Vasicine.

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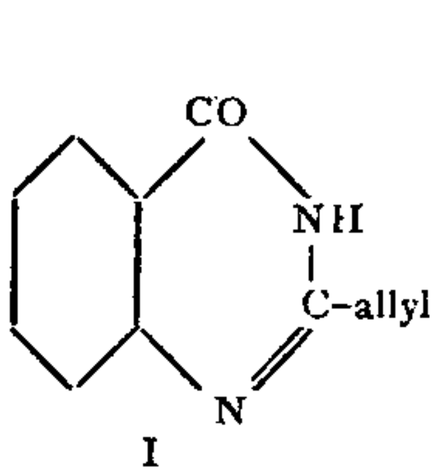
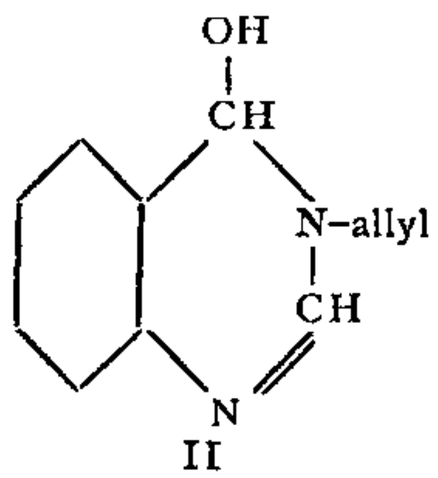
VASICINE, $C_{11}H_{12}ON_2$, an alkaloid, was isolated from the leaves of *Adhatoda Vasica*, Ness by Sen and Ghosh.[1] It was found to be a monacid base and further studies by Ghosh[2] revealed the presence of a quinazoline ring. With phosphorous penta-chloride, it was converted into chloro-desoxy vasicine indicating that a hydroxy group replaceable by chlorine exists in the molecule. With alkaline permanganate it gave a substance believed to be 4-oxyquinazoline but direct proof of its formation was furnished by Ghosh, Krishna, Narang and Ray.[3] Ghosh[2] was of the opinion that vasicine was 2-propyl 4-oxyquinazoline, a substance which was later on synthesised by De and Ray[4] and proved to be not identical with vasicine. Ghosh, Krishna, Narang and Ray[3] found evidence that vasicine is converted into an isomeric substance by traces of alkali and gave a solid acetyl derivative. But Narang and Ray[5] were of opinion that the isomeric base may be impure vasicine.

In 1934, Späth and Nikawitz[6] were supplied by the firm of E. Merck, a base isolated from the mother liquors of *peganam harmala*. This base melted at a slightly higher temperature because the m.p. was determined *in vacuo*. Its formula was $C_{11}H_{12}ON_2$ but it gave a liquid acetyl derivative and hence the question of its identity with vasicine was left open by these authors. Oxidation with permanganate furnished 4-oxy-quinazoline 3-acetic acid and hence the formula II was advanced by Späth and Nikawitz as



I



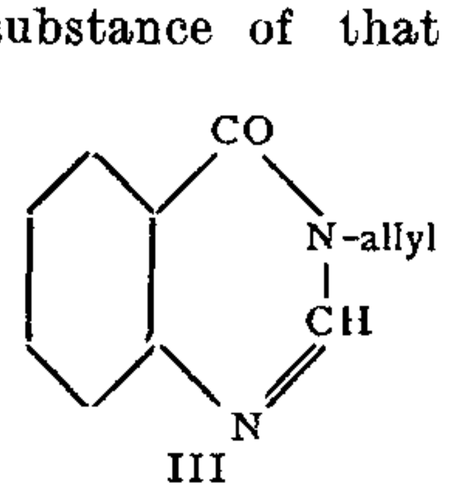
II

against (I) advanced sometime ago for vasicine by Ghosh, Krishna, Narang and Ray.[3] The solubility of vasicine in acetone also differed from the solubility of peganine in the same solvent. Hanford, Liang and Adams[10] showed the solubility of vasicine in acetone to be small as observed by Ghosh, Krishna, Narang and Ray[3] and the greater solubility of peganine must be due to associated impurities.

Narang and Ray[5] criticised the Späth-Nikawitz formula on various grounds and expressed the opinion that vasicine may not after all be identical with peganine because the acetyl derivative has been found by Späth and Nikawitz[6] to be an oil as against the solid dehydro acetyl derivative of Ghosh, Krishna, Narang and Ray.[3]

Späth and Kuffner[7] however definitely established the identity of vasicine and peganine. Reynolds and Robinson[8] suggested that in view of identity of vasicine and peganine, the latter name is redundant. These authors[8] conclusively proved the Späth-Nikawitz formula to be incorrect by synthesising a substance of the structure II by an unambiguous method. Narang and Ray[9] advanced additional evidence against formula II proposed by Späth and Nikawitz.

Narang and Ray[5] synthesised the compound III and proved that its reduction product with sodium and amyl alcohol was not identical with the similar reduction product of vasicine and hence the structure II advocated by Späth and Nikawitz was untenable. In this connection it must be stated that Späth obtained a base $C_{11}H_{16}N_2$ by the reduction of vasicine. It is impossible to get a substance of that formula from vasicine.



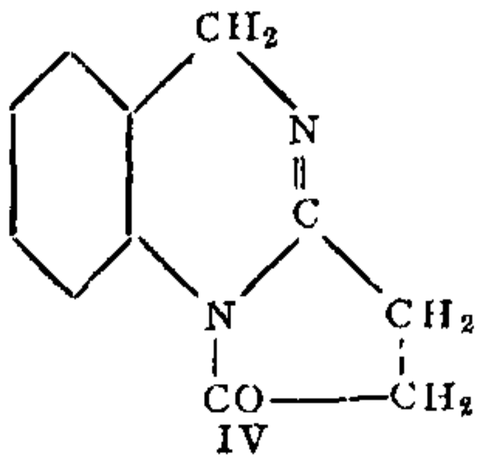
III

Narang and Ray[9] then proposed two formulæ—one a cyclic system of three rings and another, an open chain—for vasicine. If the open chain one was the correct representation of vasicine, then in oxidation and other

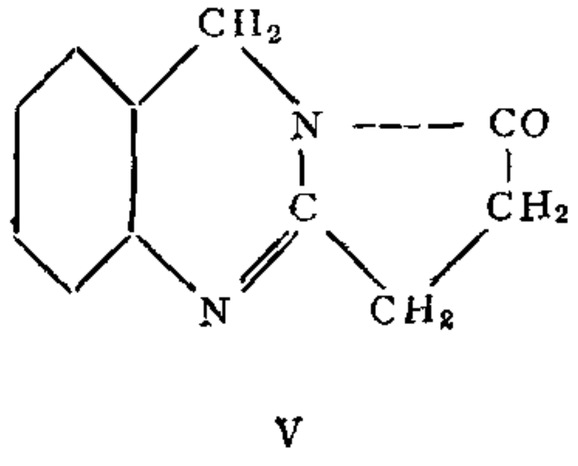
[1] *J. Indian Chem. Soc.*, 1925, **1**, 315.
[2] *J. Indian Chem. Soc.*, 1927, **4**, 1.
[3] *J. Chem. Soc.*, 1932, 2740.
[4] *J. Indian Chem. Soc.*, 1927, **4**, 541.
[5] *Curr. Sci.*, 1934, **2**, 388.
[6] *Ber.*, 1934, **67**, 45.
[7] *Ber.*, 1934, **67**, 868.
[8] *Nature*, 1934, **134**, 142.
[9] *Chem. and Industry*, 1934, **53**, 698.
[10] *J. Amer. Chem. Soc.*, 1934, **56**, 2780.

reactions it passed through an intermediate tricyclic stage. They further pointed out that desoxy-vasicine was not identical with 3-allyl 3 : 4 dihydroquinazoline as would be the case if formula II of Späth and Nikawitz was the correct structure of vasicine. Hanford, Liang and Adams,[10] besides supporting Narang and Ray,[9] advanced the additional argument that 3-allyl 4-keto 3 : 4 dihydroquinazoline can be catalytically reduced, whilst vasicine is unaffected. They advanced a cyclic formula for vasicine which is much nearer the truth than the set of random suggestions of Späth and Nikawitz.[6] Moreover the position of the hydroxyl was taken to be in β-position in the third ring whilst actually it is in α-position. It must be stated that Späth and Nikawitz only suggested in their paper all possible variations in which $C_{11}H_{12}ON_2$ can be arranged as a quinazoline and it is not fair to attribute to them the formula that later on was proved to be correct.

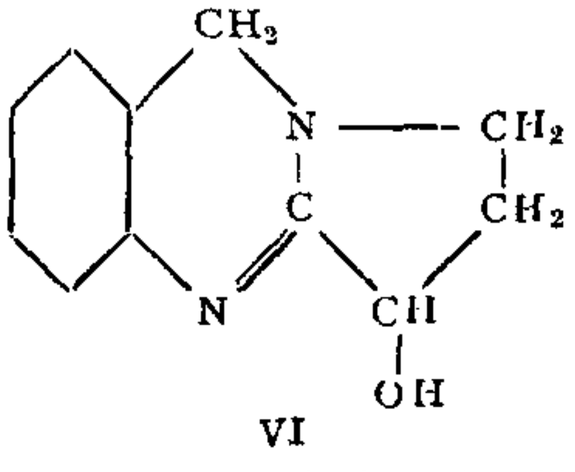
Narang and Ray[11] prepared IV and V and found that the electrolytic reduction product of IV was not identical with the similar product from vasicine but the reduction product of V was identical with the reduction product of vasicine. Hence vasicine has a linear cyclic formula. Späth, Kuffner and Platzer[12] synthesised desoxy vasicine from *o*-nitro-benzylamino butyric



IV



V



VI

acid which, on reduction and treatment with phosphoryl chloride, passed into a substance which, on reduction with sodium and amyl alcohol, furnished a product identical with the reduction product of desoxy vasicine. This product is identical with the reduction product of V. Neither the work of Späth, Kuffner and Platzer[12] nor that of Narang and Ray[11] furnishes any proof of the position of the hydroxy group. But Morris, Hanford and Adams[13] furnish an acceptable evidence of the position of the alcoholic hydroxyl group.

Finally *o*-nitrobenzyl chloride on condensation with α-hydroxy-γ-aminobutyrate furnished a product which was cyclised, after reduction to a substance identical with vasicine, by Späth, Kuffner and Platzer[14] and hence vasicine becomes VI. It will be seen that the hydroxyl group is attached to the α-position and is not in the β-position, where it figures in the various formulæ proposed by Späth and Nikawitz.[6]

Späth, Kuffner and Platzer[15] now find that vasicine gives a solid acetyl (dehydro) as stated by Ghosh, Krishna, Narang and Ray.[3] Narang and Ray[5] based their view of non-identity of vasicine and peganine on Späth's reporting the acetyl derivative to be a liquid.

Späth, Kuffner and Platzer[16] have resolved vasicine into optical enantromorphs but since natural vasicine is a *dl* compound, this paper has no bearing on the constitution of vasicine. But Ghosh, Krishna, Narang and Ray have already stated that vasicine is resolvable, a fact which Späth, Kuffner and Platzer have acknowledged.

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[11] *Curr. Sci.*, 1935, **3**, 352.
[12] *Ber.*, 1935, **68**, 497.
[13] *J. Amer. Chem. Soc.*, 1935, **57**, 921 and 961.
[14] *Ber.*, 1935, **68** (B), 702.
[15] *Ber.*, 1935, **68** (B), 935.
[16] *Ber.*, 1935, **68** (B), 1386.