

## Summary

1. New structures are proposed for retronecine, retronecanol, platynecine and desoxyretronecine which agree with all the pertinent experimental data.

2. Basic strength constants and carbon-

(7) Kuhn and Roth, *Ber.*, **66**, 1274 (1933); Pregl, "Quantitative Organic Microanalysis," P. Blakiston's Son and Co., Inc., Philadelphia, Pa., 1937, pp. 201–204.

(8) Kuhn and L'Orsa, *Z. angew. Chem.*, **44**, 847 (1931).

(9) Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 2nd ed., 1940, p. 181.

methyl analyses on these substances tend to confirm the proposed formulas and prove the incorrectness of the old formulas.

3. A von Braun degradation of retronecanol

with cyanogen bromide yielded a cyanamide ether which can be explained very satisfactorily on the basis of the new formula.

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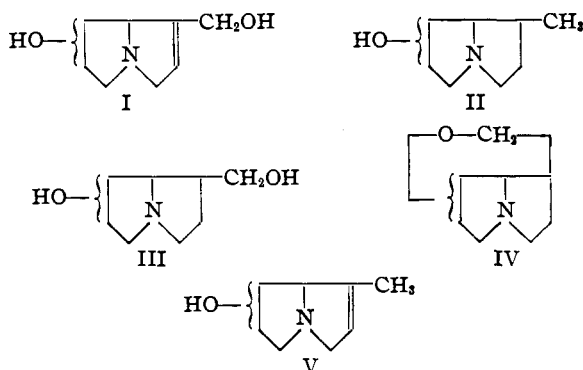
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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

## Structure of Monocrotaline. VIII. The Proof of Primary and Secondary Hydroxyl Groups in Retronecine<sup>1</sup>

BY ROGER ADAMS AND K. E. HAMLIN, JR.

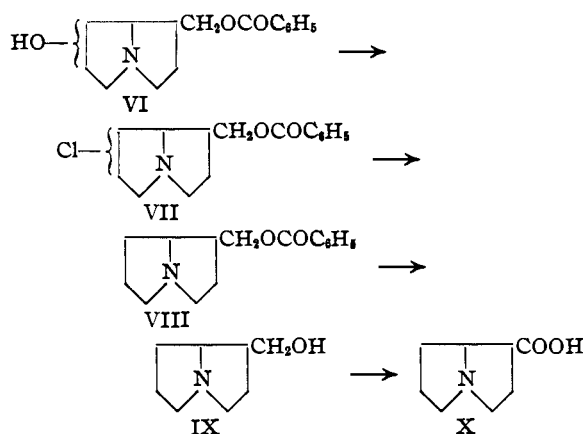
Direct experimental evidence for the structures postulated for retronecine (I), retronecanol (II) platynecine (III), anhydroplatynecine (IV) and desoxyretronecine (V) is being investigated. This



communication describes work which has served to establish beyond dispute (1) the presence of a  $\text{CH}_2\text{OH}$  group in compound I and in its reduction product (III), and (2) the presence of a secondary hydroxyl group in retronecanol (II). Since all attempts to obtain tractable oxidation products from retronecine and its associated molecules have failed, it was concluded that the molecules probably were rendered sensitive to oxidation by the presence of an hydroxyl group substituted in the nucleus. Platynecine (III), synthesized from retronecine (I), was selected for study and the mono-benzoate (VI) was prepared. This was converted to the corresponding chloride (VII) according to the directions of Konovalova and Orekhov.<sup>2</sup> These investigators reported failure in attempts to replace the chlorine by hydrogen in this molecule but in our experiments no difficulty was encountered by the use of Raney nickel and hydrogen in ethanol solution. Thus, a molecule (VIII) was produced which was the benzoate of a

(1) For previous paper see Adams, Carmack and Mahan, *THIS JOURNAL*, **64**, 2593 (1942).

(2) Konovalova and Orekhov, *Ber.*, **69**, 1908 (1936).



new base, herein designated as isoretronecanol (IX). Upon hydrolysis, isoretronecanol (IX) was obtained. Structurally this resembles lupinine and differs from it merely in that the  $\text{CH}_2\text{OH}$  group is attached to a pyrrolizidine nucleus, a fusion of two five-membered rings, rather than to a norlupinane nucleus, consisting of two analogously fused six-membered rings. The procedure described for oxidizing lupinine to lupinic acid<sup>3</sup> was followed for the conversion of isoretronecanol (IX) to 1-carboxypyrrrolizidine (X) and proved to be entirely satisfactory. The oily degradation products encountered in the oxidation of retronecine, *et al.*, were absent and a readily purified derivative with the properties of an amino acid was isolated. Analyses of the pure compound, its picrate and derivatives of the betaine, prepared from the reaction of diazomethane on the amino acid, were used for identification.

On the basis of structure II, retronecanol contains a secondary hydroxyl group. It has now been found that aluminum *t*-butoxide in the presence of cyclohexanone oxidizes the molecule without degradation and with the formation of the corresponding ketone, retronecanone (XI). The

(3) Willstätter and Fournau, *ibid.*, **35**, 1917 (1902).