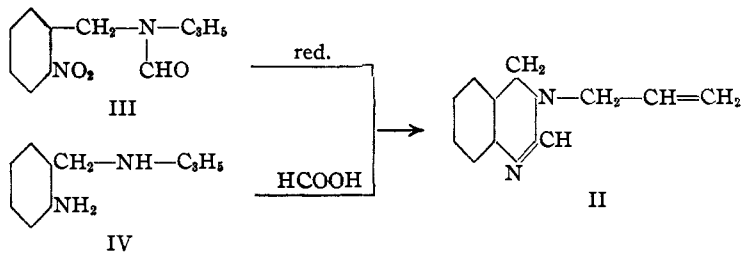
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

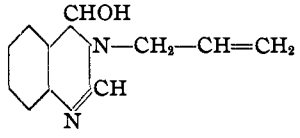
The Constitution of Vasicine

BY W. E. HANFORD, POE LIANG[1] AND ROGER ADAMS

The identity of vasicine and peganine has recently been established by Späth and Nikawitz[2] by a careful comparison of the melting points and mixed melting points of these substances and their derivatives. In further confirmation of this identity, it has been demonstrated in this investigation that dihydrodesoxyvasicine and dihydrodesoxypeganine (called by Späth "desoxytetrahydropeganine") have the same melting point. As a difference of opinion[2,3] in regard to the similarity in the solubility of vasicine and peganine in acetone and in 1% aqueous potassium hydroxide has existed, these constants have been redetermined. Vasicine melting at 206° (bloc Maquenne) showed a solubility of 0.2% in dry acetone at 25°. It was no more soluble in 1% aqueous potassium hydroxide than in water.



Späth and Nikawitz[2] have suggested several possible formulas for this naturally-occurring product, of which 4-hydroxy-3-allyl-3,4-dihydroquinazoline (I) is given preference. It is difficult



I

to believe that a substance with such a structure would have certain of the properties which have been described for it; in particular may be mentioned that by catalytic reduction no hydrogen is absorbed.[2,4] This same objection applies equally well to the structures suggested by Ghose,[4] and Narang and Rây.[3b]

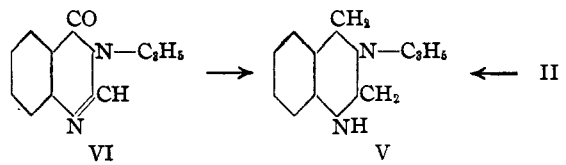
Evidence is now presented to indicate that Formula I cannot be correct for vasicine. 3-Allyl-3,4-dihydroquinazoline (II) has previously been described[5,3b] and has now been resynthesized by methods which leave no doubt as to its constitution. This substance should be identical with desoxyvasicine providing Formula I is correct for vasicine. The properties of the synthetic compound (II), of desoxyvasicine and their derivatives are compared in Table I.

TABLE I

PROPERTIES OF SYNTHETIC AND NATURAL PRODUCTS

	Desoxyvasicine, m. p., °C.	3-Allyl-3,4-dihydroquinazoline, m. p., °C.
Pure base	87–88	Oil
Oxalate	235	173–174.5
Picrate	205	180–181
Hydrochloride	255[12]	165[5]
Catalytic reduction	No reaction	Dihydro deriv. an oil; picrate, 180.5–182

Upon the reduction of vasicine with sodium and amyl alcohol, dihydrodesoxyvasicine is readily obtained and it is not identical with synthetic 3-allyl-1,2,3,4-tetrahydroquinazoline (V) produced by the reduction with sodium and amyl alcohol either of II,[5] or of 3-allyl-4-quinazolone (VI).[3]



In Table II the products from synthetic and from natural sources are compared.

TABLE II

PROPERTIES OF SYNTHETIC AND NATURAL PRODUCTS

	Dihydrodesoxyvasicine	3-Allyl-1,2,3,4-tetrahydroquinazoline
Melting point, °C.	69–70	Oil (b. p. 105–110 (3 mm.))
Acid oxalate	Oil	176–179
Picrate	185 (bloc Maquenne)	Oil

The ease of catalytic reduction of both 3-allyl-3,4-dihydroquinazoline (II) and 3-allyl-4-

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(2) Späth and Nikawitz, *Ber.*, **67**, 45 (1934); Späth and Kuffner, *ibid.*, **67**, 868 (1934).

(3) (a) Narang and Rây, *Current Science*, **2**, 388 (1934); (b) *Chem. and Ind.*, **53**, 698 (1934).

(4) Ghose, Krishna, Narang and J. N. Rây, *J. Chem. Soc.*, 2740 (1932).

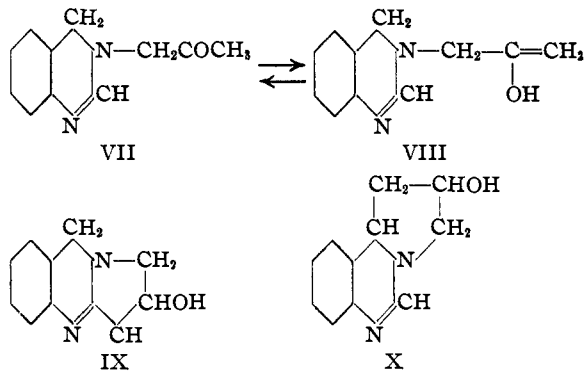
(5) Paal and Stollberg, *J. prakt. Chem.*, **48**, 569 (1893).

quinazolone (VI) is in marked contrast to vasicine or desoxyvasicine, which could not be reduced in a similar manner. The structure of the reduction product of VI as 3-propyl-4-quinazolone was proved by synthesis. Merely the presence of a hydroxyl and hydrogen in the 4-position in place of one oxygen or two hydrogens could hardly be expected to modify so markedly the reaction of the molecule toward platinum and hydrogen.

During the course of this investigation a preliminary notice by Reynolds and Robinson[6] has been published in which these authors question Späth's preferred Formula I for vasicine. Although we believe the product synthesized by Reynolds and Robinson has the structure assigned to it, nevertheless, proof of this structure is desired for confirmation, since the structure cannot with certainty be deduced from previously described analogous compounds. Gabriel[7] noted that the hydroxide from methylquinazolinium iodide did not disproportionate to methyldihydroquinazoline and methylquinazolone in a manner similar to analogous derivatives of phthalazine as described by Roser[8] and by Decker.[9] Gabriel concluded, perhaps erroneously, that he had a methylquinazolinium hydroxide rather than a carbinol base. His observation that the hydroxide was instantly reconverted to the methylquinazolinium iodide, however, can hardly be used as an argument against the carbinol base structure since carbinol bases in the quinoline series are instantly converted to quinolinium halides by halogen acids.[10]

The 4-hydroxy-3-allyl-3,4-dihydroquinazoline described by Reynolds and Robinson was resynthesized and found to be converted in the cold to the allylquinazolinium halide by means of methyl alcoholic halogen acid.

Of the other formulas (VII, VIII, IX, X) suggested by Späth and Nikawitz, those with cyclic structures (IX and X) are to be preferred. The formulation of an equilibrium between keto and enol (VII and VIII) is not entirely satisfactory, since no iodoform test can be obtained with vasicine, and if the hydroxyl of the enol modification was replaced by chlorine by means of phosphorus oxychloride and the chlorine then substituted by hydrogen, an allyl derivative should result which would be identical with Formula II.



Of the two cyclic formulas, either will explain equally well the oxidation products. Without going into detailed discussion we are inclined to favor Formula IX after careful consideration of the experimental findings on vasicine.

Experimental

Solubility of Vasicine in Acetone and Aqueous Potassium Hydroxide.—Finely ground vasicine was shaken for twelve hours in 25 cc. of dry acetone, the solution filtered and the filtrate evaporated to dryness on a steam-bath. The residue weighed 0.0508 g., which corresponds to a solubility at 25° of 0.2 g. per 100 cc. of dry acetone.

A mixture of 0.5 g. of finely ground vasicine and 25 cc. of 1% aqueous potassium hydroxide was shaken for twelve hours. The insoluble material was filtered, washed with small portions of water and dried for one hour at 110°. The loss in weight was very small and depended upon the quantity of wash water used. When untreated vasicine was washed with water the loss in weight depended upon the quantity of water employed and was no greater than with the alkali-treated product.

Attempted Catalytic Reduction of Vasicine Hydrochloride and Desoxyvasicine.—The reduction of vasicine hydrochloride was attempted in the following solvents, with platinum oxide as catalyst and at 3 atm. pressure: water, ethyl alcohol and 5% acetic acid. Reduction was also attempted in 95% ethyl alcohol with Raney nickel catalyst.[11] No reduction occurred.

Desoxyvasicine[12] could not be reduced in 10% acetic or glacial acetic acid with either platinum oxide or Raney nickel catalyst at 3 atm. pressure.

Desoxyvasicine Oxalate.—To a solution of desoxyvasicine in ethyl ether, a saturated alcoholic solution of oxalic acid was added. A white precipitate was formed which was reprecipitated several times from absolute alcohol with dry ether; m. p. 235–236° (bloc Maquenne).

Anal. Calcd. for $C_{13}H_{14}N_2O_4$: N, 10.68. Found: N, 10.82.

Desoxyvasicine Picrate.—This was prepared in 95% ethyl alcohol, m. p. 205–206° (bloc Maquenne).

(6) Reynolds and Robinson, *Nature*, **134**, 142 (1934).
(7) Gabriel and Colman, *Ber.*, **37**, 3643 (1904).
(8) Roser, *Ann.*, **232**, 363 (1894).
(9) Decker, *Ber.*, **25**, 3326 (1892); **35**, 3068 (1902); **36**, 2568 (1903).
(10) Kaufmann and Strübin, *ibid.*, **44**, 680 (1911).
(11) Adkins and Covert, THIS JOURNAL, **54**, 4116 (1932).
(12) Ghose, *J. Indian Chem. Soc.*, **4**, 1 (1927).

Anal. Calcd. for $C_{17}H_{16}N_6O_7$: N, 17.46. Found: N, 17.43.

Dihydrodesoxyvasicine.—This was prepared according to the directions given by Späth and Nikawitz[2] for preparing dihydrodesoxypeganine, m. p. 69–70° (Späth and Nikawitz 69.5°).

Anal. Calcd. for $C_{11}H_{14}N_2$: N, 16.09. Found: N, 16.08.

Dihydrodesoxyvasicine Picrate.—This was prepared in 95% ethyl alcohol, m. p. 185° (bloc Maquenne).

Anal. Calcd. for $C_{17}H_{17}N_5O_7$: N, 17.37. Found: N, 17.33.

3-*n*-Propyl-4-quinazolone. (1) By Reduction of 3-Allyl-4-quinazolone (VI) and (2) by Synthesis.—The reduction was carried out in 95% ethyl alcohol (twenty minutes) using platinum oxide as catalyst. The product was purified by crystallization from benzene and high-boiling petroleum ether, m. p. 96–98°.

Anal. Calcd. for $C_{11}H_{11}N_2O$: N, 14.97. Found: N, 14.87.

Isatoic acid anhydride suspended in alcohol was treated with a slight excess of *n*-propylamine. After the evolution of carbon dioxide ceased, the alcohol was evaporated off and the resulting base was formylated by boiling with concentrated formic acid for three hours. After distilling off most of the unused formic acid, the condensation product was purified by vacuum distillation followed by repeated recrystallizations from a mixed solvent of benzene and petroleum ether; m. p. 96–98°. A mixed melting point with the reduction product of 3-allyl-4-quinazolone showed no depression.

Bogert and May[13] prepared this same compound and reported m. p. 82°.

***o*-Aminobenzylallylamine Hydrochloride (IV).**—*o*-Nitrobenzylallylamine hydrochloride (5 g.) was reduced with iron and water. When the reduction was complete the reaction mixture was made alkaline with aqueous ammonia and the iron filings extracted four times with alcohol. The combined extracts were evaporated to dryness, the residue treated with 20% aqueous sodium hydroxide and the brown oil extracted with chloroform. The combined chloroform extracts were made acid with hydrochloric acid and evaporated to dryness. The crude product (about 2.4 g.) was crystallized from a mixture of absolute alcohol and absolute ether; white needles, m. p. 119–120°.

Anal. Calcd. for $C_{10}H_{15}N_2Cl$: N, 14.11. Found: N, 14.37.

3-Allyl-3,4-dihydroquinazoline (II).—A mixture of 0.43 g. of *o*-aminobenzylallylamine hydrochloride (IV), 0.3 g. of sodium formate and 3 cc. of anhydrous formic acid was heated under reflux for one hour. The solution, while still hot, was transferred to an evaporating dish and evaporated to dryness on a steam-bath. The residue was taken up with 20% aqueous sodium hydroxide and the oil extracted with ether. On evaporation of the ether a light yellow oil was obtained which did not solidify.

The compound was also prepared by the method described by Paal and Stollberg.[5] The picrate of this oil was prepared in 95% ethyl alcohol and after three recrystallizations from alcohol melted at 180–181° (Paal and Stollberg, 172–173°).

Anal. Calcd. for $C_{17}H_{16}N_6O_7$: N, 17.46. Found: N, 17.43.

The acid oxalate melted at 173–174.5° (Paal and Stollberg 172°).

Anal. Calcd. for $C_{13}H_{14}O_4N_2$: N, 10.68. Found: N, 10.76.

Reduction of 3-Allyl-3,4-dihydroquinazoline Acid Oxalate.—A solution of 0.2443 g. of the oxalate dissolved in 20 cc. of ethyl alcohol was reduced at 3 atm. pressure using 0.1 g. of platinum oxide as the catalyst. The hydrogen absorbed corresponded to 1 mole of hydrogen at 26°.

The reduced base was an oil and did not form a solid salt with oxalic acid. It formed a picrate, m. p. 180.5–182°, which depressed the melting point of the picrate of the unreduced molecule.

Anal. Calcd. for $C_{17}H_{17}N_5O_7$: N, 17.37. Found: N, 17.39.

Allylamide of Anthranilic Acid.—To a suspension of 10 g. of isatoic acid anhydride in 100 cc. of 95% ethyl alcohol 4 g. of allylamine dissolved in 10 cc. of 95% ethyl alcohol was added slowly. Carbon dioxide was evolved and the suspension became clear. The reaction was complete in about twenty minutes. The alcohol was evaporated and the solid recrystallized from benzene; yield, 9.0 g. (87%); m. p. 94°.

Anal. Calcd. for $C_{10}H_{12}N_2O$: N, 15.92. Found: N, 15.98.

Allylamide of Formylanthranilic Acid.—A mixture of 1 g. of the allylamide of anthranilic acid and 1 g. of 85% formic acid was heated on a steam-bath in an open beaker, to dryness. The brown solid was recrystallized from benzene and high-boiling petroleum ether, m. p. 82–82.5°.

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: N, 13.73. Found: N, 13.85.

3-Allyl-4-quinazolone (VI).—A mixture of 10 g. of the allylamide of anthranilic acid and 7 cc. of 85% formic acid was evaporated to dryness in an open beaker on a steam-bath. The brown oil was transferred to a Claisen flask and heated to 190–210° for one and one-half hours. The last traces of water were distilled off *in vacuo* and the product fractionated; b. p. 156–157° (4 mm.). The oil solidified on standing and was recrystallized from high-boiling petroleum ether containing a very little benzene. m. p. 66–67°; Narang and Rây,[3a] m. p. 67°; yield 8.4 g. (79.5%).

Anal. Calcd. for $C_{11}H_{10}N_2O$: N, 15.05. Found: N, 14.98.

3-Allyl-1,2,3,4-tetrahydroquinazoline (V).—3-Allyl-4-quinazolone was reduced in boiling amyl alcohol with an excess of metallic sodium. The resulting base was a light yellow oil having a characteristic basic odor, b. p. 105–110° (3 mm.). Its salt with oxalic acid melted at 176–179°. Its picrate, phenyl urea and benzenesulfonyl derivatives were not obtained as solids. These properties are the same as those given this product by Narang and Rây.[3a]

2-Allylquinazolinium Bromide.—This product was prepared according to the general procedure of Gabriel,[7] m. p. 130–131.5°.

(13) Bogert and May, THIS JOURNAL, 31, 507 (1909).

Anal. Calcd. for $C_{11}H_{11}N_2Br$: Br, 31.84. Found: Br, 31.96.

It was converted by alkali to the corresponding hydroxide, m. p. 129°, identical with the substance described by Reynolds and Robinson,[6] who reported m. p. 130°. This hydroxide is alkaline to litmus in dilute methyl alcohol.

On addition of concentrated hydrobromic acid to the hydroxide in methyl alcohol, it was reconverted to the original bromide and was isolated by precipitation with absolute ether. A mixed melting point of this bromide and that made by addition of allyl bromide to quinazoline gave no depression.

Summary

1. 3-Allyl-4-quinazolone and 3-allyl-3,4-dihydroquinazoline are both easily reduced catalytically with the absorption of two atoms of hydrogen and the formation of the corresponding propyl derivatives. Vasicine and desoxyvasicine, on the other hand, cannot be reduced under similar conditions.

2. Desoxyvasicine and 3-allyl-3,4-dihydroquinazoline are not identical. Their derivatives also have different properties.

3. Dihydrodesoxyvasicine and 3-allyl-1,2,3,4-tetrahydroquinazoline are not identical. Their derivatives have different properties.

URBANA, ILLINOIS RECEIVED NOVEMBER 13, 1934

NOTES

Selenium and Tellurium as Carriers in Bromination of Benzene

BY A. A. O'KELLY

Recently a series of experiments were conducted in which benzene was brominated in the presence of selenium and tellurium as carriers, bromine being present in excess. The method employed was that of Adams and Johnson ["Laboratory Experiments in Organic Chemistry," p. 203] and a comparison of degree of bromination thus obtained was made with that resulting when iron was used. In each case 70.3 g. of benzene was used together with 2 g. of carrier and 80% excess bromine. The reaction mixture was allowed to stand for twelve hours without heat and then slight heating was conducted over a period of seven additional hours in each case. The yields reported are of that fraction of boiling point 154–156°. The yield was checked in each case by duplicate preparations under the same conditions and is based on a theoretically possible 100% bromination of the benzene, either to mono- or di-bromobenzene. Table I gives the results of these experiments.

TABLE I

COMPARISON OF DEGREE OF BROMINATION OF BENZENE IN PRESENCE OF Fe, Se, Te AND Fe–Te MIXTURE

Carrier	Benzene, g.	Monobromobenzene, g.	Yield, %	Dibromobenzene, g.	Yield, %
Fe	70.3	65.6	46.2	10	4.6
Se	70.3	36.0	25.4	7	3.2
Te	70.3	43.5	30.7	15	6.9
Te–Fe	70.3	65.6	46.2	10	4.6

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The Preparation of Certain Nitrogen-Substituted Sulfon-*o*-toluidides

BY GEORGE H. YOUNG

In a previous communication from this Laboratory[1] the preparation of several N-alkyl *p*-toluene sulfonanilides was described. This paper reports the synthesis of still others, none of which, with the exception of the methyl compound, have been recorded previously in the literature. The methyl sulfon-*o*-toluidide was prepared in another manner by Witt and Uermenyi[2] who reported a melting point of 119–120°. Our compound, recrystallized four times from methanol, melted at 87–87.5°, and additional recrystallizations failed to raise the melting point.

Yields varied from 67–98% of the theoretical. All were purified by successive recrystallization from methanol, from which they deposit as colorless, odorless, prismatic plates and blunt needles. The compounds are insoluble in water, sparingly soluble in ether and methanol, and soluble in ethanol, acetic acid, acetone and the higher carbinols. They are stable in air and melt sharply without decomposition.

TABLE I

p-Toluene sulfon-*o*-toluidide	Formula	M. p., °C.	S, analyses, % Calcd.	Found
N-methyl	$C_{10}H_{17}O_2NS$	87–87.5	11.64	11.31
n-Propyl	$C_{17}H_{21}O_2NS$	72–72.5	10.56	10.69
Isopropyl	$C_{17}H_{21}O_2NS$	92–92.5	10.56	10.61
n-Butyl	$C_{18}H_{23}O_2NS$	82.5–83	10.09	9.82
Isobutyl	$C_{18}H_{23}O_2NS$	106–106.5	10.09	9.95
n-Amyl	$C_{19}H_{25}O_2NS$	80–80.5	9.55	9.49
Isoamyl	$C_{19}H_{25}O_2NS$	95–95.5	9.55	9.70

(1) Young, THIS JOURNAL, **56**, 2167 (1934).
(2) Witt and Uermenyi, *Ber.*, **46**, 296–308 (1913).