

Reserpine

For centuries, the Indian snake-like root, *Rauwolfia serpentina* got favourable reputation in its habitat as a valuable medicinal agent. Schlittler first isolated reserpine, and demonstrated that it is responsible for hypotensive activity. This discovery and the remarkable effect which reserpine was subsequently found to exert upon the central nervous system, rapidly won for the alkaloid an important place in the treatment of hypertensive, nervous and mental disorders. Thus, reserpine is used for controlling hypertension, fever, cholera, dizziness, headache and epilepsy.

Structure

1. The molecular formula of reserpine is $C_{33}H_{40}N_2O_9$.

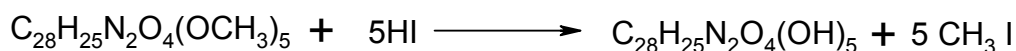
2. Nature of Nitrogen atoms

Reserpine is a weak base thus both nitrogen atoms must be in the ring. Reserpine has no hydroxy groups but it forms an acetyl derivative indicating the presence of one $-NH-$ group.

The second nitrogen atom is present in the form of tertiary atom as revealed by I.R. spectroscopy. Reserpine readily gives a methiodide, so the second nitrogen atom must be tertiary.

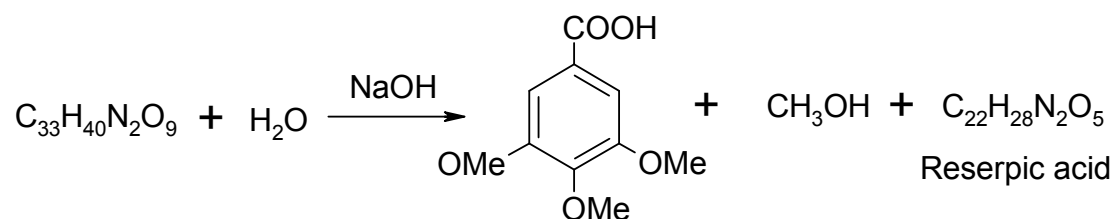
3. Nature of Oxygen atoms

Reserpine on heating with HI gives five moles of methyl iodide (**Ziesel** method) indicating the presence of five methoxy groups in reserpine.



The remaining four oxygen atoms are present in the form of ester.

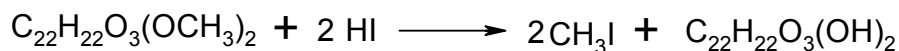
4. Reserpine gives 3,4,5-trimethoxy benzoic acid, methanol and reserpic acid upon alkaline hydrolysis.



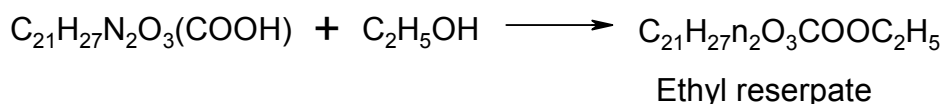
From above reaction it is evident that reserpine is a diester since it gives two carboxylic groups (one in 3,4,5- trimethoxybenzoic acid and second in reserpic acid) and two alcoholic groups 9 one in methanol and other in reserpic acid).

5. Structure of Reserpic acid

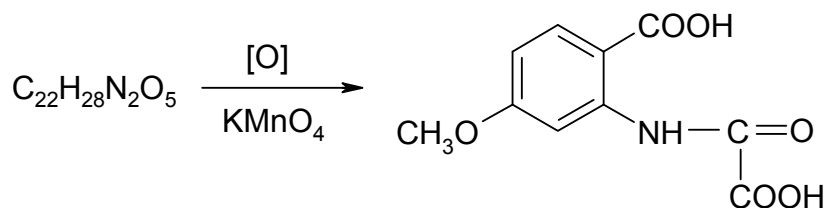
- (i) Its molecular formula is $C_{22}H_{28}N_2O_5$.
- (ii) Usual tests show that reserpic acid contains two methoxy groups.



- (iii) It evolve one molecule of CO_2 which indicates that it contains one carboxylic acid. It forms monoester with alcohol which also indicates that it contains one carboxylic group.

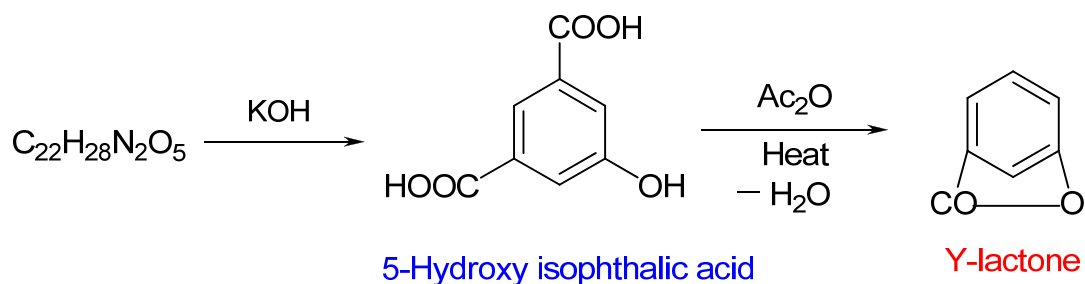


- (iv) Reserpine on oxidation gives ketone which indicates that it contains a secondary alcoholic group.
- (v) Regular tests show that it contains a secondary NH group and a tertiary nitrogen atom.
- (vi) Reserpine on oxidation with potassium permanganate gives 4-Methoxy- N-oxalyl anthranilic acid which indicates the presence of indole ring and methoxy group at meta position to indole nitrogen.



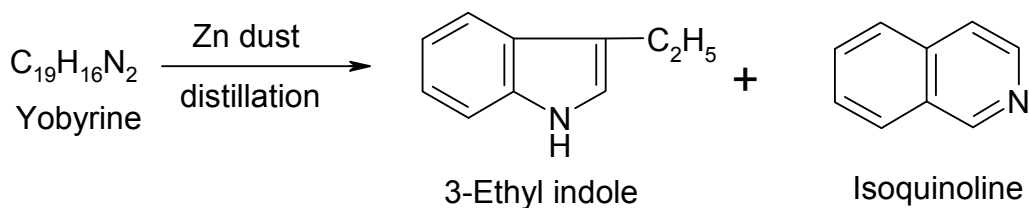
4-methoxy-N(Oxalyl) anthranilic acid

- (vii) Reserpic acid on hydrolysis with KOH gives 5-Hydroxyisophthalic acid which indicates that OH group and $-COOH$ group in reserpic acid are at meta position to each other because the second carboxylic group in 5-hydroxyisophthalic acid is at meta position to both OH and $-COOH$ groups.

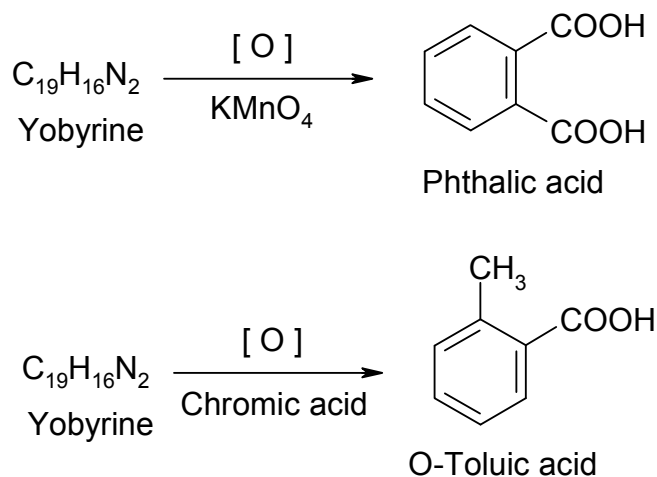


(viii) Methyl reserpate on selenium dehydrogenation gives a principal compound having molecular formula $\text{C}_{19}\text{H}_{16}\text{N}_2$ (Yobyryne). Thus the structure of the reserpate acid depends on the carbon skeleton of this compound. This compound ($\text{C}_{19}\text{H}_{16}\text{N}_2$) possess following properties.

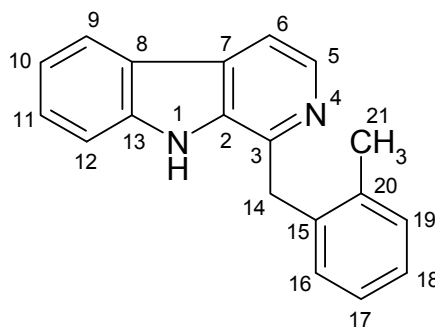
- (A) It reacts with aldehyde which indicates that there is a $-\text{CH}_2-$ group at adjacent to nitrogen atom.
- (B) It gives 3-Ethylindole and isoquinoline on zinc dust distillation which indicates that these two rings are present.



(C) On oxidation with chromic acid it gives o-Toluic acid and on oxidation with potassium permanganate gives phthalic acid.

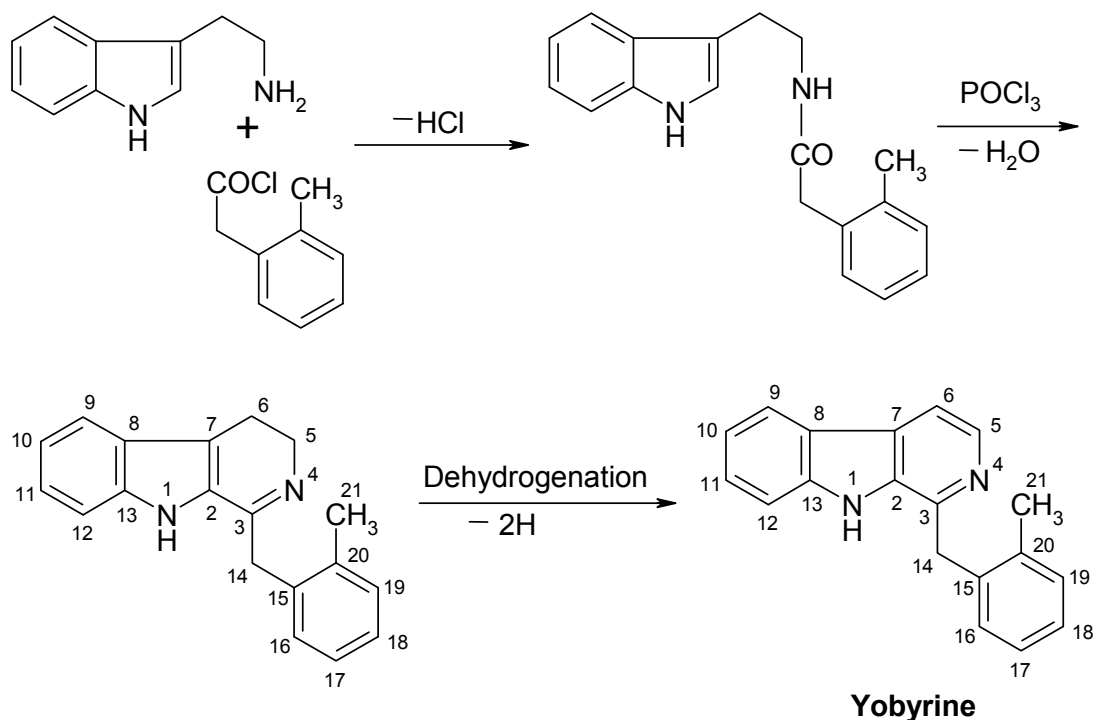


These observations indicate that the compound of molecular formula $\text{C}_{19}\text{H}_{16}\text{N}_2$ should have the following structure.

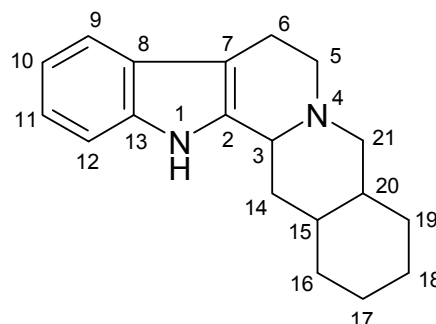


The structure of yobyryne was confirmed by its synthesis.

Synthesis of Yobyryne



The hydrocarbon byobyryne is obtained from reserpine acid hence the possible skeleton for reserpine acid may be as follows.



(ix) Position of methoxy groups

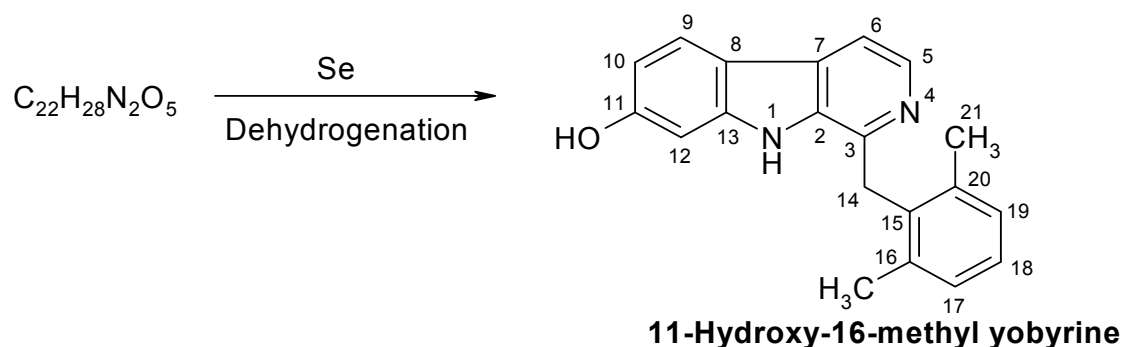
- (a) Since 4-Methoxy-N-(oxalyl) anthranilic acid is obtained from the reserpine acid on oxidation which indicates that one methoxy group

must be at meta position corresponding to nitrogen of indole ring i.e. at C-11.

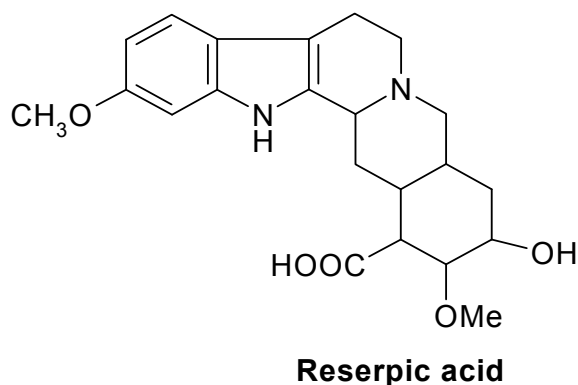
(b) From biogenic point of view the second methoxy group is always at C-17.

(x) **Position of –COOH and -OH groups**

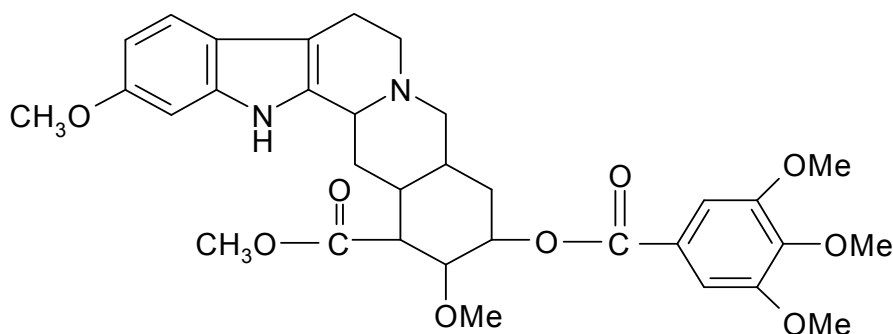
Reserpine acid on selenium dehydrogenation gives 11-Hydroxy-16-methylpyrroline. The formation of this compound indicates that there is a carboxylic group at position C-16 which is being converted into –CH₃ group during dehydrogenation.



Since –COOH group and –OH group are always at meta position to each other and hence –OH group must be at C-18. Thus, complete structure of reserpine acid is as follows.



On the basis of above the complete structure of reserpine can be formulated because it is a diester as follows.



Reserpine

Finally, the structure of reserpine was confirmed by its synthesis.

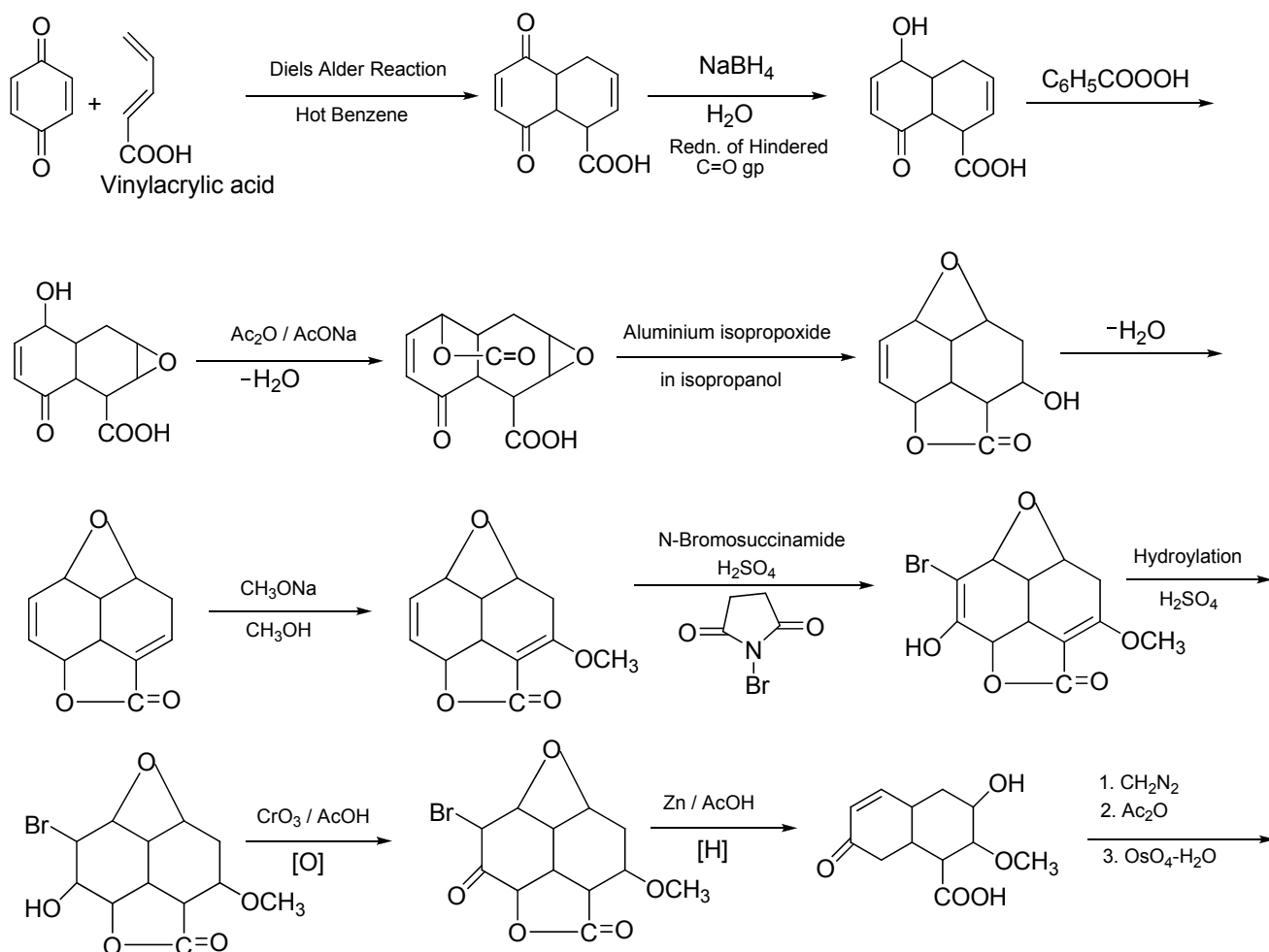
Synthesis of Reserpine (Woodward et.al. 1956)

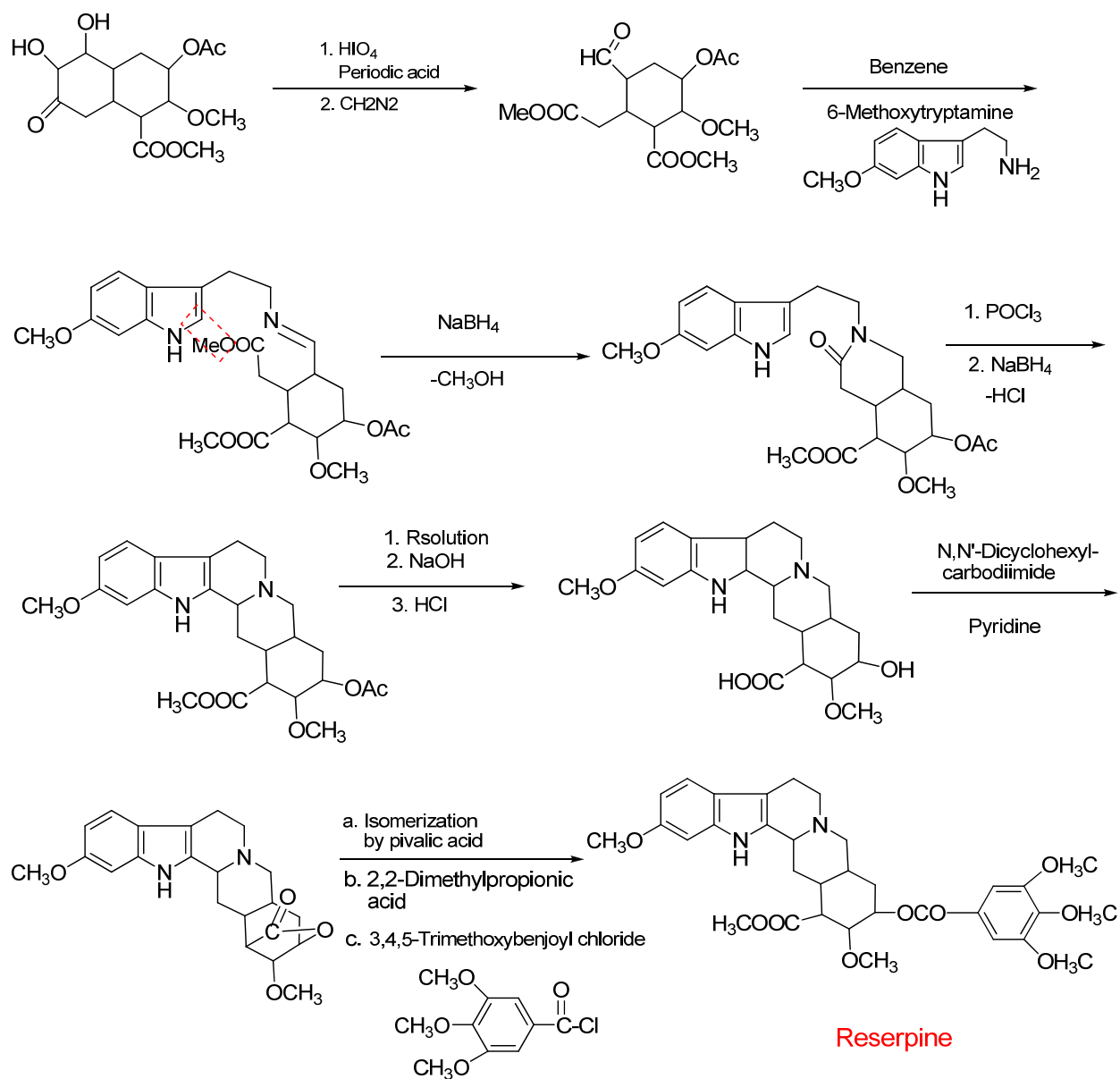
The total synthesis of Reserpine

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J. Am. Chem. Soc., 1956,**78** ,2023,2657 ; **Tetrahedron** 1958,**2**,1-57.





References:

Organic Chemistry , I. L. Finar