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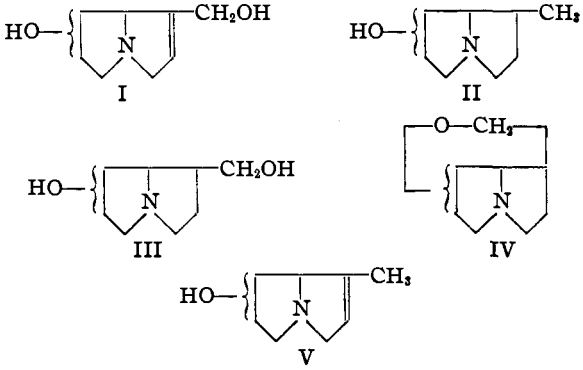
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

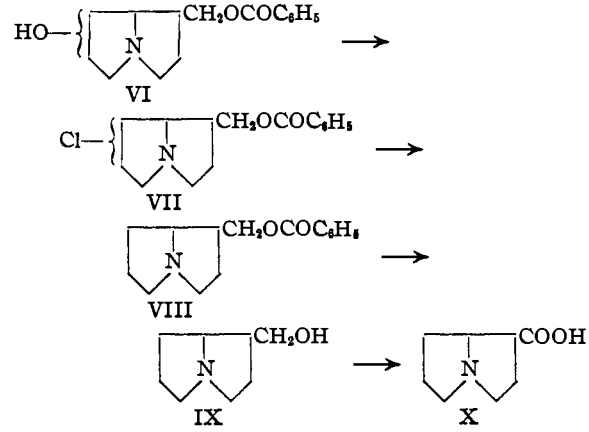
Structure of Monocrotaline. VIII. The Proof of Primary and Secondary Hydroxyl Groups in Retronecine[1]

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 CH_2OH 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 monobenzoate (VI) was prepared. This was converted to the corresponding chloride (VII) according to the directions of Konovalova and Orekhov.[2] 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



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 CH_2OH 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 lupininic acid[3] was followed for the conversion of isoretronecanol (IX) to 1-carboxypyrrolizidine (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.

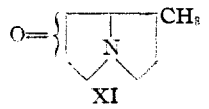
On the basis of structure II, retronecanol contains a secondary hydroxyl group. It has now been found that aluminum *t*-butoxide in the presence of cyclohexanone oxidizes the molecule without degradation and with the formation of the corresponding ketone, retronecanone (XI). The

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

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

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

ketone group was identified through its semicarbazone and its oxime.



XI

By these experiments the presence of a CH_2OH group and a secondary hydroxyl have been established directly in retronecine. The results serve to support the structures I–V postulated on the $C\text{-}CH_3$ determinations and the chemical properties of these molecules.

Experimental

Monobenzoylplatynecine (VI).—This was prepared from platynecine as described by Orekhov, Konovalova and Tiedebel.[4] It crystallized from ether–petroleum ether (b. p. 30–60°) in colorless prisms m. p. 118–119° (cor.). The reported melting point is 119–120°.

Rotation. 0.4081 g. made up to 15 cc. with absolute ethanol at 29° gave α_D −2.41; *l*, 1; $[\alpha]^{29}D$ −88.6°. The reported value is $[\alpha]_D$ −87.9° in ethanol.

Monobenzoylplatynecine Chloride (VII).—This was prepared as described by Konovalova and Orekhov.[2] Recrystallization from petroleum ether (b. p. 30–60°) gave colorless tufts of needles, m. p. 72–73° (cor.). The reported melting point is 73–74°.

Rotation. 0.6092 g. made up to 15 cc. with absolute ethanol at 29° gave α_D −0.59; *l*, 1; $[\alpha]^{29}D$ −14.5°.

Benzoylisoretronecanol Hydrochloride.—A solution of 7 g. of monobenzoylplatynecine chloride in 100 cc. of ethanol, to which was added about 4 g. of Raney nickel, was hydrogenated at 2–3 atm. pressure. Hydrogen was absorbed to the theoretical end-point in four and one-half hours. After filtration, the solution was made just acid to congo and the solvent removed *in vacuo*. The highly colored crystalline residue was taken up in chloroform, boiled with Darco, and the solution filtered. The colorless chloroform solution was treated with anhydrous ether until it became cloudy. The hydrochloride separated as fine colorless needles; recrystallized from chloroform–ether, m. p. 181–182° (cor.); yield, 6.02 g. (86%).

Anal. Calcd. for $C_{15}H_{19}O_2N\cdot HCl$: C, 63.91; H, 7.16; N, 4.97. Found: C, 63.84; H, 7.12; N, 4.80.

Rotation. 0.5056 g. made up to 15 cc. with absolute ethanol at 28° gave α_D −1.62; *l*, 1; $[\alpha]^{28}D$ −48.6°.

Benzoylisoretronecanol (VIII).—A solution of the base hydrochloride in water was treated with one equivalent of *N* aqueous sodium hydroxide. The mixture was thoroughly extracted with ether and the ethereal solution dried over anhydrous potassium carbonate. After carefully distilling off the ether, the residue was distilled *in vacuo*, b. p. 161.5–162.5° (1–2 mm.). The colorless, mobile distillate readily crystallized on cooling in a dry-ice–acetone bath. The crystalline product could be recrystallized from petroleum ether (b. p. 30–60°); large prisms, m. p. 56–57° (cor.).

Anal. Calcd. for $C_{15}H_{19}O_2N$: C, 73.42; H, 7.81; N, 5.71. Found: C, 73.51; H, 7.86; N, 5.70.

(4) Orekhov, Konovalova and Tiedebel, *Ber.*, **68**, 1886 (1935).

Rotation. 0.1578 g. made up to 5 cc. with absolute ethanol at 28° gave α_D −1.92; *l*, 1; $[\alpha]^{28}D$ −60.8°.

Benzoylisoretronecanol Picrate.—Prepared in and recrystallized from ethanol, the picrate formed yellow needles, m. p. 130–131° (cor.) with decomposition.

Anal. Calcd. for $C_{21}H_{22}O_9N_4$: C, 53.14; H, 4.67; N, 11.81. Found: C, 53.32; H, 4.82; N, 11.81.

Isoretronecanol (IX).—An aqueous solution of 4.4 g. of benzoylisoretronecanol hydrochloride was refluxed for three hours with 100 cc. of 10% aqueous sodium hydroxide. The alkaline solution thus obtained was extracted continuously with ether for twenty-four hours. On acidification of the residual alkaline layer, white crystals were obtained which were identified by melting point as benzoic acid.

The ethereal extract was dried well over anhydrous sodium carbonate and the ether removed by distillation. The oily residue was distilled *in vacuo*, b. p. 115–116° (1–2 mm.); yield 1.62 g. (74%). The colorless viscous distillate crystallized readily on cooling in dry-ice–acetone bath; m. p. 39–40° (cor.).

Anal. Calcd. for $C_8H_{15}ON$: C, 68.02; H, 10.71; N, 9.93. Found: C, 68.11; H, 10.69; N, 10.07.

Rotation. 0.1407 g. made up to 5 cc. with absolute ethanol at 27° gave α_D −2.20; *l*, 1; $[\alpha]^{27}D$ −78.2°.

Isoretronecanol Methiodide.—This product was prepared by treating a dry ether solution of isoretronecanol with an excess of methyl iodide. It was purified from methanol–ether; white needles, m. p. 281–282° (cor.) with decomposition.

Anal. Calcd. for $C_8H_{15}ON\cdot CH_3I$: C, 38.14; H, 6.41; N, 4.95. Found: C, 38.21; H, 6.50; N, 4.78.

Rotation. 0.0725 g. made up to 5 cc. with absolute ethanol at 26° gave α_D −0.44; *l*, 1; $[\alpha]^{26}D$ −31.0°.

Isoretronecanol Picrate.—Prepared in and recrystallized from ethanol, the picrate formed yellow needles, m. p. 194–195° (cor.) with decomposition.

Anal. Calcd. for $C_{14}H_{18}O_8N_4$: C, 45.34; H, 4.90; N, 15.12. Found: C, 45.51; H, 5.00; N, 15.02.

1-Carboxypyrrolizidine (X).—Following the procedure described by Willstätter and Fourneau[3] for oxidizing lupinine to lupininic acid, 0.5 g. of isoretronecanol was dissolved in a solution of 0.15 g. of sulfuric acid (sp. gr. 1.84) in 2 cc. of water. This mixture was added carefully to a cooled solution of 0.3 g. of chromic anhydride in 0.35 g. of sulfuric acid and 4 cc. of water. After warming this mixture a few minutes on a steam-cone until reduction of the chromic anhydride was complete, a second charge of the oxidizing mixture described above was added. The solution was now heated on a steam-cone for one and one-half hours. From this point the degradation product was worked up as described for lupininic acid. Before recrystallization, 0.22 g. of 1-carboxypyrrolizidine was isolated. After dissolving in absolute ethanol, boiling with a Darco–Norite mixture and filtering, excess dry acetone was added. At this point white flat plates crystallized, m. p. 228–229° (cor.) with decomposition.

Anal. Calcd. for $C_8H_{13}O_2N$: C, 61.91; H, 8.45; N, 9.03. Found: C, 62.06; H, 8.66; N, 9.13.

Rotation. 0.0996 g. made up to 5 cc. with absolute ethanol at 28° gave α_D −1.31; *l*, 1; $[\alpha]^{28}D$ −65.8°

The amino acid was very soluble in water, fairly soluble in ethanol but insoluble in acetone, ether, and chloroform.

1-Carboxypyrrolizidine Picrate.—Prepared in and recrystallized from ethanol, the picrate formed beautiful yellow needles, m. p. 220–221° (cor.) with decomposition.

Anal. Calcd. for $C_{14}H_{16}O_9N_4$: C, 43.75; H, 4.20; N, 14.58. Found: C, 44.02; H, 4.25; N, 14.54.

Action of Diazomethane on 1-Carboxypyrrolizidine.—Following the procedure of Kuhn and Brydowna,[5] 0.1 g. of the 1-carboxypyrrolizidine was treated with a large excess of a moist ethereal solution of diazomethane. An immediate evolution of nitrogen took place which continued until the solid amino acid disappeared. After standing overnight, the ether was decanted from the small aqueous layer which appeared. The latter was diluted to about 1 cc. with water. The product was found to be predominantly in this aqueous portion. Identification of the compound as the betaine of the amino acid was made by analyses of the chloroaurate and the picrate.

Chloroaurate of the Betaine.—The gold salt was prepared from 10% aqueous auric chloride and an acidified (with hydrochloric acid) portion of the above aqueous solution of the betaine. Recrystallized from water, the yellow crystalline chloroaurate melted at 224–225° (cor.) with decomposition.

Anal. Calcd. for $C_9H_{16}O_2NAuCl_4$: C, 21.23; H, 3.17; Au, 38.73. Found: C, 21.72; H, 3.38; Au, 39.30.

Picrate of the Betaine.—The yellow crystalline picrate was prepared by adding a saturated ethanolic solution of picric acid to the aqueous solution of the betaine. After recrystallization from ethanol, the product melted at 194–195° (cor.) with decomposition.

Anal. Calcd. for $C_{15}H_{18}O_9N_4$: N, 14.06. Found: N, 13.81.

Retronecanone (XI).—A mixture of 5 g. of retronecanol, 15 g. of aluminum *t*-butoxide, 200 cc. of dry cyclohexanone and 700 cc. of dry toluene was refluxed for six hours. After cooling, the orange suspension was carefully extracted with 10% sulfuric acid. The acid extract, after washing well with ether to remove unchanged cyclohexanone, was treated with an excess of 50% sodium hydroxide. The basic solution was extracted continuously with ether for twenty-four hours and the ethereal extract dried over anhydrous magnesium sulfate. After carefully removing the ether, the residue was distilled *in vacuo;* the fraction boiling between 94 and 100° (15 mm.) was collected, yield 1.5 g. (30%). The pure amino ketone is a colorless, mobile liquid, distilling at 95–96° (15 mm.); $n^{20}D$ 1.4818; d^{20}_4 1.030.

Anal. Calcd. for $C_8H_{13}ON$: C, 69.03; H, 9.41; N, 10.06. Found: C, 68.76; H, 9.46; N, 10.14.

Rotation. 0.1127 g. made up to 5 cc. with absolute ethanol at 30° gave αD −2.18; *l*, 1; $[\alpha]^{30}D$ −96.7°.

Retronecanone is not stable and tends to decompose readily even when kept at 0°, protected from light and moisture.

Retronecanone Picrate.—Prepared in and recrystallized from ethanol, the picrate formed fine yellow needles, m. p. 195° (cor.) with decomposition.

Anal. Calcd. for $C_8H_{13}ON \cdot C_6H_3O_7N_3$: C, 45.65; H, 4.38; N, 15.21. Found: C, 45.99; H, 4.36; N, 15.34.

A mixed melting point with an authentic sample of retronecanol picrate (m. p. 214°) gave a depression to 182–183°.

Retronecanone Semicarbazone.—A solution of 0.7 g. of semicarbazide hydrochloride and 1.5 g. of sodium acetate in 10 cc. of water was added to 0.5 g. of retronecanone. After heating in a water-bath for one hour and then cooling, the solution was made alkaline to litmus. On further cooling and scratching, the crystalline derivative precipitated. After recrystallization from a mixture of chloroform–petroleum ether, the semicarbazone was obtained as white platelets, m. p. 209–210° (cor.) with decomposition.

Anal. Calcd. for $C_9H_{16}ON_4$: C, 55.08; H, 8.22; N, 28.55. Found: C, 55.01; H, 8.23; N, 28.31.

Retronecanone Oxime—To a solution of 1 g. of hydroxylamine hydrochloride in 6 cc. of 10% aqueous sodium hydroxide was added 0.6 g. of retronecanone. After heating twenty minutes on a steam-cone, the solution was cooled and the *p*H adjusted to about 8.5. The oxime was removed from the mixture by continuous ether extraction for twenty-four hours. After drying the ethereal extract and removing the solvent, a yield of 0.5 g. (75%) of the oxime was obtained. The most practical means of purification was found to be vacuum sublimation; small, white needles, m. p. 167–168° (cor.).

Anal. Calcd. for $C_8H_{14}ON_2$: C, 62.31; H, 9.15; N, 18.17. Found: C, 62.59; H, 9.16; N, 18.36.

Rotation. 0.0204 g. made up to 5 cc. with absolute ethanol at 26° gave αD −0.31; *l*, 1; $[\alpha]^{26}D$ −76.0°.

Summary

1. The base, isoretronecanol, has been prepared by the removal of the stable hydroxyl from platynecine. It has the formula $C_8H_{15}ON$. Isoretronecanol undergoes chromic acid oxidation to yield an optically active amino acid. Since there is no loss of carbon atoms, this product has been designated as 1-carboxypyrrolizidine (X) and thus establishes beyond doubt the presence of a CH_2OH group in retronecine (I) and platynecine (III).

2. Retronecanol by oxidation with aluminum *t*-butoxide and cyclohexanone gives retronecanone from which typical ketone reagent derivatives were prepared.

3. These experiments confirm the presence of a primary and a secondary hydroxyl group in retronecine.

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(5) Kuhn and Brydowna, *Ber.*, **70B**, 1333 (1937).