413. *Vasicine.*

By TARAK P. GHOSE, SRI KRISHNA, KARTAR S. NARANG, and JNANENDRA N. RÂY.

DE and RÂY (*J. Indian Chem. Soc.*, 1927, **4**, 541) having shown that vasicine, an alkaloid present in *Adnatoda vasica*, Nees (Sen and Ghose, *ibid.*, 1924, **1**, 315), was not 2-propyl(or *iso*propyl)-4-quinazolone, the work upon which this structure was based has been re-examined and extended.

Fresh analyses and molecular-weight determination on very pure material support the earlier formula $C_{11}H_{12}ON_2$. The base is mono-acid but possesses weak phenolic properties. From its solution in alkali, it can only partly be recovered unchanged. Moreover, when heated with a trace of potassium hydroxide at 170° or when boiled in acetone solution with a trace of alkali, vasicine is converted into an isomeric substance, m. p. 164°, which we designate as *iso-vasicine* (III). This tendency to isomerise to structure (III) is evident in many of its reactions. Vasicine gives a stable hydrochloride, from which it can be regenerated unchanged. Hence it seems that the isomerisation is caused only by alkaline reagents.

Vasicine was said to give a monomethiodide, but the action of methyl iodide has now been found to effect a profound change in the structure of the alkaloid (see p. 2742), and therefore the conclusion that vasicine is a tertiary base is erroneous.

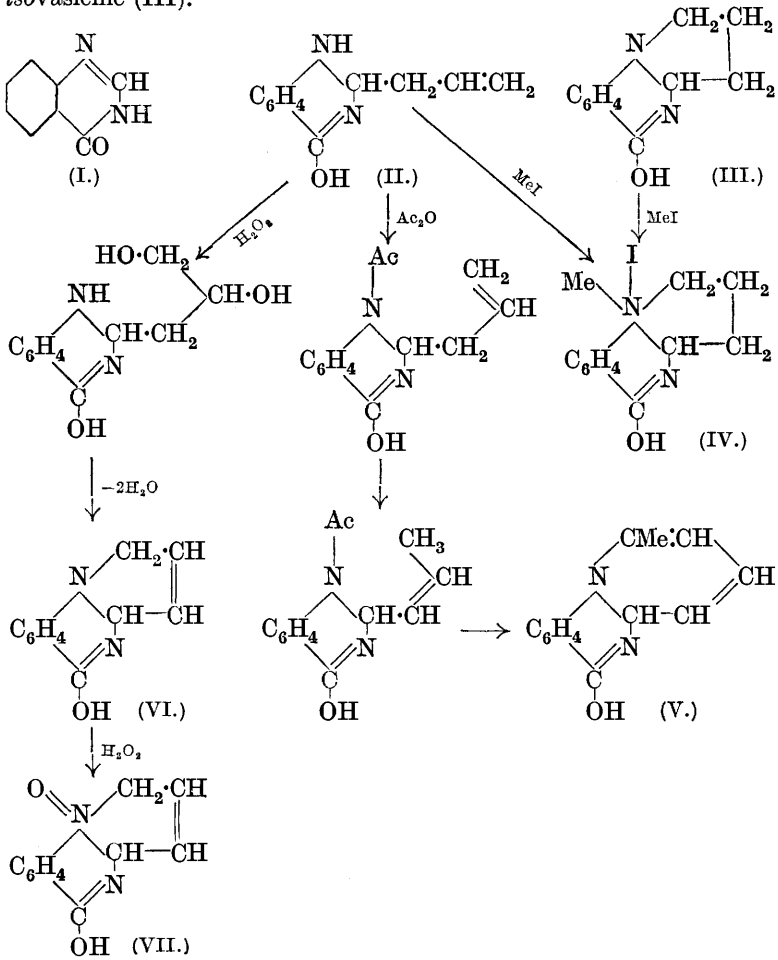
Vasicine decolorises potassium permanganate solution at 0° instantaneously and a cold aqueous solution of its hydrobromide absorbs bromine, indicating an unsaturated side chain. On fusion with potassium hydroxide, it furnishes anthranilic acid, thereby indicating that a skeleton $C_6H_4\langle{}^{C}_{N}$ exists in the molecule. Oxidation with acid 5% aqueous potassium permanganate yields a substance $C_8H_6ON_2$, m. p. 214°, together with traces of acetic and probably formic acid. This substance has now been identified as 4-quinazolone (I) by direct comparison with a sample synthesised by the method of Niementowski (*J. pr. Chem.*, 1895, **51**, 565). Therefore both the nitrogen atoms of the alkaloid are in the same ring system. The formation of (I) does not necessarily fix the position of the oxygen atom of vasicine for quinazolines are known to acquire an oxygen atom at this position on oxidation; but in view of its weak phenolic properties, the alkaloid probably contains an oxygen atom in this position.

Vasicine contains no NMe group. With nitrous acid at 0° it apparently forms a nitroso-derivative, but this could not be purified.

Oxidation with hydrogen peroxide in acetone solution yields

successively two *products*, (A) $C_{11}H_{10}ON_2,\frac{1}{2}H_2O$, m. p. 168°, and (B) $C_{11}H_{10}O_2N_2$, m. p. 212°: (A) is a much stronger base than vasicine, whilst (B) is neutral (cf. Polonowski and Polonowski, *Compt. rend.*, 1925, **180**, 1755, who note the neutral character of amine oxides of alkaloids). These are assigned the structures (VI) and (VII).

The clue to the constitution of the alkaloid was revealed by the observation that whilst vasicine shows the presence of an unsaturated side chain, *iso*vasicine does not. Since 4-quinazolone (I) is the main product in the oxidation of vasicine, the side chain can only be linked at position 2 in (I). Therefore vasicine is (II) and *iso*vasicine (III).



On methylation, vasicine first isomerises to (III) and thence forms the methiodide (IV), since the methiodide of *iso*vasicine is identical with that prepared from vasicine directly. The methiodide can be converted into the methohydroxide which is not further affected by boiling aqueous alkali.

Hydrogenation of vasicine was attempted in presence of barium sulphate–palladium, but without success (cf. analogous behaviour of safrole).

The action of acetic anhydride upon vasicine gives a *substance* to which the formula (V) is ascribed; apparently the mobile hydrogen atom is acetylated, thus preventing the transition to the *iso*-structure, but a change takes place similar to that of safrole to *iso*safrole; the product then loses a further molecule of water. The mode of isolation of the product precludes the possibility of an acetyl group's remaining attached to the oxygen atom even if the enolic hydroxyl had been simultaneously acetylated. The substance (V) is as basic as vasicine and does not furnish ethyl acetate when heated with alcohol and sulphuric acid.

EXPERIMENTAL.

The crude alkaloid (1 part; Sen and Ghose, *loc. cit.*) was refluxed with C_6H_6 (16 parts) for 1 hr., cooled, and filtered from resinous material; the filtrate, on being made turbid with Et_2O, deposited further impure material. After addition of charcoal and agitation, the filtered soln. was left to crystallise. Recryst. thrice from hot dil. EtOH, vasicine had m. p. 196° (decomp.). The hydrochloride, prep. in C_6H_6 soln., was fractionally cryst. from Et_2O–EtOH; m. p. 208° (after drying at 110°; cf. Ghose, *loc. cit.*). The regenerated base was recryst. successively from acetone and C_6H_6 and then had m. p. 198° (decomp.) [Found: C, 70·2*, 70·11; H, 6·3*, 6·3; N, 15·0*, 14·9; *M*, by titration, 188; *M*, from $B_2H_2PtCl_6$, 188. Calc. for $C_{11}H_{12}ON_2$: C, 70·2; H, 6·5; N, 14·9%; *M*, 188].

The alkaloid contained no NMe group and was optically inactive. Preliminary experiments indicate that it is resolvable.

A cold soln. of vasicine (0·1 g.) in acetone (dist. over $KMnO_4$, 10 c.c.) instantly decolorised *N*/20-$KMnO_4$; a soln. of 4-quinazolone (I) of the same concn. required 4—5 mins., and *iso*vasicine took 7—8 mins. at 30°. A C_6H_6 soln. of vasicine reduced moist Ag_2O, but neither of the other two substances did so under similar conditions. An aq. soln. of vasicine hydrobromide decolorised Br aq. at 0°. Basification of the decolorised soln. with Na_2CO_3 aq. pptd. a *substance*, which, cryst. from hot dil. EtOH, had m. p. 225° (Found: N, 10·65. $C_{11}H_{11}ON_2Br$ requires N, 10·44%).

When CO_2 was passed into a soln. of vasicine in 1% KOH aq., a small ppt. was formed, from which vasicine was isolated by careful crystn.; but the main product, isolated after neutralisation of the filtrate with dil. HOAc, was another substance, m. p. 192—194° (mixed m. p. with vasicine 150—160°), which was not obtained analytically pure.

* Microanalyses.

Conversion of Vasicine (II) *into* iso*Vasicine* (III).—(*a*) Vasicine (0·5 g.) was ground with a trace of KOH and kept at 170—175° for 5 mins., and a substance, m. p. 164° (decomp.) after crystn. (twice) from C_6H_6, was isolated from the cooled mass. This formed a methiodide, m. p. 191° alone or mixed with vasicine methiodide (cf. Sen and Ghose, *J. Indian Chem. Soc.*, 1924, **1**, 315, who give m. p. 187°).

(*b*) A soln. of vasicine (0·5 g.) in acetone (50 c.c.) and a trace of NaOH were refluxed for 2 hrs.; the filtrate from a small insol. residue was conc. to crystn. in presence of CO_2. Recryst. from C_6H_6–ligroin, iso*vasicine* had m. p. 164° (decomp.), not depressed on admixture with the foregoing substance; the yield was poor (Found : C, 70·1; H, 6·5; N, 14·8. $C_{11}H_{12}ON_2$ requires C, 70·2; H, 6·5; N, 14·87%). Its hydrochloride, prep. in C_6H_6 soln., had m. p. 222° (decomp.) (mixed m. p. with vasicine hydrochloride, <180°).

(*c*) Vasicine (2·5 g.) was gradually stirred into a fused mixture of KOH (10 g.) and H_2O (3 c.c.) at 150°, and then heated to *ca.* 210° (frothing) for 10 mins. The cooled melt was dissolved in H_2O, the soln. extracted with Et_2O, the alkali nearly neutralised with dil. H_2SO_4, concentrated, and then treated with $AgNO_3$ aq. After decomp. of the Ag salt in the usual manner, Et_2O extracted anthranilic acid, m. p. 142—143° (mixed m. p. 145°). When the alk. melt was acidified with dil. H_2SO_4 and steam distilled, acetic acid was isolated as Ag salt (Found : Ag, 64·3. Calc. : 64·6%).

Oxidation of Vasicine with Potassium Permanganate : Isolation of 4-*Quinazolone.*—The product isolated by following the details given by Ghose (*loc. cit.*) was further purified by sublimation; m. p. 214° (Found : C, 66·0*; H, 4·3*; N, 19·18*. Calc. for $C_8H_6ON_2$: C, 65·8; H, 4·1; N, 19·2%). It was identical (mixed m. p.) with 4-quinazolone (I), prepared as described by Niementowski (*loc. cit.*).

Oxidation of Vasicine with Hydrogen Peroxide.—Vasicine (1·0 g.) was suspended in acetone (10 c.c.), and H_2O_2 (12 c.c.; 12 vol.) stirred in. The mixture was kept at 50—60° for 1½ hrs., and a colourless cryst. *substance* B (VII) was deposited on cooling (0·28 g.); recryst. twice from H_2O, it had m. p. 214° (Found : C, 64·9*, 64·8*; H, 4·8*; N, 14·1*, 14·09. $C_{11}H_{10}O_2N_2$ requires C, 65·4; H, 4·9; N, 13·9%). The mother-liquor on standing for 12 hrs. deposited another *substance* A (VI), m. p. 166°; cryst. successively from dil. acetone and water, it had m. p. 168° (decomp.) (Found : C, 67·4*, 67·4; H, 5·8*, 5·9; N, 14·3*. $C_{11}H_{10}ON_2,\frac{1}{2}H_2O$ requires C, 67·6; H, 5·6; N, 14·35%). The crystals lost H_2O at 110°, and partially decomposed. The substance A (0·2 g.), when dissolved in acetone (5 c.c.) and further oxidised with H_2O_2 (1·5 c.c.) at 60° for 1 hr., gave 0·18 g. of B (m. p. and mixed m. p., 214°).

Action of Acetic Anhydride on Vasicine.—Vasicine (10 g.), Ac_2O (30 c.c.), and NaOAc (fused, 1·0 g.) were boiled for 2½ hrs. The product was worked up as usual, and when repeatedly crystallised from EtOAc (charcoal) afforded pale brownish needles, m. p. 165° (depressed on admixture with III and VI) (Found : C, 72·9*, 73·0*; H, 5·4*, 5·6; N, 13·4*, 13·3*. $C_{13}H_{12}ON_2$ requires C, 73·5; H, 5·6; N, 13·2%). The *substance* dissolves easily in dil. acids and reacts alk. to litmus. Acetyl determination by Perkin's method gave no EtOAc.

Vasicine methohydroxide (Sen and Ghose, *loc. cit.*) was boiled for 2 hrs. with 20% KOH aq. without change. When it (0·5 g.) was dissolved in H_2O (200 c.c.), cooled to 40°, treated with $KMnO_4$ aq. (0·5%, 150 c.c.) (stirring),

and the filtered solution concentrated to 10 c.c., and just acidified with AcOH, an orange-coloured cryst. ppt. was obtained, m. p. 209° after crystn. from H_2O (Found : N, 13·4%). The yield was too small to allow of characterisation.

FOREST RESEARCH INSTITUTE,
DEHRA DUN.
UNIVERSITY OF THE PUNJAB, LAHORE.

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