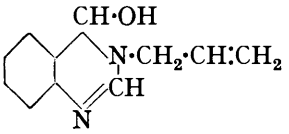
42. *Derivatives of Quinazoline.*

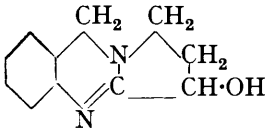
By (Miss) T. M. Reynolds and Robert Robinson.

The constitution (I) was proposed by Späth and Nikawitz (*Ber.*, 1934, **67**, 45) for vasicine (peganine), but was later withdrawn (Späth, Kuffner, and Platzer, *Ber.*, 1935, **68**, 699). The formula did not commend itself to us for two reasons: (1) it is not in harmony with the chemical behaviour of vasicine; (2) vasicine is identical with "peganine," a congener of harmaline, but the structure (I) bears no relation to that of the alkaloids of the indole group. For the latter reason we synthesised (I) and found it to differ from vasicine in the anticipated way (compare *Nature*, 1934, **134**, 142). The true constitution (II) of vasicine has now been elucidated by the work of Rây, Späth, Adams, and their several collaborators, and it is seen that the N·C·C·C·C·N group characteristic of the ornithine series of amino-acids and alkaloids is present in the molecule. The fact that Späth's first formula (I) could not be reconciled with a view of the biogenesis of *harmala* alkaloids which has been put forward in several places by one of us is a sufficient explanation of our interest in the matter. But, as Professor Späth has protested (*Ber.*, 1935, **68**, 938) that we had no right to perform our very simple experiment, we find it necessary to point out that the field of study in question, if reserved at all, was the preserve of Ghose and Rây and their colleagues

and we were favoured by some private discussions with Professor J. N. Rây on the subject of vasicine at a time when he was travelling in Europe. Professor Rây's views on



(I.)



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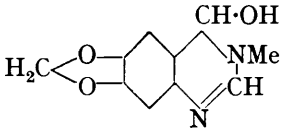

(III.)

Späth's formula were identical with our own, but he, being separated from his laboratory, was unable to apply the obvious crucial test himself.

Having obtained (I), we took the opportunity to examine the extent of its analogy with carbinol-amines of the *iso*quinoline series and prepared the hydrastinine analogue (III) with the same object. The quinazoline carbinol-amines do not closely resemble cotarnine and hydrastinine, although some similar condensations are recorded below.

Experimental.

3-Allylquinazolinium Iodide.—A cold mixture of quinazoline (4 g.), allyl iodide (4 c.c.), and ethyl acetate (5 c.c.) was kept for 12 hours and the resulting crystalline mass (3·8 g.) was collected and washed with ethyl acetate. The bright yellow product dissolved freely in alcohol and was precipitated as an oil by the addition of ethyl acetate, benzene, or ether. When rubbed with ether, the oil crystallised and the specimen (m. p. 104—107°) used for analysis was triturated thoroughly with ethyl acetate to remove coloured impurities (Found: C, 44·6, 44·6; H, 4·4, 4·3; N, 9·3. $C_{11}H_{11}N_2I,0{\cdot}33C_2H_6O$ requires C, 44·7; H, 4·2; N, 9·0%). The presence of alcohol was qualitatively confirmed. A further quantity of the *iodide* separated from the ethyl acetate mother-liquor and after 48 hours an almost quantitative yield was obtained.

4-Hydroxy-3-allyl-3 : 4-dihydroquinazoline (I).—A mixture of 3-allylquinazolinium iodide (5 g.), water (15 c.c.), and an excess of freshly precipitated silver chloride was shaken for 30 minutes, the liquid filtered, and the silver salts washed with cold water. The combined filtrate and washings (*ca.* 30 c.c.) were cooled to 0° and potassium hydroxide solution (5 c.c. of 33%) was gradually added. The liquid clouded, then cleared, and after a few minutes a colourless solid began to separate; this was collected (1·8 g.) after 30 minutes and recrystallised from benzene; m. p. 130—131° (Found: C, 70·4; H, 6·4; N, 14·6. $C_{11}H_{12}ON_2$ requires C, 70·2; H, 6·4; N, 14·9%). The substance is easily decomposed by cold alkali and it is essential to observe the prescribed conditions for its preparation. An oily, ether-soluble, diazotisable amine is formed when 4-hydroxy-3-allyl-3 : 4-dihydroquinazoline is heated with dilute aqueous alkali. The carbinol-amine is also decomposed by heating with water and, except in small quantities, cannot be recrystallised in this way; it is alkaline to litmus. It is easily soluble in alcohol and in acetone and is recovered unchanged by evaporation of the solutions at their boiling point or at room temperature in a desiccator, and it does not react with acetone in the presence of saturated aqueous sodium carbonate.

3-Allylquinazolinium Picrate.—When cold aqueous picric acid (1%) was added to a solution of 3-allylquinazolinium chloride, prepared as described above, a bright yellow picrate separated as a quickly solidifying oil. It crystallised from alcohol in plates, m. p. 124° after sintering (Found: C, 51·4; H, 4·4; N, 15·8; loss in a high vacuum at 104°, 10·3. $C_{17}H_{13}O_6N_5,C_2H_6O$ requires C, 51·2; H, 4·3; N, 15·7; C_2H_6O, 10·3%).

The addition of cold saturated aqueous picric acid to an alcoholic solution of 4-hydroxy-3-allyl-3 : 4-dihydroquinazoline afforded the same picrate (m. p. and undepressed mixed m. p.).

4-Nitromethyl-3-allyl-3 : 4-dihydroquinazoline Picrate.—A solution of 4-hydroxy-3-allyl-3 : 4-dihydroquinazoline (0·2 g.) and nitromethane (0·7 c.c.) in alcohol (1·5 c.c.) was gently heated on a steam-bath for 5 minutes and then evaporated, leaving an almost colourless oil which did not crystallise. The residue was dissolved in a little alcohol, and cold aqueous picric acid (1%) added, precipitating an oily *picrate*, which eventually crystallised and separated from alcohol in prisms, m. p. 152—153° (Found: C, 47·0; H, 3·6. $C_{18}H_{16}O_9N_6$ requires C, 47·0; H, 3·5%).

4-Nitromethyl-3-methyl-3 : 4-dihydroquinazoline.—A solution of 4-hydroxy-3-methyl-3 : 4-dihydroquinazoline (0·2 g.) and nitromethane (1 c.c.) in alcohol (2 c.c.) was kept for 24 hours, then concentrated, and a yellow crystalline solid precipitated by ether. The *substance* crystal-

lised from benzene–light petroleum in prismatic needles, m. p. 137° (Found: C, 58·8; H, 5·4. $C_{10}H_{11}O_2N_3$ requires C, 58·5; N, 5·3%).

6-*Nitropiperonylidenediformamide.*—A mixture of formamide (100 c.c.), 6-nitropiperonal (60 g.), and benzene (150 c.c.) was heated to 60° and then stirred vigorously without further heating while a rapid stream of dry hydrogen chloride was passed. Crystals soon separated and after 1·5—2 hours the liquid could no longer be stirred; at the same time the temperature, which had remained sensibly constant at 50°, quickly rose to 80—85°. After 3 hours the benzene layer was decanted and the semi-solid mass was washed with hot benzene, then mixed with alcohol, and filtered. After being washed successively with alcohol, 50% aqueous alcohol, and water, the solid was triturated thoroughly with cold aqueous sodium hydroxide (5%), collected, and washed with sodium hydroxide solution and water, leaving pale yellow crystals (28 g.). The benzene layer and washings were combined, heated to 60° with formamide (50 c.c.), and treated in the same way, yielding a further quantity (13 g.) of 6-*nitropiperonylidenediformamide*. The substance was almost insoluble in non-hydroxylic solvents and crystallised from water as light yellow needles, m. p. 248—250° (decomp.) after sintering (Found: C, 45·2; H, 3·2; N, 15·6. $C_{10}H_9O_6N_3$ requires C, 44·9; H, 3·4; N, 15·7%).

Acidification of the alkaline extracts afforded a cream-coloured amorphous solid (*ca.* 20 g.), the nature of which has not been determined. Variations of the above procedure led in most cases to an increase in the amount of this by-product or to incomplete reaction.

6 : 7-*Methylenedioxyquinazoline.*—Crushed ice (180 g.) and glacial acetic acid (60 g.) were slowly added to a mixture of finely powdered 6-nitropiperonylidenediformamide (15 g.) and zinc dust (45 g.) with vigorous shaking. After 30 minutes the mixture was mechanically stirred for 1·5 hours, during which small quantities of zinc dust were frequently added; the maximum temperature reached was 50°. The mixture was filtered, and aqueous sodium hydroxide (300 c.c. of 50%) added to the filtrate with cooling. After dissolution of the precipitated zinc hydroxide the crystalline methylenedioxyquinazoline was collected, dried, and crystallised from ethyl acetate and then from water, forming colourless plates (6 g.), m. p. 171—172° (Found: C, 62·0; H, 3·5; N, 16·2. Calc. for $C_9H_6O_2N_2$: C, 62·1; H, 3·4; N, 16·1%). Wilkendorff (*Ber.*, 1919, **52**, 609) gives m. p. 172—173° after distillation. 6 : 7-Methylenedioxyquinazoline is easily soluble in hot ethyl acetate, acetone, water, and ether and in cold chloroform and benzene; less readily soluble in light petroleum.

When the reaction mixture was filtered and basified after being shaken for 1 hour, the temperature not being allowed to rise above 15°, as in the preparation of quinazoline, a mixture of substances was obtained. The product was much less soluble in ethyl acetate and the first fraction which separated was a pale-coloured, weak, non-diazotisable *base*. This was recrystallised from alcohol; m. p. 260—261° (Found: C, 57·2; H, 3·1; N, 14·9. $C_9H_6O_3N_2$ requires C, 56·8; H, 3·2; N, 14·7%). The second fraction was a mixture, and the third almost pure 6 : 7-methylenedioxyquinazoline.

6 : 7-*Methylenedioxy*-3-*methylquinazolinium Iodide.*—A mixture of methyl iodide (5 c.c.), 6 : 7-methylenedioxyquinazoline (4 g.), and ethyl acetate (75 c.c.) was gently refluxed for 10 hours. Shining yellow plates separated (7 g.); recrystallised from alcohol, they had m. p. 239—240° after sintering (Found: C, 38·5; H, 3·0; N, 8·6. $C_{10}H_9O_2N_2I$ requires C, 38·0; H, 2·8; N, 8·9%).

4-*Hydroxy*-6 : 7-*methylenedioxy*-3-*methyl*-3 : 4-*dihydroquinazoline* (III).—Finely powdered 6 : 7-methylenedioxy-3-methylquinazolinium iodide (7 g.) and an excess of freshly prepared silver chloride were shaken with water (12 c.c.), the liquid filtered, and the silver salts washed with water. The combined filtrate and washings (*ca.* 20 c.c.) were cooled to 2°, and potassium hydroxide solution (2 c.c. of 50%) added. The temperature rose to 10°, the solution became orange and then yellow, and after a few minutes a pale brown oil separated and crystallised on rubbing. After cooling in ice-water for 15 minutes, the solid was collected (3 g.) and crystallised by addition of water (2—3 vols.) to its solution in hot alcohol (charcoal). The *substance* separated as colourless, flat, diamond-shaped prisms, m. p. 158—159° with evolution of gas, after softening at 154° (Found: C, 58·5; H, 5·0; N, 13·3. $C_{10}H_{10}O_3N_2$ requires C, 58·2; H, 4·8; N, 13·6%). Its solution in concentrated sulphuric acid is pale yellow and after a few minutes becomes light green with a bright pink fluorescence. The solutions in dilute acids are non-fluorescent (cf. the bright fluorescence of hydrastininium salts).

Methylenedioxymethylquinazolinium picrate was obtained by the addition of cold aqueous picric acid (1%) to a solution of the carbinol base in aqueous alcohol (50%), and crystallised from alcohol, in which it was sparingly soluble; m. p. 185—186° after softening at 183° (Found: C, 46·2; H, 2·8. $C_{16}H_{11}O_9N_5$ requires C, 46·0; H, 2·6%).

When hydroxydihydromethylenedioxymethylquinazoline was boiled with aqueous sodium hydroxide (2%) for 30 seconds, the solution became yellow and deposited an oil, which solidified, on cooling, as pale yellow needles. These were recrystallised once from aqueous alcohol and identified by m. p. and undepressed mixed m. p. as 6-aminopiperonal. [6-Aminopiperonal dissolved when warmed in the steam-bath for 10 minutes with aqueous methylamine (33%), and a colourless solid separated; this was collected and washed with water, m. p. 108—109°, mixed with 6-aminopiperonal, m. p. 75—80°. The condensation product was resolved into 6-aminopiperonal and methylamine during recrystallisation from water or 50% alcohol.]

6 : 7-*Methylenedioxy*-4-*nitromethyl*-3-*methyl*-3 : 4-*dihydroquinazoline*.—A solution of nitromethane (0·7 c.c.) and hydroxymethylenedioxymethyldihydroquinazoline (0·5 g.) in alcohol (1·5 c.c.) was kept at room temperature for 24 hours, then concentrated to small bulk, and the residue cooled; a bright yellow, crystalline solid separated on the addition of ether. The *substance* was readily soluble in alcohol and ethyl acetate, but less freely soluble in benzene, from which it crystallised in clusters of small prisms, m. p. 159—160° after sintering (Found: C, 53·1; H, 4·2; N, 16·7. $C_{11}H_{11}O_4N_3$ requires C, 53·0; H, 4·4; N, 16·9%).

4-*Acetonyl*-6 : 7-*methylenedioxy*-3-*methyl*-3 : 4-*dihydroquinazoline Picrate*.—Saturated aqueous sodium carbonate was added to a solution of hydroxymethylenedioxymethyldihydroquinazoline (0·2 g.) in acetone (3 c.c.) and the mixture was shaken for about 30 minutes and then at intervals during 2 days. The liquid was then filtered, and water added to the concentrated filtrate. The oil which separated could not be crystallised; it was converted into a *picrate*, which crystallised from alcohol; m. p. 187° after sintering from 184° (Found: C, 48·0; H, 3·8. $C_{19}H_{17}O_{10}N_5$ requires C, 48·0; H, 3·7%).

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