# THE STRUCTURE OF THE ALKALOID RENARDINE. III. STRUCTURE OF DIHYDRODESOXYOTONECINE

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1. N-methyl-N-(β-carboxyethyl)-γ-amino-α-methylbutyric acid is a product of oxidative degradation of dihydrodesoxyotonecine. This is shown by synthesis of the acid.
2. The structure of dihydrodesoxyotonecine is established. The structure of otonecine is identical with that of the necine of retusamine.
3. A structural formula is suggested for anhydrootonecine.

While studying the structures of the alkaloids renardine [1] and onetine [2], the present authors established that they are complex esters, formed by the action of an amino alcohol, otonecine, on the corresponding necine acids. E. S. Zhdanovich and G. P. Men'shikov [3] were the first to produce otonecine, by acid hydrolysis of the alkaloid otosenine, but up to now its structure has not been determined.

Culvenor and Smith [4] in 1957 isolated a new alkaloid, retusamine, from Crotalaria retusa L., and advanced a hypothesis, based on spectrum data, that it is of the otosenine type. The authors did not succeed in obtaining the amino alcohol of retusamine. Wunderlich [5] in 1962 established the structure of the alkaloid; he investigated the monohydrate of the α-bromo-d-camphor-trans-π-sulfonate of retusamine, and proposed a structural formula for it from X-ray analysis and IR spectral data. The author showed that all published spectroscopic data for otosenine, renardine, and onetine can be explained on the basis of the suggested structure of necine in retusamine, and gave structural formulae for these alkaloids, pointing out that they were correct if the necine of retusamine is otonecine.

According to Wunderlich the necine of retusamine (I) contains an eight-membered ring with a tertiary nitrogen atom and a keto group situated at diametrically opposite places in the ring. The existence of transannular interaction between the tertiary nitrogen atom and the carbonyl group in similar cyclic systems [16] affords a good explanation of the previously mentioned contradictory properties of otonecine and dihydrodesoxyotonecine [1, 3] (hydrootonecine [1]).

The basis of the present authors' working hypothesis was Wunderlich's assumption that the necine of retusamine is otonecine, the starting point being the structure advanced by him. Continuing the work previously begun on the structure of dihydrodesoxyotonecine, and comparing the structural formulae of otonecine and retronecine [7], the conclusion was reached that hydrogenation of otonecine most probably involves reduction of a double bond and a primary hydroxyl group, in which case the structure of this part of the molecule of the dihydrodesoxyotonecine formed resembles that of retronecanol [8]. It proved possible to demonstrate the correctness of this view of oxidizing dihydrodesoxyotonecine with chromic anhydride. The oxidation product, isolated as a diethyl ester of formula $C_{13}H_{25}NO_4$, can correspond to a dicarboxylic amino acid of formula $C_9H_{17}NO_4$. Assuming that the structure of dihydrodesoxyotonecine is (II), it is considered that the above-mentioned amino acid must be N-methyl-N-(β-carboxyethyl)-γ-amino-α-methylbutyric acid (III).

To confirm the structure of the oxidation product from dihydrodesoxyotonecine, the ethyl ester of N-methyl-N-(β-carbethoxyethyl)-γ-amino-α-methylbutyric acid was synthesized. The ester was obtained by condensing the ethyl ester of β-methylamino propionic acid with the ethyl ester of α-methyl-γ-bromobutyric acid. The ethyl ester of β-methylaminopropionic acid was synthesized by a method previously described in a paper [9], the starting material being β-bromopropionic acid. α-Methyl-γ-bromobutyric acid was obtained by treating α-methylbutyrolactone [10] with a saturated aqueous solution of hydrogen bromide. The lactone was prepared by condensing methylmalonic ester with ethylene oxide, with subsequent decarboxylation of the α-methylbutyrolactone carboxylic acid. The properties of the resultant α-methylbutyrolactone were in complete accord with those given in the literature [11].

The IR spectrum of the ethyl ester of N-methyl-N-(β-carbethoxyethyl)-γ-amino-α-methylbutyric acid thus synthesized seemed identical with that of the diethyl ester of the amino acid formed on oxidation of dihydrodesoxyotonecine.

The ethyl ester of N-methyl-N-(β-carbethoxyethyl)-γ-amino-α-methylbutyric acid obtained by oxidizing dihydrodesoxyotonecine is optically active, since reduction of otonecine and its esters as well as of retronecine [7] proceeds asymmetrically with the formation of only one isomer with a fixed configuration at C—$CH_3$.

The work carried out demonstrated the structure of dihydrodesoxyotonecine and supported the view that otonecine has the same structure as the necine of retusamine, i.e., that they are identical. Hence the structures of otonecine, renar-

dine, and onetine can at present be regarded as almost completely determined. Final elucidation of the structures of these alkaloids awaits direct demonstration of the relative positions of the carboxyl and amino glycol groups of their molecules, connected in the cyclic part of the diester. It is very probable that the primarily alcohol group of otonecine in these bases is esterified by the carboxyl $\alpha$ to it (i.e., is acylated by that carboxyl of the two carboxyl groups of the corresponding acid to which the hydroxyl group is in the $\alpha$ position). A similar diester structure has been established for the alkaloids isatidine [12], riddelline [13], and jacobine bromohydrin [14]. In that case the structures of otosenine (IV), renardine (V), and onetine (VI) will be those suggested by Wunderlich.

It is considered that the previously described anhydrootonecine [1] is formed from otonecine by splitting out of a molecule of water and formation of an ether bridge, and that its structure is analogous to that of anhydroplatinecine [15, 7].

Up to recently it was thought that of all the known pyrrolizidine amino alcohols only platinecine and rosmarinecine [16] are sterically capable of undergoing this type of reaction. Adams [17], by considering molecular models of retronecine, established that the double bond hinders convergence of the hydroxyl groups of the molecule, so that an ether bridge cannot arise. Nonetheless, Culvenor and Smith [18] prepared anhydroretronecine. It is thought that because of considerable strain in the anhydroretronecine molecule, the substituents at the double bond are not coplanar.

In the 8-membered otonecine ring, convergence of the hydroxyls appears to be possible despite the double bond. When anhydrootonecine is formed, the transannular interaction between the keto groups and the tertiary nitrogen atom vanishes, as is readily seen on comparing the IR spectra of the hydrochlorides of otonecine and anhydrootonecine. The absorption band in the carbonyl absorption region, characteristic of an O-protonated structure [5, 6], is absent from the spectrum of otonecine hydrochloride (VII). Absorption bands for hydroxyl groups are present, but the characteristic tertiary amine salt band is absent. The IR spectrum of anhydrootonecine hydrochloride (VIII) has a different appearance. There is an absorption band in the 1773 $cm^{-1}$ region, but no absorption bands for hydroxyl groups. The absorption band characteristic of salts of tertiary amines appears as three peaks. The increased carbonyl absorption frequency (1773 $cm^{-1}$) can be ascribed to increased ring strain due to the presence of a bridged ring structure [19].

## Experimental

IR spectra were measured on a IKS-14 spectrophotometer with a NaCl prism, the crystalline substance being made into a paste with vaseline, or a liquid layer 0.01 mm thick being used.

Otonecine, hydrochloride. Bands at 3178 and 3350 $cm^{-1}$ (hydroxyl groups) in the IR spectrum.

Anhydrootonecine, hydrochloride. Bands at 1773 (carbonyl group), 2592, 2694, 2783 (tert- amine salt) $cm^{-1}$ in the IR spectrum.

Chromic anhydride oxidation of dihydrodesoxyotonecine. A solution of 9.4 g $CrO_3$ and 4 g $H_2SO_4$ in 56 ml water was added with cooling to 3.73 g dihydrodesoxyotonecine [1]. When the vigorous reaction had ceased the mixture was boiled for one hour. Excess chromic acid was destroyed by $SO_2$ gas. The reaction mixtures was diluted with 500 ml distilled water and made alkaline while hot with 25% $NH_3$. The chromium hydroxide was filtered off, the filtrate boiled to remove excess ammonia, and the $SO_4^{-2}$ ions precipitated by barium hydroxide. The solution was heated until excess $NH_3$ was completely removed, and the excess of barium ions precipitated by adding $H_2SO_4$ dropwise. The solution, free from inorganic salts, was taken to dryness in a vacuum. Traces of water were removed by repeatedly dissolving the residue in anhydrous alcohol, and vacuum distilling off the latter. The residue was a glassy greenish mass (3.29 g), which was dissolved in 20 ml anhydrous alcohol, HCl gas passed through until the solution was saturated, and the mixture boiled 1.5 hr on a water bath. The alcohol was distilled off in a vacuum. 5 ml water were added to the residue, which was then neutralized with $NaHCO_3$ and extracted with ether to give 2.64 g of a mobile oil; bp 138--140° (6 mm); $d_4^{21}$ 0.988; $n_D^{21}$ 1.441; $[\alpha]_D^{21}$ + 7.64°, $MR_D$ 69.31., calc. 69.48; $R_f$ 0.62 (butanol-5% acetic acid(1:1), visualizer: Dragendorf's reagent).

Found %: C 60.24; H 9.68; N 5.79; $OC_2H_5$ 32.38; $C_{13}H_{35}O_4$. Calculated %: C 60.20; H 9.72; N 5.40; $OC_2H_5$ 34.75.

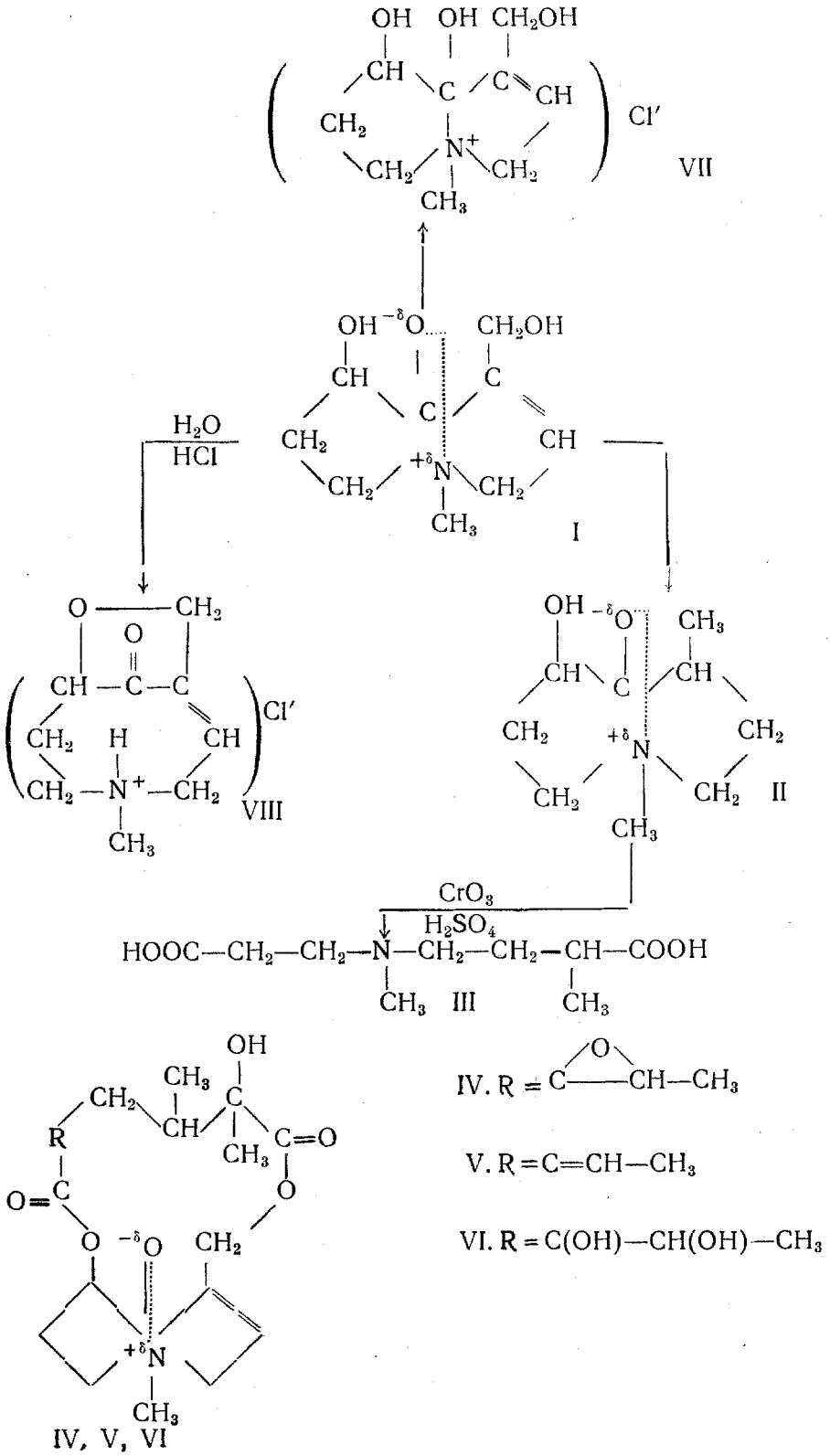
Ethyl ester of $\beta$-methylaminopropionic acid. This was prepared by a recognized method [9]. Bp 53-54° (6 mm); $d_4^{23}$ 0.9491; $n_D^{23}$ 1.421; $MR_D$ 35.05; calc. 35.16.

Found %: N 10.71. $C_6H_{13}NO_2$. Calculated %: N 10.68.

$\alpha$-Methylbutyrolactone. 100 g methylmalonic ester [20] bp 197.5-199.5°, 14 ml freshly-distilled piperidine, and 90 ml ethylene oxide were heated together in a thick-walled glass autoclave in a boiling water bath for 20 hours. The autoclave was cooled in ice, and the mixture then left 1 hr at room temperature to allow excess ethylene oxide to evaporate, after which it was acidified with 10% HCl and extracted with ether. The residue remaining after removal of the ether was boiled 3 hr with 250 ml 20% NaOH. The alkaline solution was washed with ether, acidified with HCl (1:1), and then extracted with ether. The acid aqueous solution was evaporated to dryness in a vacuum, and

the residue extracted with ether. The two ether extracts were combined and dried over $Na_2SO_4$. The residue remaining after evaporating off the ether was distilled in a current of $CO_2$. The distillate was shaken with 50 ml of a saturated solution of $NaHCO_3$ and extracted with ether. The ether extract was dried over $K_2CO_3$, the ether distilled off, and the residue distilled, 39.04 g of a fraction with bp 200-202° being collected; $d_4^{23}$ 1.060; $n_D^{23}$ 1.432; $MR_D$ 24.50; calc. 24.74.

Found %: C 59.72; H 8.22. $C_5H_8O_2$. Calculated %: C 59.98; H 8.05.



Ethyl ester of α-methyl-γ-bromobutyric acid. Nine grams of α-methylbutyrolactone in 25 ml 57% aqueous HBr were left for 24 hrs. at 20°, and the reaction mixture was then poured into ice water and extracted with ether. The ether extract was washed with water and dried over $H_2SO_4$ (after removing the ether, presumably, Tr.) The residue remaining after removing the ether (5 g) was dissolved in 20 ml anhydrous alcohol and saturated with dry HCl. After standing for 24 hr the solution was poured into 30 ml water and extracted with ether. The ether extract was washed with water and $NaHCO_3$ solution, then dried over $Na_2SO_4$, and evaporated to give 5.48 g of a volatile oil with bp 77-78° (5 mm); $d_4^{23}$ 1.2335; $n_D^{23}$ 1.441; $MR_D$ 44.76; calc. 43.95.

Found %: Br 39.30. $C_7H_{13}BrO_2$ Calculated %: Br 38.27.

Ethyl ester of N-methyl-N-(β-carbethoxyethyl)-γ-amino-α-methylbutyric acid. 5.2 g ethyl ester of α-methyl-γ-bromobutyric acid, 3.26 g ethyl ester of β-methylaminopropionic acid, and 7 g finely powdered anhydrous potassium hydroxide in 50 ml anhydrous alcohol were refluxed for 7 hr on a steam bath. The precipitate was filtered off and the solution evaporated in a vacuum. The resultant residue was dissolved in 20 ml 10% HCl, the solution washed with ether, neutralized with $NaHCO_3$, and then extracted with ether. The ether extract was dried over $Na_2SO_4$, and on evaporation yielded 1.23 g residue. Two spots were obtained by paper chromatography, the main one with $R_f$ 0.62, and a lesser one with $R_f$ 0.48. The substance was purified by running a petroleum ether solution through a column of 30 g $Al_2O_3$ (grade 2 activity), and then eluting with petroleum ether. The residue remaining after evaporating off the petroleum ether was distilled in a vacuum, to give a substance with bp 140-142° (7 mm); $n_D^{23}$ 1.441; $[\alpha]_D^{20}$ 0.0; $R_f$ 0.62.

Found %: C 59.90; H 9.52; N 5.71. $C_{13}H_{25}NO_4$. Calculated %: C 60.20; H 9.72; N 5.40.

The IR spectrum of the synthetic material completely coincided with that of the diethyl ester obtained by oxidizing dihydrodesoxyotonecine with chromic anhydride.

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