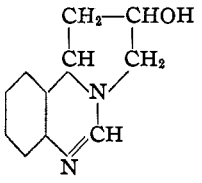
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

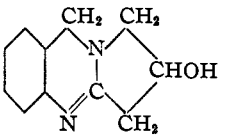
The Structure of Vasicine. II. Synthesis of Desoxyvasicine

BY W. E. HANFORD[1] AND ROGER ADAMS

A recent discussion of the structure of vasicine[2] led to the selection of Formulas I and II as the most probable for this substance. These two structures were among those suggested by Späth[3] for the constitution of peganine which, later, was shown by him to be identical with vasicine.[4]



I



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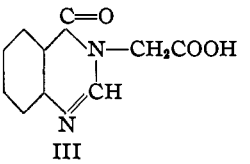
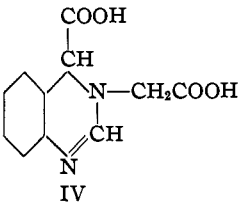
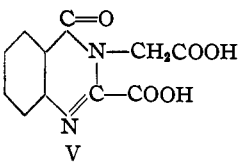


III

The reactions of vasicine thus far described do not admit a distinction between the two. Even the oxidation of vasicine by means of permanganate,[3] which resulted in the formation of quinazolone acetic acid (III), can be equally well accounted for from Formula I or II. The hypothetical intermediate oxidation product from I might be IV and from II might be V.



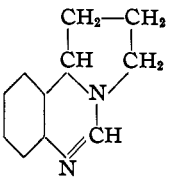
IV



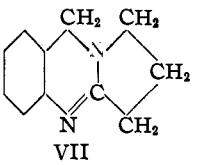
V

A molecule of structure IV should oxidize readily to III, and molecule V would be expected to lose carbon dioxide with great ease, a property already described for the analogous 2-carboxy-3-phenylquinazolone.[5]

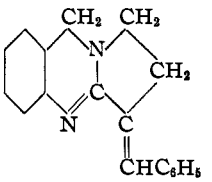
Experimental evidence favoring Formula II has now been obtained from a study of desoxyvasicine which must have Formula VI or VII, provided no rearrangement occurs during replacement of the hydroxyl group by hydrogen.



VI

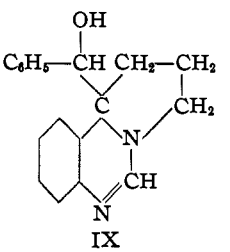


VII

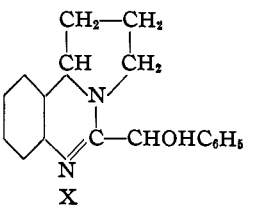


VIII

Desoxyvasicine reacts with benzaldehyde to yield a well-defined benzal derivative to which has been assigned structure VIII. It is characteristic of 2-alkylquinazolones[6] to condense under similar conditions to benzal derivatives. Such a condensation on the basis of Formula VI would be difficult to explain since the two possible, but improbable, products from the condensation would be IX or X and neither would be expected to lose water.



IX



X

With this indication that Formula VII for desoxyvasicine is most probably the correct one, the synthesis of a molecule of this structure was undertaken. The first series of reactions was unsuccessful in that conditions which would allow the final step in the synthesis to take place were not discovered. The procedure was as follows: (1) preparation of the *o*-nitrobenzylamide of γ-chlorobutyric acid (XI), (2) conversion with alkali to N-*o*-nitrobenzylpyrrolidone (XII), (3) reduction to N-*o*-aminobenzylpyrrolidone (XIII), and (4) attempted elimination of water to give VII.

(1) Submitted as a thesis in partial fulfilment of the Degree of Doctor of Philosophy in Chemistry, University of Illinois. Since submission for publication an article by Späth, Kuffner and Platzer, *Ber.*, **68**, 497 (1935), has appeared describing the synthesis of desoxypeganine, a compound identical with desoxyvasicine.

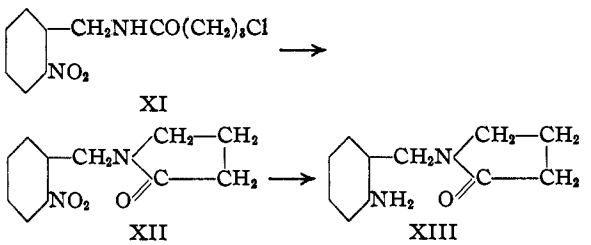
(2) Hanford, Liang and Adams, THIS JOURNAL, **56**, 2780 (1934).

(3) Späth and Nikawitz, *Ber.*, **67B**, 45 (1934).

(4) Späth and Kuffner, *ibid.*, **67B**, 868 (1934).

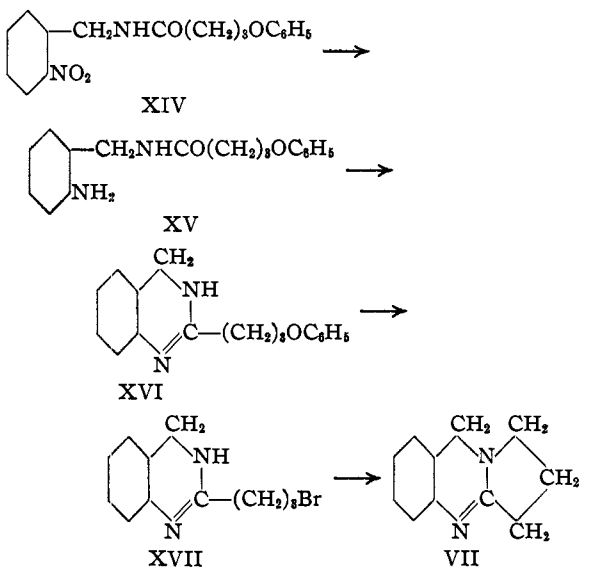
(5) Paal and Krecke, *ibid.*, **24**, 3055 (1891).

(6) Bogert, Beal and Amend, THIS JOURNAL, **32**, 1657 (1910).



XI XII XIII

The second series of reactions resulted in the compound desired and leaves no doubt as to the constitution of the synthetic product. The following steps were used: (1) preparation of *o*-nitrobenzylamide of γ-phenoxybutyric acid (XIV) from the acid chloride and *o*-nitrobenzylamine, (2) reduction to the corresponding amine (XV), (3) ring closure by heating to form the dihydroquinazoline (XVI), (4) replacement of the phenoxy group by bromine by means of hydrobromic acid (XVII) and (5) conversion to 2,3-trimethylene-3,4-dihydroquinazoline (VII) by means of alkali.



XIV XV XVI XVII VII

The identity of the synthetic product (VII) and desoxyvasicine was confirmed by a careful comparison of the bases and several corresponding derivatives. Mixed melting points showed no depression.

TABLE I

MELTING POINTS OF DESOXYVASICINE, 2,3-TRIMETHYLENE-3,4-DIHYDROQUINAZOLINE AND THEIR DERIVATIVES

	Desoxyvasicine	2,3-Trimethylene-3,4-dihydroquinazoline
Base	(77) 96.5–97.5	(77) 96.5–97.5
Hydrochloride	246 bloc Maquenne	246 bloc Maquenne
	260 m. p. tube	260 m. p. tube
Picrate	205–206	205–206
Oxalate	234 bloc Maquenne	234 bloc Maquenne
Benzal deriv.	161–163	161–163

A brief description of desoxyvasicine base is desirable. Ghose[7] obtained it by the reduction of chlorodesoxyvasicine and reported a m. p. of 77° for a dihydrate which, on drying over sulfuric acid, went to a product containing half a molecule of water and melting at 88–89°. These experiments have been confirmed but other pertinent properties have been observed. Desoxyvasicine was prepared directly from the zinc complex described by Ghose, merely by decomposing with small amounts of aqueous ammonia. The necessity of the complicated procedure previously used was thus avoided. On crystallization from water, the dihydrate was formed and when pure was dried for three hours at 56° *in vacuo* over phosphorus pentoxide. Anhydrous desoxyvasicine, m. p. 96.5–97.5°, resulted. A similar treatment of the product of m. p. 88–89° also gave the anhydrous material. The anhydrous desoxyvasicine was hygroscopic and rapidly absorbed sufficient moisture from the air in the course of a few minutes to cause a lowering of the melting point by several degrees.

The synthetic product showed similar melting points and properties. The x-ray photographs of synthetic and natural hydrated crystals by the Debye–Scherrer powder method showed identical patterns.[8]

As Formula VII has been established for desoxyvasicine, the presence of a 3,4-trimethylene ring as represented in Formula I is excluded. The position of the hydroxyl group still remains to be confirmed. Experimental evidence is now available and will be published shortly, which indicates that the hydroxyl is very probably on the methylene group attached to the 2-carbon of the 2,3-trimethylene-3,4-dihydroquinazoline.

Experimental[9]

γ-Phenoxybutyryl Chloride.—To 23.5 g. of γ-phenoxybutyric acid[10] was added 40 cc. of pure thionyl chloride. The mixture was heated under reflux for one and one-half hours, the excess thionyl chloride removed under reduced pressure and the γ-phenoxybutyryl chloride distilled, b. p. 154–156° at 20 mm.; yield, 19.3 g. (74.5%).

γ-Phenoxybutyramide.—From a mixture of γ-phenoxybutyryl chloride and excess concentrated aqueous ammonia, the amide separated as white needles from benzene, m. p. 113°.

Anal. Calcd. for $C_{10}H_{13}NO_2$: N, 7.82. Found: N, 7.63.

(7) Ghose, *J. Indian Chem. Soc.*, **4**, 1 (1927).
(8) The x-ray photographs were kindly taken for us by A. F. Smith.
(9) All melting points described have been corrected.
(10) Lohmann, *Ber.*, **24**, 2640 (1891).

Preparation of the *o*-Nitrobenzylamide of γ-Phenoxybutyric Acid (XI).—To 90 cc. of 10% aqueous sodium hydroxide was added 10.5 g. of *o*-nitrobenzylamine hydrochloride and 200 cc. of benzene. The flask was shaken until the oil dissolved in the benzene layer and then 12.5 g. of γ-phenoxybutyryl chloride dissolved in 15 cc. of benzene was added slowly. The flask was shaken after each addition until the white precipitate formed had disappeared. The aqueous layer was separated and extracted once with benzene. The combined benzene solutions were washed with water, the benzene solution evaporated to a small volume and, after cooling, petroleum ether (b. p. 65–120°) was added; long white needles from benzene and petroleum ether (b. p. 65–120°), m. p. 75–76°; yield 14.5 g. (83.4%).

Anal. Calcd. for $C_{17}H_{18}N_2O_4$: C, 65.00; H, 5.73; N, 8.92. Found: C, 64.84; H, 5.72; N, 9.03.

Preparation of *o*-Aminobenzylamide of γ-Phenoxybutyric Acid (XII).—A solution of 13.5 g. of the *o*-nitrobenzylamide of γ-phenoxybutyric acid in 200 cc. of 95% ethyl alcohol was reduced with 0.05 g. of platinum oxide and hydrogen at 2–3 atm. pressure. The product was purified from benzene and petroleum ether (b. p. 65–120°); colorless needles, m. p. 97.5–98°; yield, 12 g. (98.5%).

Anal. Calcd. for $C_{17}H_{20}O_2N_2$: C, 71.77; H, 7.11; N, 9.87. Found: C, 71.77; H, 7.19; N, 9.87.

Preparation of 2-γ-Phenoxypropyl-3,4-dihydroquinazoline (XIII).—In a small Claisen flask equipped with a capillary tube through which nitrogen was passed, 5 g. of the *o*-aminobenzylamide of γ-phenoxybutyric acid was heated in a Wood's metal bath at 270° for one-half hour. During this time water distilled over. The system was then evacuated to 15 mm. and a yellow oil distilled which solidified on standing. The product was dissolved in benzene, treated with norite, and filtered. The solution was evaporated to a small volume and petroleum ether (b. p. 65–120°) added; white needles from petroleum ether (b. p. 65–120°); m. p. 111.5–112.5°; yield, 2 g. (50%).

Anal. Calcd. for $C_{17}H_{18}ON_2$: N, 10.52; C, 76.66; H, 6.80. Found: N, 10.68; C, 76.61; H, 6.85.

Derivatives of 2,3-Trimethylene-3,4-dihydroquinazoline.—The picrate, oxalate and hydrochloride were prepared from pure anhydrous material in exactly the same way as described for similar derivatives[2] of desoxyvasicine. Mixed melting points with corresponding desoxyvasicine derivatives showed no depression.

Picrate, m. p. 205–206°.

Anal. Calcd. for $C_{17}H_{15}O_7N_5$: N, 17.47. Found: N, 17.36.

Oxalate, m. p. 234° (bloc Maquenne).

Anal. Calcd. for $C_{13}H_{14}N_2O_4$: N, 10.67. Found: N, 10.85.

Hydrochloride (dried *in vacuo* over phosphorus pentoxide at 56° for three hours), m. p. 260° (m. p. tube); m. p. 246° (bloc Maquenne).

Anal Calcd. for $C_{11}H_{13}N_2Cl$: N, 13.43. Found: N, 13.70.

Benzaldesoxyvasicine and Benzal-2,3-trimethylene-3,4-dihydroquinazoline.—In a small test-tube, 100 mg. of pure anhydrous desoxyvasicine (or 2,3-trimethylene-3,4-dihydroquinazoline) and 0.05 cc. (0.85 mole equiv.) of pure benzaldehyde were heated in an oil-bath at 140–145° for forty-five minutes. On cooling, the reaction mixture solidified. It was treated three times with petroleum ether (b. p. 35–65°), and then washed twice with dilute aqueous potassium hydroxide to decompose any salt which may have formed with benzoic acid. The yellow product was dried and crystallized by dissolving in benzene and adding petroleum ether (b. p. 65–120°) to the turbidity point. The material was crystallized from anhydrous ethyl acetate; yellow needles, m. p. 161–163°, for derivative of desoxyvasicine; 161–163° for derivative of synthetic compound.

Anal. Calcd. for $C_{18}H_{18}N_2$: N, 10.77. Found (natural): N, 10.63; (synthetic) N, 10.68.

The melting points of the benzal derivatives described above varied slightly in different preparations. The maximum melting point obtained was, in each instance, 161–163° but, in general, it was very difficult to obtain this value. Frequently the melting point was 157–159° after several crystallizations. Mixed melting points of the two products, whether lower or higher melting samples were used, showed no depression.

Preparation of Desoxyvasicine.—Chlorodesoxyvasicine made by the method of Späth[3] was reduced with zinc and hydrochloric acid according to the directions of Ghose[7] but with the following modification. The zinc complex was filtered, powdered and 2 g. was suspended in 20 cc. of water. Concentrated aqueous ammonia was added slowly. The compound first went into solution and then desoxyvasicine separated as a white precipitate. After filtering (3.5 g. of dry, crude desoxyvasicine from 5 g. of vasicine), it was recrystallized from water as colorless needles, m. p. 77°, when the melting point tube was plunged into a bath at that temperature. After drying for three hours at 56° *in vacuo* over phosphorus pentoxide, it had a melting point of 96.5–97.5°.

Anal. Calcd. for $C_{11}H_{12}N_2$: N, 16.28. Found: N, 16.30.

It should be stated that in an ordinary melting point tube gradually heated in a bath in the usual way, the desoxyvasicine dihydrate merely shrunk at 77° and then did not melt until a temperature of 88–89° was reached. Upon dipping the melting point tube in a bath at 77° the product melted and immediately resolidified.

The product melting at 77°, on exposure to air, gradually effloresced until it had a melting point of 88–89°. Either of the specimens melting at 77° or 88–89°, on drying for three hours at 56° *in vacuo* over phosphorus pentoxide, melted at 96.5–97.5°. This latter anhydrous form quickly absorbed moisture from the air and the melting point was lowered from one to five degrees.

Many experiments were carried out using petroleum ether as a solvent. The melting points from this solvent varied and it was seldom possible to convert the hydrated form to one melting higher than 93–95°. In some cases the product melting at 88–89° was unchanged in melting point by recrystallization from petroleum ether. The melting point of anhydrous material was unchanged on recrystallization from petroleum ether. It was, as a consequence, advisable always to crystallize from water and to dry as previously described. The anhydrous product was used in preparing derivatives.

The synthesis of a compound of structure VII was first attempted through the series of reactions mentioned in the introduction (XI, XII, XIII). Conditions for preparing the pyrrolidone were first completed with the benzyl derivative and then *o*-nitrobenzyl chloride was used. The final product desired was not obtained as the usual method of heating did not convert the N-*o*-aminobenzylpyrrolidone to the corresponding dihydroquinazoline. The intermediate products are described below.

Benzylamide of γ-Chlorobutyric Acid.—To a solution of 10.6 g. of benzylamine in 200 cc. of absolute ether was added 7.0 g. of γ-chlorobutyryl chloride. A vigorous reaction ensued with the formation of a white precipitate. After standing for about fifteen minutes, the precipitate was filtered and the ether solution evaporated. White needles separated, which were recrystallized from benzene and petroleum ether (b. p. 65–120°); m. p. 68°; yield, 6.7 g. (64%).

Anal. Calcd. for $C_{11}H_{14}NOCl$: N, 6.62; Cl, 16.78. Found: N, 6.69; Cl, 16.58.

N-Benzylpyrrolidone.—The general directions of Lipp and Cooper[11] were used. The product boiled at 122.5–123° at 2 mm.; yield, quantitative; $n^{20}D$ 1.5570, d^{20}_{20} 1.0983.

Anal. Calcd. for $C_{11}H_{13}NO$: N, 8.00. Found: N, 8.14.

To prove that a pyrrolidone had actually formed, it was hydrolyzed to the corresponding amino acid.

γ-Benzylaminobutyric Acid Hydrochloride.—A mixture of 0.4 g. of N-benzylpyrrolidone and 5 cc. of concentrated hydrochloric acid was heated under reflux for three hours. The solution was then evaporated to dryness, the resulting oil dissolved in absolute methyl alcohol, filtered and absolute ether slowly added. A white hygroscopic solid separated which was dried over sulfuric acid for twelve hours; m. p. 158–161°.

Anal. Calcd. for $C_{11}H_{16}NO_2Cl$: N, 6.1. Found: N, 6.7.

***o*-Nitrobenzylamide of γ-Chlorobutyric Acid.**—To a mixture of 100 cc. of 10% aqueous sodium hydroxide, 12 g. of *o*-nitrobenzylamine hydrochloride and 200 cc. of ether was added slowly 13 g. of γ-chlorobutyryl chloride dissolved in 20 cc. of dry ether. The flask was shaken after each addition until turbidity had gone. After all the acid chloride had been added, the water layer was separated and the ether layer washed with water, dried and evaporated to dryness. A white solid was obtained and purified from benzene and petroleum ether (b. p. 65–120°); m. p. 73°; yield, 15.5 g. (94%).

Anal. Calcd. for $C_{11}H_{13}N_2O_4Cl$: N, 10.92. Found: N, 11.11.

N-*o*-Nitrobenzylpyrrolidone.—The general procedure of Lipp and Caspers[11] was not suitable. In a three-necked flask equipped with a mechanical stirrer and a thermometer, was placed 1 g. of *o*-nitrobenzylamide of γ-chlorobutyric acid, 3.0 g. of powdered potassium hydroxide and 50 cc. of dry benzene. The temperature of the reaction mixture was slowly raised to 50° where it was held for half an hour. On cooling, the mixture was filtered. On evaporation, a light yellow solid remained which was purified by crystallization from benzene and petroleum ether (b. p. 65–120°); m. p. 100°; yield, 0.13 g. (14%).

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: N, 12.72. Found: N, 12.89.

Preparation of N-*o*-Aminobenzylpyrrolidone.—A solution of 0.100 g. of N-*o*-nitrobenzylpyrrolidone in 20 cc. of 95% ethyl alcohol was reduced with hydrogen and 0.05 g. of platinum oxide at atm. pressure; white crystals from benzene, m. p. 63–65°. This compound was available in such small amounts that it was not completely purified.

Anal. Calcd. for $C_{11}H_{14}N_2O$: N, 14.72. Found: N, 14.23.

Attempts to Prepare 2,3-Trimethylene-3,4-dihydroquinazoline by the Loss of Water from N-*o*-Aminobenzylpyrrolidone.—N-*o*-Aminobenzylpyrrolidone was heated in an air-bath to 245–255°. It distilled without decomposition to an oil which solidified on standing and proved to be unchanged material.

Summary

2,3-Trimethylene-3,4-dihydroquinazoline has been synthesized through the following series of reactions: (1) *o*-nitrobenzylamide of γ-phenoxybutyric acid from the acid chloride and *o*-nitrobenzylamine, (2) reduction to the *o*-aminobenzylamide of γ-phenoxybutyric acid, (3) ring closure by heating to form 2-(γ-phenoxypropyl)-3,4-dihydroquinazoline, (4) replacement of the phenoxy group with bromine by means of hydrobromic acid to form 2-(γ-bromopropyl)-3,4-dihydroquinazoline, and (5) conversion with alkali to 2,3-trimethylene-3,4-dihydroquinazoline.

This synthetic product was identical with desoxyvasicine as shown by a comparison of the bases and their derivatives, the hydrochloride, picrate, oxalate and benzal derivatives.

URBANA, ILLINOIS RECEIVED MARCH 18, 1935

(11) Lipp and Caspers, *Ber.*, **58**, 1011 (1925).