THE CONSTITUTION AND THE SYNTHESIS OF THE ALKALOID ANONAINE

by

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Preface.

This thesis embodies the results of a Research carried out in the Chemistry laboratory of the University of Glasgow during the sessions 1937-1938, 1938-1939 under the supervision of the late Prof. G. Barger, F.R.S.

Unfortunately Prof. Barger did not live to see the end of this work. I cannot express how much I owe to the interest which he took in the subject of this thesis and to the good advice which he always gave me. We students lost in him an exemplary research worker and one whose kindness towards all was unfailing. Such of his research students as are foreigners will especially remember him for the fatherly interest he took in them at all times.

CONTENTS.

A. THE ORIGIN OF ALKALOIDS IN PLANTS.

The botanical relationship and chemical constitution.

If one considers the structural formulae of all known and investigated alkaloids, it is obvious that nature uses certain principles in the synthesis of those alkaloids. Those principles are bounded by:

1. a limited number of primary chemical compounds.
2. a limited number of chemical reactions.

If on one hand Nature is in a position to complete many reactions, which the chemist cannot repeat in vitro, on the other hand Nature cannot carry out all the reactions possible to the chemist.

Regarding the phytochemical synthesis of alkaloids, theories have been put forward first by Pictet (1) and later by Robinson (2). According to Robinson's theory, suggested to him by his synthesis of tropinone (3), almost all alkaloids are formed by the following primary materials:

1. Amino acids (from desintegration of proteins)
2. Products formed by Oxydation of those amino acids

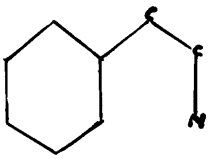
Formaldehyde

3. Formaldehyde and ammonia.

4. Carbohydrate degradation products.

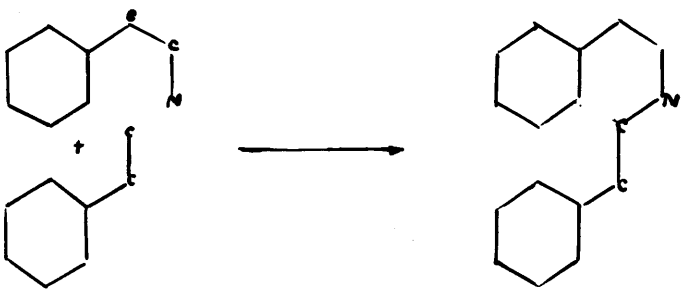
The phytochemical formation of alkaloids may be illustrated schematically by the different isoquinoline types.

Fundamental form I.



(e.g. Tyrosine)

Fundamental form II.

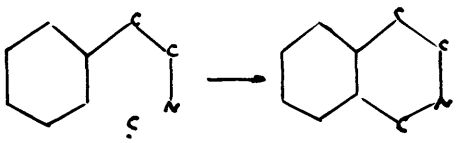


not occurring in Nature.

Following structures can be derived from those two fundamental forms:

Ringclosure

1. Ringclosure between fundamental form I and formaldehyde

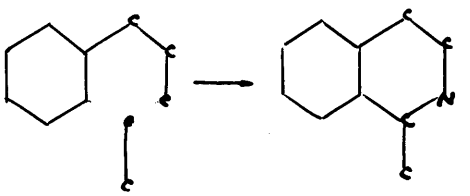


Cotarnine

Hydrocotarnine

Anhalamine

2. Ringclosure between fundamental form II and acetaldehyde



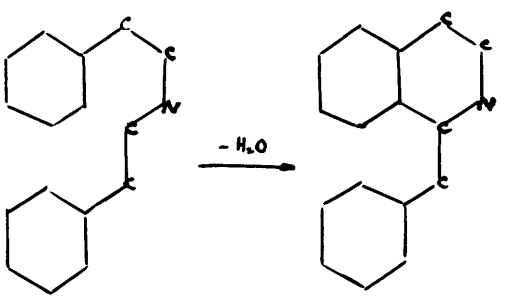
Pellotine

Anhalonine

Anhalonidine

Lophophorine

3. By water elimination from fundamental form II, which does not occur in Nature, we obtain the benzylisoquinoline type.



Laudanosine

Laudanine

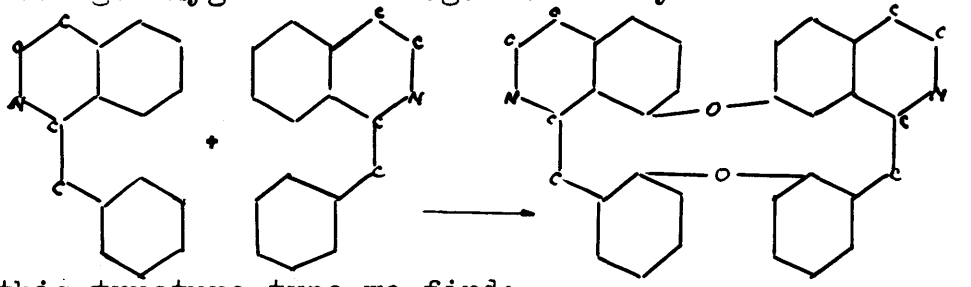
Papaverine

Codamine

Coclaurine

Two

4. Two benzylisoquinolines joined together by bridge oxygen atoms e.g. as in oxyacanthine



In this structure type we find:

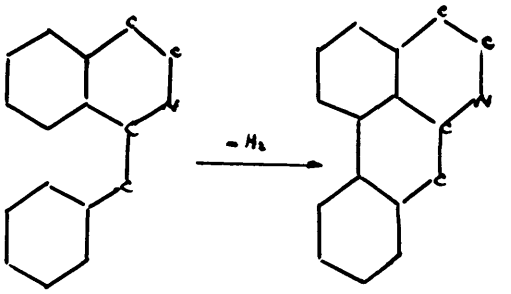
Oxyacanthine

Iso-chondendrine

Trilobine

Daphnandrine

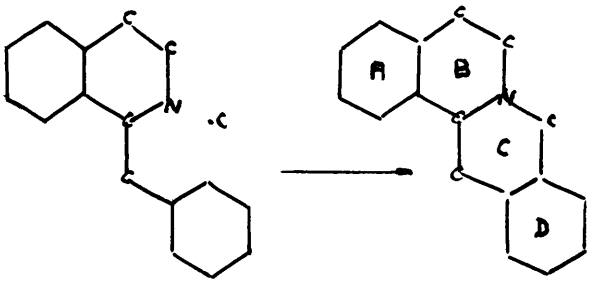
5. By a second ringclosure from the benzylisquinoline type we obtain the aporphine type.



Corydine
Isocorydine
Corytuberine
Bulbocapnine
Isothebaine
Morphothebaine
Laureline
Pukateine
Glaucine
Boldine
Laurotetanine
Dicentrine
Actinodaphnine
Artabotrine
Artabotrinine

Structure-type

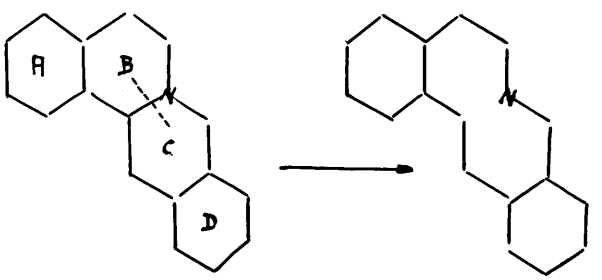
6. Structure-type 6 obtained from type 3 by ringclosure with formaldehyde



Berberine
Canadine
Palmatine
Corypalmine
Corydaline
Corybulbine
Isocorybulbine

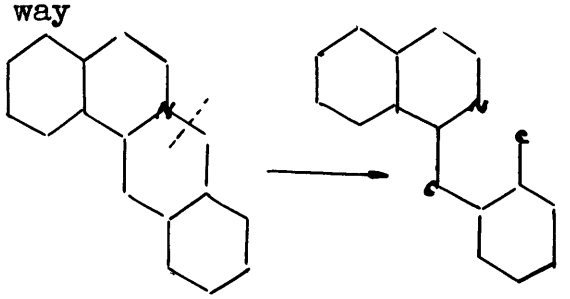
Structure-type 6 can be split open in different ways.

7. By a split between ring B and ring C we obtain a deca-ring



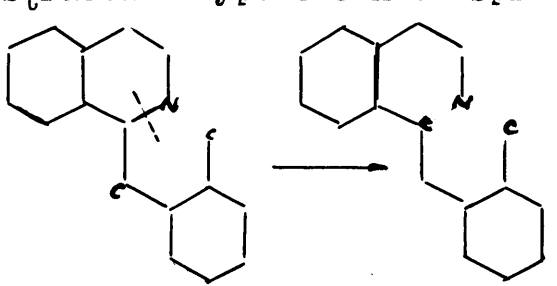
Protopine
Cryptopine
Corycavine

8. Structure-type 6 can be split open in another way



Narcotine
Hydrastine

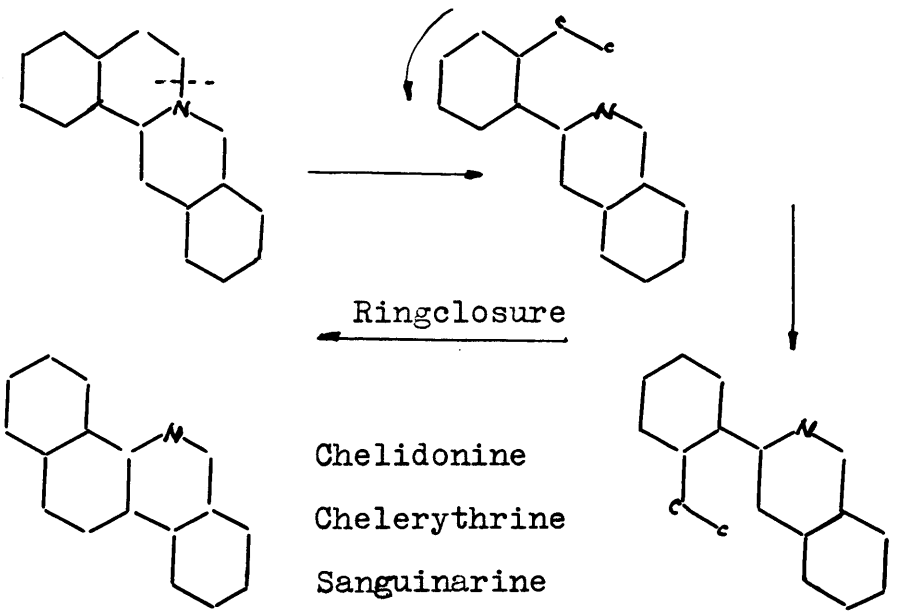
9. Structure-type 8 can be split open once more:



Narceine

Structure-type

10. Structure-type 6 can be split open in a third way and afterwards undergo a new ring-closure.



The investigation of the constitution of new alkaloids will be considerably facilitated by the existence of certain natural principles of formation as was demonstrated schematically above in the case of isoquinoline alkaloids. Nature helps us still further, in as much as, similar alkaloids are found in plants which are botanically related.

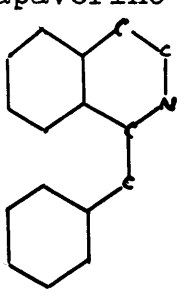
Willes in his Flowering Plants and Ferns has adopted the Engler system for classification of [4]

plants

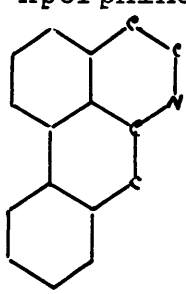
plants according to which, botanically related natural orders are grouped together into cohorts, in the same way as species are grouped into genera and genera into natural orders. In the cohort Ranales of the Engler system we find the following alkaloid bearing natural orders: Ranunculaceae, Berberidaceae, Menispermaceae, Calycanthaceae, Anonaceae, Monimiaceae, Lauraceae and Hernandiaceae. The Papaveraceae occur in the immediately following cohort Rhoedales.

We find four types of alkaloids in the cohort Ranales:

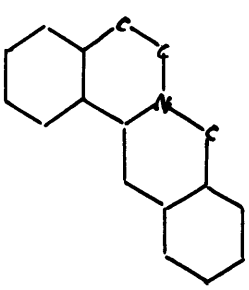
1. Papaverine Type.



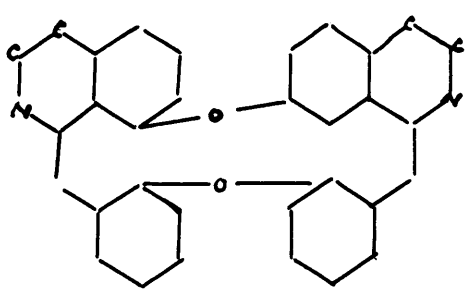
2. Aporphine Type.



3. Berberine Type.



4. Oxyacanthine Type.



Thus from the beginning it was very probable that the constitution of anonaine would possess one of the four carbon skeletons mentioned above.

The

B. THE ALKALOIDS BEARING SPECIES OF THE NATURAL-ORDER OF ANONACEAE.

Botanical and Pharmacological.

Baillon, H. The natural History of Plants. Vol.I (1871).

Watt, Sir George A Dictionary of the Economic Prod. of India. Vol. I (1885).

Birkhill, I.H. A Dictionary of the Economic Products of the Malay Peninsula. Vol. I. (1933).

Merrill, E.D. Enumeration of Philippine Flowering Plants. Vol. II (1923).

Heyne, K. De nuttige Planten van nederlandsch India. 2nd ed. 1927. Vol.I. p.635.

The fruit bearing tree Anona reticulata, occurs in the natural order of Anonaceae, which is related to the natural order of Magnoliaceae. The Anonaceae are almost exclusively inhabitants of hot climats.

Although the natural order of Anonaceae comprises over 800 species, the most of which have been investigated for alkaloids, the presence of alkaloids has been demonstrated with certainty only

in

in a few.

The following table brings together those species of anonaceae which are known to be alkaloid bearing.

Species.	Alkaloid.	Reference.
Anona squamosa,L	Anonaine	Triburti (5)
	$C_{17}H_{16}O_3N$	Reyes and Santos (6)
Anona reticulata,L	Anonaine	Santos (7)
Anona muricata	amorphous alkaloids (not investigated)	Callan and Tutin (8)
Anona triloba	Asiminine (not investigated)	Lloyd (9) Fletscher (10)
Alphonsea ventricosa	Alphonseine (not investigated)	Czapek (11)
Poponia pisocarpa	Toxic alkaloid (not investigated)	Boorsma (12)
Xylopia polycarpa,Oliv.	Berberine(?)	Stenhouse. (13)
Phaeanthus ebracteolatus	Phaeanthine $C_{34}H_{38}O_6N_2$	Santos (14)
Artabotrys suaveoleus,Blume	Artabotrine Artabotrinine	Greshoff (15) Maranon (16) Santos (17) Rochebrune (18) Sargent (22)

The

The following is known about the alkaloid bearing species Anona.

Anona squamosa,L.

(The sweet sop or sugar apple).

A native of the Antilles, cultivated for its fruit in all the tropical regions of both hemispheres Its perfume is sweet and its taste agreeable. The young fruit is astringent and the seeds are acrid; these when powdered are used to destroy vermin. Triburti(5) first reported the presence of an alkaloid in both the leaves and seeds of this species. Although he prepared both the hydrochloride and chloroplatinate he was unable to crystallize the free base, obtaining it, instead, in the form of a white powder. The actual crystallization of the base was achieved somewhat later by Reyes and Santos (6) who showed that this alkaloid was identical with anonaine, which they isolated from anona reticulata.

Anona muricata.

(The sour sop).

is cultivated in Arabia, and, when ripe is supposed to be an antiscorbutic and febrifuge, moreover, picked before maturity, dried and powdered, it is administered

in

in case of dysentery, after the inflammatory symptoms have been removed by appropiate treatment. The seeds are astringent and from the leaves are prepared poultices.

Callan and Tutin (8) from an examination of a small quantity of leaves at their disposal found an amorphous substance which gave positive tests with most alkaloid reagents, The substance, however, was not further investigated.

Anona reticulata, L.

A fruit bearing tree (10-20 feet high) cultivated in Mauritius, East India and Brazil is the source of the custard apple, which although edible, is not much favoured. The leaves have a strong odour and the juice that flows from the cut branches is acrid and inflames the conjunctiva if dropped into the eye. As a drug the green fruit and leaves are employed just like those of anona muricata.

From the bark of this tree, Santos (7) isolated a crystalline non phenolic alkaloid for which he suggested the name anonaine. He was able to show a little later on (6) that this anonaine

was

was identical with the alkaloid present in anona squamosa, which although investigated earlier by Triburti had not previously been obtained in crystalline form. From the analysis of two salts of the base Santos was able to ascribe the formula $C_{17}H_{16}O_3N$ to anonaine.

C. PRESENT INVESTIGATION OF ANONAINE.

I. Part.

Constitution.

A. Theoretical.

Previous Chemical Investigations of Anonaine.

The following are Santos' results of his chemical investigation of one alkaloid which he obtained from the bark of anona reticulata and for which he suggested the name anonaine.

1. The percentage yield of alkaloid from powdered and air dried bark of anona reticulata was 0,03%.
2. The base crystallized from etherical solution in needles melting at 122° - 123°.

   A solution of anonaine was found to be optically active.

   $(\alpha)_D^{32.5^{\circ}} = -83.01^{\circ}$ (Chloroform).
3. The hydrochloride and the chloroplatinate of this base were prepared.
4. The hydrochloride was analysed and the empirical formula $C_{17}H_{16}O_3N$ was suggested, without giving the results of the analyses.

Molecular

5. Molecular weight estimation according to Kost gave

285.7
274.4

Calculated for $C_{17}H_{16}O_3N$ 282.

6. Molecular weight was checked by platinum determination of anonainechloroplatinate

calculated for $C_{17}H_{16}O_3N$	282
Found	272.4
	269.3

7. Methoxyldetermination according to Zeisel-Pregl gave negative results.

8. The presence of a methylene-dioxy group was shown qualitatively using the method according to Gaebel.

It should be remarked that the formula $C_{17}H_{16}O_3N$ suggested by Santos is impossible as such. It should be either $C_{17}H_{15}O_3N$ or $C_{17}H_{17}O_3N$.

B. Present Investigation.

We modified Santos' method of extraction in order to improve the yield of anonaine. With the new method we obtained anonaine in a yield of 0,12% compared with 0.03%.

The

1. The melting point of anonaine was found to be: 123^{o} - 124^{o}.
   The optical rotation of anonaine was $(\alpha)_{D}^{20^{\circ}} = -52^{o}$ (Chloroform).
2. Anonaine was a secondary base, being able to form a nitroso and an neutral acetyl compound.
3. Anonaine contained a methylenedioxy-group (Gaebel's test positive).
4. Anonaine did not possess a methoxylgroup (Estimation according to Zeisel-Pregl negative).
5. Anonaine did not possess a carbonyl group (Did not react with phenylhydrazine).
6. Anonaine contained one reactive hydrogen atom (Zerewitinoff).
7. Several analyses of the hydrochloride did not correspond at all to $C_{17}H_{16}O_{3}N$, the formula suggested by Santos.
   The results of the analyses led us to adopt the formula $C_{17}H_{15}O_{2}N$.

If Santos' formula was correct, the third oxygen of the empirical formula should be present as an alcoholic hydroxyl group.

The

1. The base beeing insoluble in sodium hydroxyde cannot possess a phenolic hydroxyl-group.
2. As mentioned above anonaine does not possess any methoxyl- or Carbonyl-groupings.

According to the Zerewitinoff estimation anonaine has only 1 active hydrogen atom, already included in the secondary amino group. The acetylation of anonaine at 100^{o} in acetic anhydride gave a neutral compound. If an alcoholic group were present it would also have been acetylated. The analysis of this compound proved quite definetely that the new formula $C_{17}H_{15}O_2N$ was correct.

We pointed out already (page 7) that anonaine possesses probably one of the following types of structure:

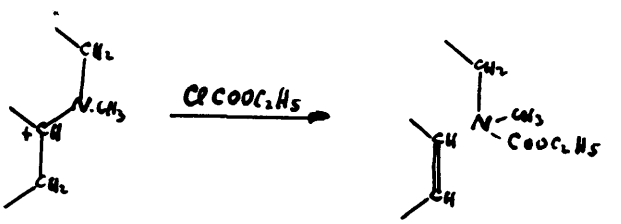
1. Papaverine type.
2. Aporphine type.
3. Berberine type.
4. Oxyacanthine type.

The action of chloroethylcarbonate on N.methyl-Anonaine proved that anonaine really possessed an isoquinoline structure. According to Gadamer and Knoch (19) who first studied the action of this reagent on various alkaloid structures, the formation of a neutral, optically inactive product is good evidence

evidence for the presence of a tetrahydroiso-quinoline ring system. Moreover, they pointed out, that the reagent could also be used to differentiate with a fair degree of certainty, between the tetrahydro-papaverine type, e.g. as in Laudanosine and the aporphine type of ring system, e.g. as in bulbocapnine. Thus they showed that although the bond between the nitrogen atom and the asymetric carbon was broken down in the case of laudanosine the chlorine atom of the reagent had attached itself to the asymmetric carbon with the result that the product was still optically active.

+ asymmetric carbon

On the other hand the product with bulbocapnine was optically inactive and contained no chlorine



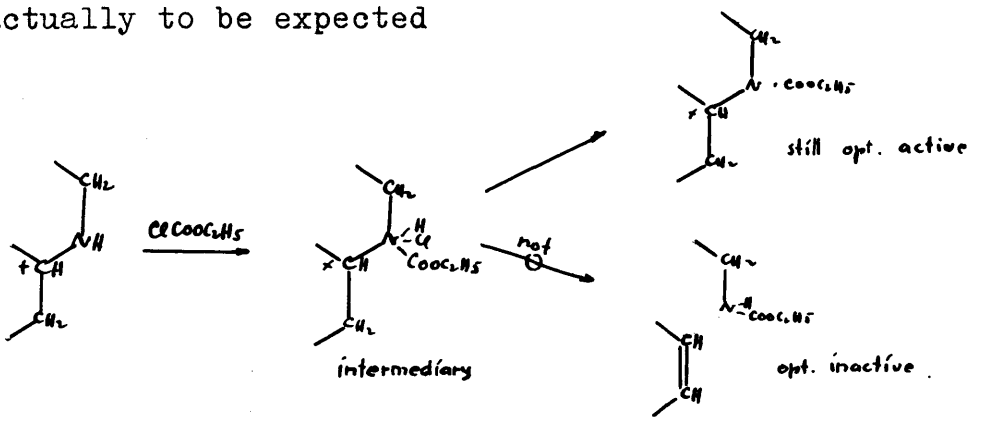
+ asymmetric carbon

The

The specifity of this reagent for tetrahydro-isoquinoline ring system has been borne out by other investigators as for example with pukateine (20), boldine-ethylester (21) and artabotrine (22).

Anonaine itself reacted with chloroethylcarbonate yielding a neutral crystalline product. It did not contain chlorine but was still optically active.

The formation of an optically active compound was actually to be expected



N.CH_3-Anonaine reacted with chloroethylcarbonate yielding a neutral compound, which did not contain chlorine. It could not be crystallized. The optical activity could not be determined exactly due to the darkness of its solution. But it was definitely in the neighbourhood of zero.

Two of the four alkaloid types mentioned above were out of the question, namely

1. The berberine type, since anonaine is a secundary base.

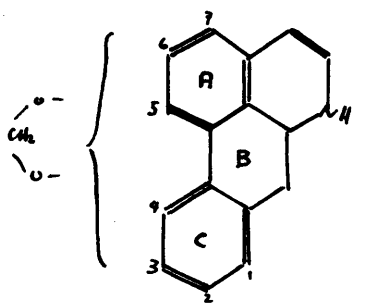
The

2. The oxyacanthine type, since the two oxygen atoms present in anonaine are already required for the dioxymethylene group.

The formation of a neutral optically inactive compound, which did not contain chlorine, by the action of chloroethylcarbonate on N.CH_3-anonaine, made the structure type of papaverine not very probable.

This left only the aporphine type.

Thus after these few investigations and considerations, we could already suggest for anonaine the following structural formula



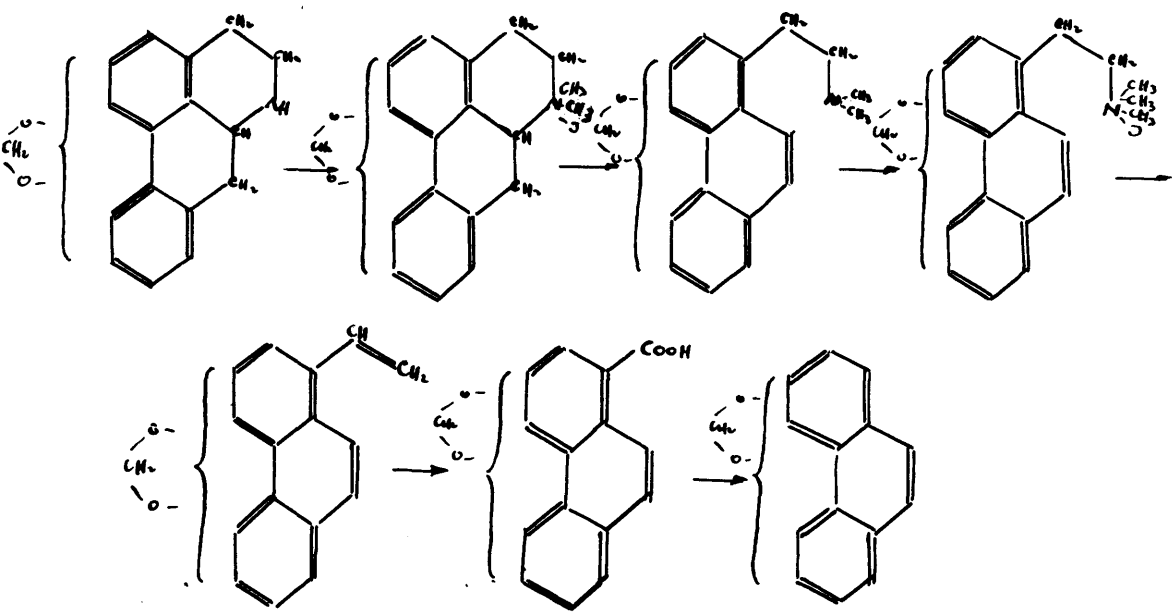
Additional evidence as to the nature of ring system in anonaine was obtained from the study of Hofmann degradation. Treating the alkaloid with methyljodide and boiling with methylalcoholic potash an optically inactive methine base was obtained. Further treatment of the methine base

with

with methyljodide afforded the methine-methiodide and on boiling with 15% methylalcoholic pottash trimethylamine was splitt off (determined by its picrate) and a crystalline non-nitrogenous product was obtained. The product possessed a unsaturated double bond.

After twice having treated the original base with methyljodide and boiling with pottash the nitrogen was eliminated, thus showing that the nitrogen atom in anonaine belongs to one and only one ring. We oxydized the substituted vinyl-phenanthrene to the corresponding acid. This acid could easily be decorboxylized giving us in the end a methylenedioxyphenanthrene.

The complete degradation can be represented as follows:



The oxydation of the alkaloid in neutral solution with potassium permanganate gave only one crystalline compound, pthalic acid, in small amounts. The presence of pthalic acid was shown by a strong positive fluoresceine test, by its melting point, the melting point of its anhydride and the mixed melting points with authentic specimen of phthalic acid respectively phthalic anhydride. The formation of phthalic acid by the oxydation of the alkaloid showed, that anonaine contained an unsubstituted aromatic nucleus, which at the same time forms part of another nucleus. Thus excluding the possibility of the papaverine type,

Furthermore the methylenedioxy-group can only be attached to ring A (see page I9) either in position 5,6 or 6,7.

Since with the exception of only one alkaloid (23) all aporphine alkaloids known to date have the methylenedioxy group in 5,6 position we therefore preferred position 5,6 through reason of analogie.

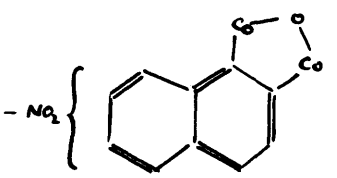
The synthesis of the alkaloid proved this assumption.

Warnat's

Warnat's method in the investigation of aporphine alkaloids has always been satisfactory in proving the presence of a phenanthrene structure. One obtains by this method 1,2,3,4 benzene-tetracarboxylic acid (= mellophanic acid) on the oxydation of the methine base with nitric acid, thus proving definitely the presence of a phenanthrene structure in the investigated alkaloid. (24)

Therefore on oxydizing our methine base with conc.nitric acid we expected likewise mellophanic acid or napthalene-1,2-dicarboxylic acid, considering that ring C (see page 19) is not substituted as in all the other investigated aporphine alkaloids, and therefore more stable to oxydation.

The product obtained contained nitrogen and gave a doubtful fluoresceine test. The results of its analysis corresponded fairly well with the formula $C_{12}H_6O_3N$, that would mean a nitrated Naphthalene-1,2-dicarboxylic acid anhydride.



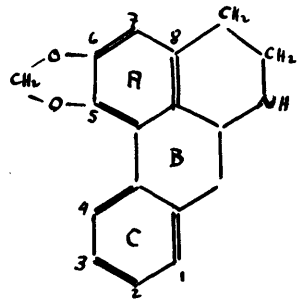
Such an acid is not known in the literature. We tried to reduce and to decarboxylaze this acid, without achieving any satisfactory results.

Therefore

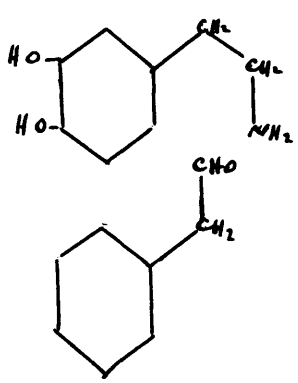
Therefore we abandoned the investigation of this acid as it was no longer necessary for establishing the constitution of anonaine.

Hence we were able to suggest the following structural formula for anonaine.

The synthesis of the alkaloid described in the second part of this paper, confirmed the formula.



From all isoquinoline alkaloids known to date anonaine is the only one which possesses an unsubstituted ring C. It is interesting in so far as its phytochemical formation must be explained by the condensation of the aromatic aldehyde I (derived from phenylethylamine) with the hydroaromatic base II (compare (2)).



II

I

C. Experimental.

1. Isolation of anonaine.

Through the kind cooperation of Messrs. Duncan, Flockhart & Co. of Edinburgh, to whom I wish to express my thanks, 25 kg of air dried bark were ground and then percolated with 95% alcohol. The alcohol was removed under reduced pressure, and the viscous resinous extract which remained (2.75 kg) represented about 11% by weight of the bark used.

2 preliminary experiments with 100 g in each case were carried out as follows:

100 g of the extract were heated on the water-bath at about 50° in order to make the extract more fluid. It was then slowly poured into 1 l $\frac{n}{16}$ hydrochloric acid with continual stirring, and stirred for further 15 minutes, whereby the resin separated out and sank to the bottom. The supernatant liquid, clear and yellow in colour, was decanted. The resin was again heated at 50° and poured into 1 l. $\frac{n}{16}$ hydrochloric acid

and

and the supernatant liquid decanted. This operation was repeated eight times. After 8 such treatments the acid extract still gave a distinctly positive Mayer's test. The 8 acid extracts were worked up separately in the following way:

Acid extract (A)

↓ rendered alkaline with ammonia

Precipitate

↓ extracted repeatedly with ether

Ether extract

↓ washed with H_2O then

I.

↓ extracted repeatedly with n/2 NaOH

alkaline solution

↓ rendered acid at once

acid solution (Mayer's reagent gave a positive test)

↓ rendered alkaline with ammonia

Slight turbidity

↓ extracted with ether

etherical solution washed with water, dried over Sodium sulphate. After evaporation of the ether we obtained a trace of a non-crystalline compound which quickly decomposed.

II.

↓ ether extract washed with H_2O, extracted with n/2 HCl in small portions

The Hydrochloride of Anonaine separated out in crystalline form was filtered off and dried.

All 8 acid extracts (A) together gave 0.745 g of impure anonainehydrochloride, corresponding to a yield of 0.07% alkaloid based on the weight of the bark.

The

The amount of a phenolic alkaloid, which Santos (7) also had noticed was so little, that we gave up its investigation. Neglecting this phenolic alkaloid we could work up the main portion of the alcoholic extract in another way, which took less time and gave a better yield of anonaine. This was first tried out in a small preliminary experiment:

The whole extract (about 2.4 kg) was slowly poured into 5 l water with continual stirring. The clear aqueous solution was poured off, after the resin had separated out. The resin was diluted with a little alcohol and again poured into 5 l water. Both aqueous extractions were made alkaline with NaOH and extracted several times with ether (ether extract I). The residual resin was mixed with about 1,5 l 4n NaOH bringing the greater part of the resin into solution. This alkaline, dark brown suspension was extracted several times with ether. The combined ether extractions were worked up together with ether extraction I. The combined ether solutions were washed with water and then repeatedly extracted with dil. acetic acid. The acid solution was washed with ether and then made alkaline with NaOH. and the base redissolved in ether. The ethereal solution was washed with

a

a little H_2O and extracted with small quantities of 2n hydrochloric acid. The hydrochloride of anonaine is so sparingly soluble in dil. hydrochloric acid that it precipitated out almost completely in crystalline form.

The hydrochloride thus obtained was coloured yellowish-orange, and could be recrystallized from water or ethyl alcohol.

We obtained by this method from the whole extraction 31.5 g of the hydrochloride which gave a percentage yield of 0.12% free base based on the 25 kg bark.

2. Properties of Anonaine.

It is difficult to crystallize the free base. We proceeded as follows:

Pure anonainehydrochloride was suspended in a little water and a small excess of ammonia was added. The free base was shaken out with ether. The colourless ethereal solution was washed with H_2O and dried over Na_2SO_4. The ether solution was put in a crystallizing dish and was allowed to evaporate at room temperature into a small volume. The ether solution had now a greenish

colour

colour and was put in a refrigerator. Long white needles mixed with a greenish oil were formed over night. The oil was washed out with a small quantity of benzene, leaving the crystalline base which melted at 123° - 124°.

Anonaine is, in crystalline form, fairly stable, but when dissolved in an organic solvent, the colour of its solution soon turns greenish and finally brownred.

Anonaine is very soluble in the most common organic solvents except ligroin in which it is almost insoluble, and water.

Anonaine showed the following <u>colour reactions</u>:

1. Conc. H_2SO_4 orange
2. Conc. HNO_3 pink-red-violett-brown
3. Conc. H_2SO_4 + conc. HNO_3 (Erdmanns reagent) orangered-orange-yellow
4. Conc. H_2SO_4 + MoO_3 (Froehdes reagent) greenish-grey-yellow brown
5. Conc. H_2SO_4 + V_2O_5 yellowish-green-red-violett-brown
6. Conc. H_2SO_4 + WO_3 yelloworange - Orange brown
7. Conc. H_2SO_4 + As_2O_5 (Rosenthaler-Turksches reagent) violett-pink-red-brown
8. Conc. H_2SO_4 + little $KClO_3$ violett - red
   + more $KClO_3$ red-darkred-orange--yellow.

Anonaine is <u>optically active</u>

$(\alpha)_D^{20^\circ} = -52^\circ$ (Chloroform)

$\alpha = -0.63^\circ$ l = 2 dm c = 0.605 t = 20°

Some

3. Some salts from Anonaine.

Hydrochloride.

The original impure yellowish-orange anonaine-hydrochloride can be recrystallized from water, water + HCl, alcohol, or alcohol + ether, in white needles

m.p. 277.5° (decomposition)

Analyses. (For these analyses the hydrochloride was dried in a high vacuum at 110° in the presence of P_2O_5).

	% C	% H	%N	% Cl
Calculated for $C_{17}H_{15}O_3N$. HCl (formula suggested by Santos)	64.25	5.04	4.41	11.0
Calculated for $C_{17}H_{15}O_2N$. HCl	67.65	5.30	4.64	11.77
Found	67.85	5.40		
	67.63	5.70	4.75	II.7I
	67.48	5.87		
	67.37	5.02	4.88	

Determination of active hydrogen (according to Zerewitinoff)

found 2.06 and 1.97 for anonaine hydrochloride for the base 1.06 and 0.97

Methoxyldetermination according to Zeisel-Pregl:

negative.

Hydrobromide

Needles from 20% alcohol, slightly yellowish

m.p. 281° (dec)

Hydrojodide

Hydrojodide.

Needles from 50% alcohol, slightly grey

m.p. 274° (dec)

Perchlorate

Yellowish, long falted needles from water

m.p. 240° (dec)

Sulphate

White needles from 95% alcohol

m.p. 245° (dec)

Nitrate

Microscopic crystals from CH_3OH+ ether

m.p. 250° (dec)

Oxalate

long plates from CH_3OH

m.p. 211° (dec)

d- tartrate needles from 95% alcohol (more soluble than the l-tartrate)

m.p. 218° (dec)

l-tartrate needles from 95% alcohol

m.p. 224° (dec)

Picrate orange needles from alcohol

m.p. 204- 206° (dec)

4. Anonaine did not react with phenyl-hydrazine.

5. Qualitative

5. Qualitative determination of the methylene-dioxygroup (Test according to Gaebel).

10 mg of Anonainehydrochloride were dissolved in 5 cc phloroglucinol-sulphuric acid by boiling, 2 cc conc. H_2SO_4 were added to the hot solution, which was shaken and left in a bath of boiling water for 20 minutes. The solution turned red after some time, a thick flaky precipitate of phloroglucide was obtained.

6. Action of nitrous acid on anonaine.

We added a concentrated solution of $NaNo_2$ in water to a solution of the base in an excess of acetic acid. The nitrosocompound crystallized out very soon in faintly yellow needles. It was recrystallized from acetone by adding water. m.p. 189 °

Analyses.	%C	%H	%N
Calculated for $C_{17}H_{14}O_4N_2$ (Santos' formula)	65.8	4.5	9.0
Calculated for $C_{17}H_{14}O_3N_2$	69.4	4.8	9.6
Found	68.9	4.8	9.8 9.8
	69.5	4.7	9.1

7. Acetylation of Anonaine.

100 mg of the alkaloid were dissolved in 1 cc acetic acid anhydride and heated on the water bath for 15 minutes and the excess of acetic anhydride then carefully destroyed with water. On cooling the neutral optically

optically active acetylcompound separated out in long white needles. It was recrystallized from acetone by adding water m.p. 229 -230°

α = -5.04° l = 2dm c = 1.14 t = 20°

$(\alpha)_D^{20°}$ - 221° (acetone)

Analyses.

	% C	%H	%N
Calculated for $C_{21}H_{15}O_5N$	69.0	5.2	3.9
(supposing that two acetyl-groups have entered the molecule in Santos' formula)			
Calculated for $C_{19}H_{17}O_3N$	74.3	5.5	4.6
Found	74.4	6.1	4.8
	74.1	5.8	

8. Methylation of Anonaine to N-methylanonaine.(25)

1.235 g base (= 1 mol) were refluxed at 100° for two hours with 1.2 mol (0.26 g) of formic acid in 2.4 mol (0.84 g) of 40% formaldehyde solution in 20 cc H_2O. The cooled solution was made alkaline with conc. ammonia and extracted with ether, which after evaporation left behind tertiary and unchanged secundary base, as a brownish oil. To separate these the residue was dissolved in 9 cc acetic anhydride and left over night at room temperature. The excess of acetic anhydride was destroyed with approx. 30 cc H_2O. 3 cc of conc. hydrochloric acid were added and the solution extracted with ether

ether. The acid solution was then made alkaline with sodium hydroxyde and repeatedly extracted with ether. The ether solution was washed with H_2O and dried over Na_2SO_4 . After evaporation of the ether 0.930 g (72% yield) of the N-methyl-anonaine were obtained as a brownish oil, which could not be crystallized, even after destillation under high vacuum. The base was purified as its hydriodide. The hydriodide formed by adding an excess of sodium iodide to a concentrated solution of the base in acetic acid, was recrystallized twice from water. The crystals so formed (plates) were yellow-grey and melted at 246° - 247° with decomposition.

Analyses.

	%C	%H	%N
Calculated for $C_{18}H_{18}O_2NJ$	53.0	4.4	3.4
Found	52.5	4.9	3.1

9. Action of Chloroethylcarbonate on anonaine.

A solution of anonaine in chloroform was refluxed for half an hour with an excess of chloroethylcorbonate in presence of solid KOH. The chloroform solution was then washed with water and dried over Na_2SO_4. The residue left after evaporation of the chloroform was recrystallized from 20% alcohol.

White needles melting at 170°

The same

The same compound was also formed by shaking a solution of $\frac{1}{1000}$ mol anonaine in 15 cc chloroform with $\frac{4}{1000}$ mol chloroethylcarbonate and $\frac{7}{1000}$ mol solid potassium hydroxyde for two hours, to which several chips of ice were added from time to time.

The compound obtained was neutral, did not contain chlorine but was still optically active (approx. 40 mg in 20 cc chloroform in a 2 dm tube caused a laevo-rotation of about 1.2°).

Analyses.

	%C	%H	%N
Calculated for $C_{20}H_{19}O_4N$	71.1	5.7	4.2
Found	70.9	6.2	4.5

10. Action of chloroethylcarbonate on N-CH_3-anonaine.

To a solution of 0.57 g (1 mol) NCH_3-anonaine in 12 cc chloroform, to which several chips of ice had been added 0.44 g (2 mol) chloroethylcarbonate and 0.40 g (3.5 mol) solid KOH were added and the mixture shaken constantly for one hour. After this interval more ice and another 0.44 g chloroethylcarbonate and 0.40 g KOH were added and the mixture again shaken for one hour. The chloroform layer was run off, washed several times with dilute

(1 n)

(1 n) hydrochloric acid then with water and dried over Na_2SO_4. After evaporation of the chloroform a yellowish oil was left behind. It could not be crystallized even after destillation under high vacuum. The compound was neutral and did not contain any chlorine.

The rotation of a solution of 0.4876 g of this oil dissolved in 20 cc chloroform in a 2 dm tube could not be estimated exactly because of dark colour of the solution. It definitely was about the Zero-point.

11. Hofmann degradation of Anonaine.

a. Quaternary Ammonium iodide of Anonaine.

5 g of anonaine-hydrochloride were mixed with 70 cc water. Approx. 5 times the amount of Na_2CO_3 necessary for the liberation of the base were added, an excess of methyljodide was then added and boiled for 1½ hours under reflux. The excess of methyl-iodide was destilled off. The methiodide had already begun to separate out during the operation. The separation was completed on cooling. The product was recrystallized from water forming white felted needles.

m.p. 217°.

The compound was soluble in alcohol, acetone and hot water; insoluble in ether.

We obtained 6.730 g of the methyliodidecompound (yield 96%).

Analyses

Analyses.

	%C	% H	% N
Calculated for			
$C_{19}H_{20}O_2NJ$	54.2.	4.8	3.3
Found	54.2	4.7	3.3

b. Methine Base of anonaine.

The quaternary ammonium iodide (6.730 g) was suspended in 370 cc water. 100 g solid KOH in 50 cc CH_3OH were added, and refluxed for four hours on the water bath. The quaternary ammonium iodide soon went into solution and after one hour an oil began to separate out. The solution became red towards the end. After 4 hours the solution was cooled and extracted several times with ether. The ether solution had a brownish-green colour. It was washed and dried over Na_2SO_4. After evaporation of the ether a greenish coloured oil remained behind. On scratching with a glass rod and leaving over night in the refrigerator the oil turned into a compact crystalline mass composed of long needles, m.p. 87-90°. 5.160 g of the methine base were obtained, corresponding to a yield of 91%.

Due to the darkness of its solution the rotation of the base itself could not be estimated. For this purpose the methiodide of the base was used.

Methiodide

c. Methiodide of the methine base.

4 g methine base were dissolved in 20 cc acetone and an excess of CH_3J added. The methiodide of the methine base soon separated out in long white plates. The product was recrystallized from water. 5.17 g were obtained (87% yield).

m.p. 270.5° (with decomposition).

The product was optically inactive (0.050 g in 30 cc ethyl alcohol in a 2 dm tube).

Analysis.

	% C	% H	% N
Calculated for $C_{20}H_{22}O_2NJ$	55.2	5.1	3.2
Found	55.3	4.9	3.3.

d. Formation of a substituted Vinyl-phenanthrene.

Methine-methiodide (1.20 g) was suspended in a solution of 2.5 g solid potassium hydroxyde in 50 cc methylalcohol and heated under reflux on the water bath. The trimethylamine formed by the reaction was led into an alcoholic solution of picric acid and characterized as the trimethylamino-picrate (m-p. 217° mixed m.p. with an authentic specimen of trimethylamino-picrate 217°). After half an hour the solution had become clear. It was

heated

heated for one hour longer and then cooled and left at room temperature overnight. The vinyl compound separated out in long white needles. It was filtered off, washed with H_2O, dil. acetic acid and again with H_2O and then dried. It was recrystallized from CH_3OH by the addition of water. m.p. 87°.

It is very soluble in acetone and chloroform, soluble in alcohol and ether.

It immediately decolourized a solution of bromine in chloroform.

When left for some time, especially when impure or when heated above its melting point, the compound polymerized to a resin which was then soluble only in chloroform and pyridine.

0.518 g crystalline vinylcompound was obtained (75.5% yield).

Analysis.

	% C	% H
Calculated for $C_{17}H_{12}O_2$	82.3	4.8
Found	82.4	4.8

e. Oxydation of the substituted Vinyl-phenanthrene to the corresponding acid.

0.610 g vinylcompound was dissolved in 60 cc acetone (purified with potassium permanganate) and 1.3 g well powdered potassium permanganate were added. The solution

solution was left overnight. 20 cc of water were added and the manganese dioxyde was dissolved by passing in SO_2. The acetone was destilled off, conc.hydrochloric acid added and the precipitate thus obtained extracted with ether. The ethereal solution was coloured orange. It was washed with water and extracted with dil. sodium carbonate solution. The ether solution still contained 0.110 g neutral products, a part of which could be obtained crystalline by sublimation. They were not investigated. The sodium carbonate solution was acidified and an orange precipitate separated out. It was extracted with ether. The ether solution was washed, driedk over sodium sulphate and the ether removed by destillation, when 0.430 g of a yellow-orange residue was obtained. This substance was boiled with a very little acetone, which almost completely extracted the orange coulour. The product thus obtained was still impure. It was sublimed under high vacuum.

We obtained three different sublimation compounds:

1. between 110-130° a crystalline product m.p. 150° containing 73.2% C and 4.11% H. Not investigated any further.
2. Yellow oil.
3. between 150-190°. The expected acid in faintly yellow

yellow needles. The acid was obtained pure by recrystallisation from benzene and by resublimation. The acid did not melt sharply but sublimed from 240° upwards with partial decomposition.

The acid gave a positive Gaebel's test (methylenedioxy group).

Analysis.	% C	% H
Calculated for $C_{16}H_{10}O_4$	72.2	3.8
Found	72.4	3.8

d. Decarboxylation of the above methylenedioxy-phenanthrene-8-carboxylic acid. (26)

We tried to decarboxylate this acid by heating the acid under various conditions of temperature (150-250°) and pressure (14-760 mm), but failed to obtain satisfactory results.

The acid could however be easily decarboxylated by the method of Reichstein. (26)

0.024 g acid and 0.010 g $CuCrO_3$ were heated in 2 cc quinoline at 180-190°. The CO_2 produced by the reaction was carried over into a solution of $Ba(OH)_2$ in water by a stream of nitrogen. After 45 minutes the evolution of carbon dioxyde ceased. The solution was then diluted with water and extracted several times with ether. The quinoline was completely removed from this

this ether solution by repeated extraction with hydrochloric acid. The ether solution was then washed with dil. sodium carbonate solution and water and dried. After evaporation of the ether a yellow-brown oil remained, which was destilled under high vacuum (1 mm). It destilled at 140° as a colourless oil which soon became yellow again. A yield of 17.5 mg was obtained. This oil was dissolved in 5 cc abs. ethyl-alcohol and heated to boiling-point when a saturated solution of 17 mg picric acid in alcohol was added. On cooling fine red needles of the picrate separated out. These were filtered off washed with a little methylalcohol and dried. m.p. 168° (dec).

Analysis.

	% C	% H
Calculated for $C_{15}H_{10}O_2 \cdot C_6H_3O_7N_3$	55.9	2.9
Found	56.4	2.6

12. Oxydations.

a. Oxydation of the alkaloid with potassium permanganate.

Pure anonaine hydrochloride (1.325 g) was dissolved in 200 cc boiling water and a 3% solution of potassium permanganate added in small amounts (5 cc - 0.28 oxygen). After adding 140 cc (approx. 8 atoms) the oxydation

was

was completed as shown by the fact that a further portion of 5 cc potassium permanganate required almost half an hour to decolourize. After filtering the hot solution the precipitated manganese dioxyde was suspended in water and dissolved by passing in SO_2. This solution was added to the filtrate, which was then concentrated to about 20 cc. The solution had an orange colour. After cooling the solution was acidified with conc. hydrochloric acid and extracted in a continuous extracter for 15 hours with ether. The ether was evaporated and the residue thoroughly dried in a dessiccator. The residue thus obtained was sublimed under high vaccuum. Long white needles sublimed between 80° and 140° mixed with a little oil. The crystals after resublimation between 80-110° gave a distinctly positive phluoresceine test and melted at 129°. The mixed melting point with an authentic specimen of phthalic anhydride melting at 129° showed no depression. The sublimate was recrystallized from hot water, m.p. 197° mixed m.p. with phthalic acid 197°.

b. <u>Oxydation of the methine base of anonaine with conc. nitric acid</u>.

0.908 g of the methine base was dissolved in conc. nitric acid, a vigorous evolution of nitrous fumes taking place. The solution evaporated almost to dryness on the water bath. Canc. nitric acid was again added until the residue

the residue was completely dissolved and the solution again evaporated almost to dryness. This operation was repeated 8 times. The product obtained by this treatment was recrystallized from conc. nitric acid, filtered off, washed with water and dried. The product (0.116 g) was suspended in a little dil. hydrochloric acid and extracted several times with ether. The ethereal solution was shaken up with dil. Na_2CO_3, and the free acid obtained by acidifying the alkaline solution with hydrochloric acid redissolved in ether. After evaporation of the ether a partly crystalline yellow residue was left behind. It was destilled under high vacuum. Faintly yellow needles sublimed mixed with an oil (130° - 180°). Most of the oil was washed out with a little boiling methylalcohol and the remaining yellowish crystals resublimed and again washed out with little methylalcohol.

The crystals softened at 137° and were completely melted at 157°.

Analysis.

	% C	% H	% N
Calc. for $C_{12}H_{15}O_5N$	59.2	2.1	5.8
Found	59.0	2.7	5.8

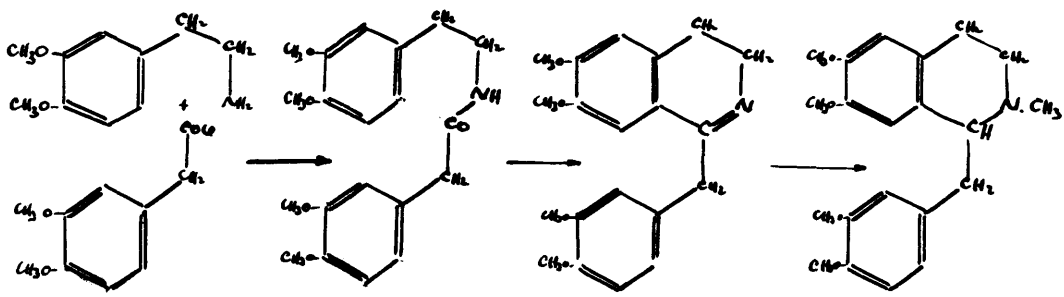
P A R T 2.

Synthesis of d.l-anonaine and d.l-N.CH_3-anonaine.

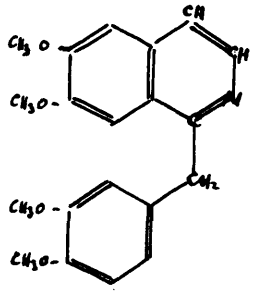
A. Synthesis of Isoquinoline Alkaloids.

The artificial synthesis of isoquinoline alkaloids has been accomplished in a manner which was often very similar to the natural phytochemical formation although the organic chemist who does not possess the natural synthetic ability of Nature has often to resort to means not found in Nature. The fundamental work on this subject was done by Pictet.

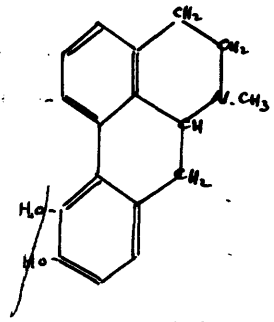
Pictet and Finkelstein (27) achieved the synthesis of laudanosine using the isoquinoline synthesis of Bischler and Napieralski(28) in the following way:



As was shown already in the first part papaverine and aporphine have similar structures:



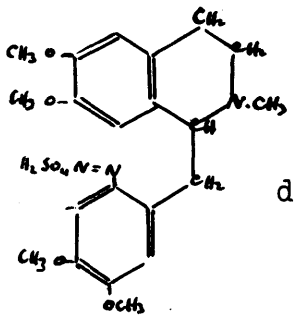
papaverine



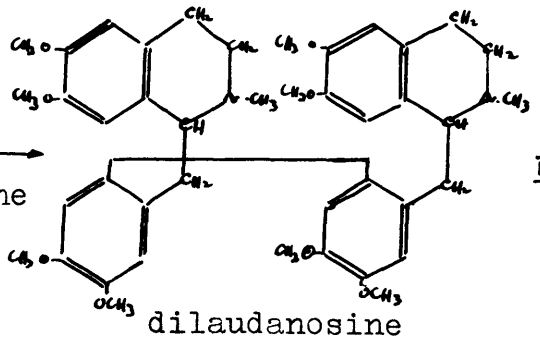
aporphine

It was shown in the phytochemical formation of isoquinoline alkaloids that the aporphine type can be derived from the papaverine-type by a simple ring-closure. Pschorr, Silberbach and Stahlin (29) conceived the idea of attempting experimentally the transformation of papaverine into a phenanthrene-derivative. The only applicable method for this transformation was Pschorr's method of phenanthrene synthesis. The presence of a phenanthrene derivative was not definitely established. Nevertheless Pschorr paved the way for Gadamer's synthesis of glaucine, the first synthetic aporphine alkaloid (30). Gadamer showed that in addition to the aporphine base itself many other by-products are formed.

Following table is reproduced from the work of Gadamer.

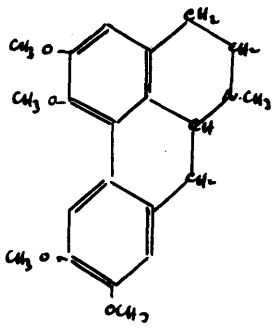


diazolaudanosine



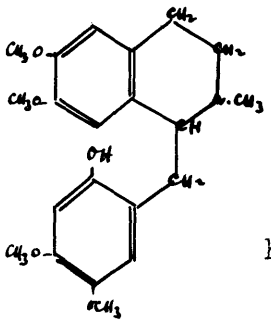
dilaudanosine

I



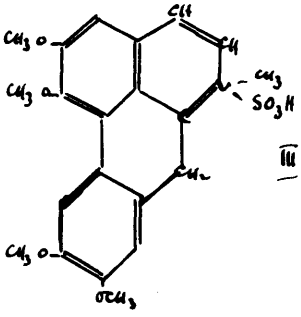
II

glaucine



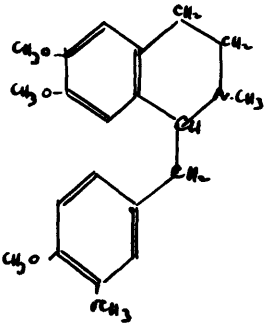
IV

hydroxylaudanosine



III

Dehydroglaucine-bisulphate

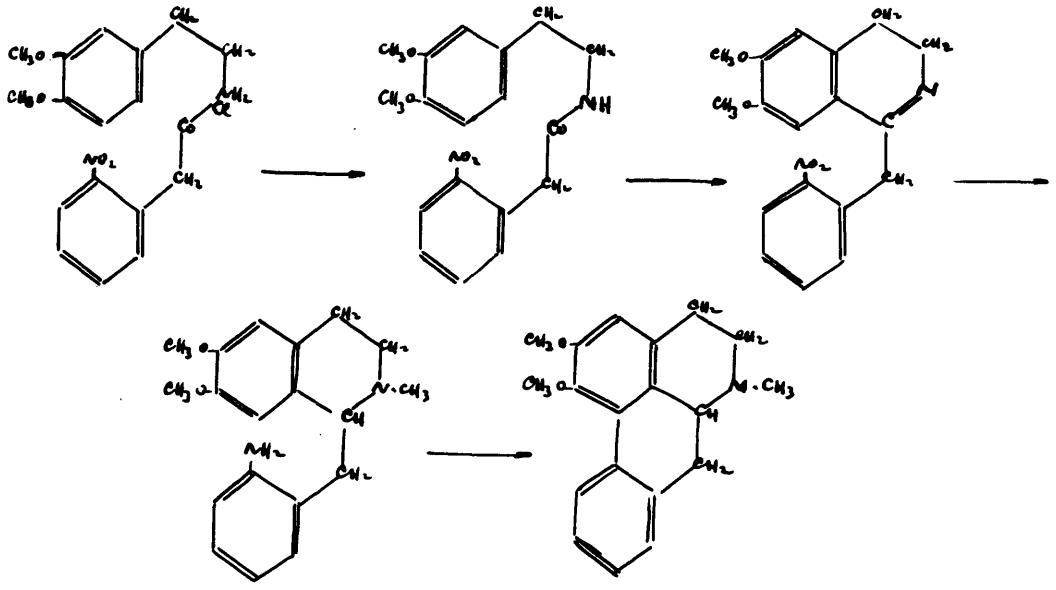


V

laudanosine

Glaucine and dicentrine are the only known aporphine-alkaloids which have substituents in position 2,3.

The general synthesis of aporphine alkaloids was achieved at the same time by Haworth and Späth. 5,6-dimethoxyaporphine, an alkaloid which does not occur in Nature was synthesised in the following way: (31)



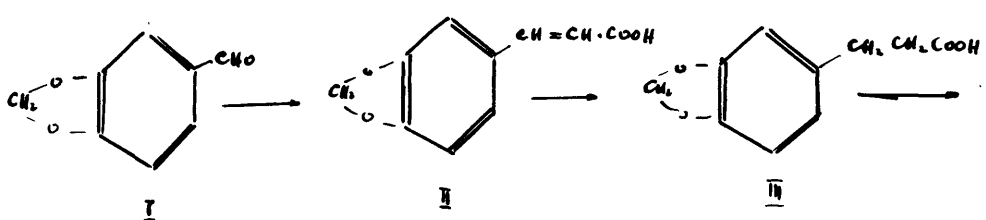
Many aporphine alkaloids have since been synthesised in the same way.

The synthesis of d.l-anonaine and d.l-N-CH_3-anonaine was accomplished by the same series of reactions.

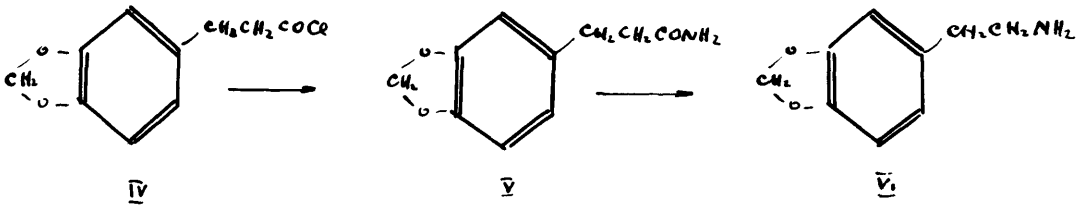
B. Theoretical.

As starting materials for the synthesis of anonaine homopiperonylamine and o-nitro-phenyl-acetic acid were required.

Homopiperonylamine was synthesised by the method of Perkin, Haworth and Rankin,(32) in the following way:



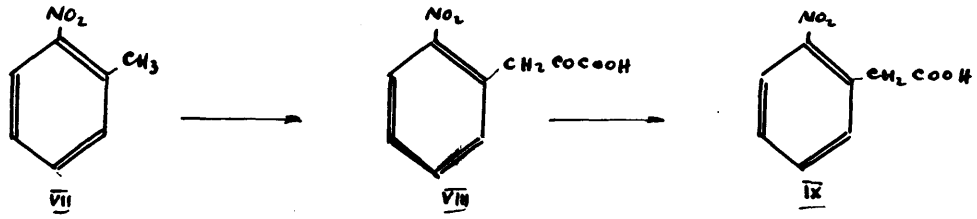
I II III



IV V VI

The yields of the various intermediate products were fairly good.

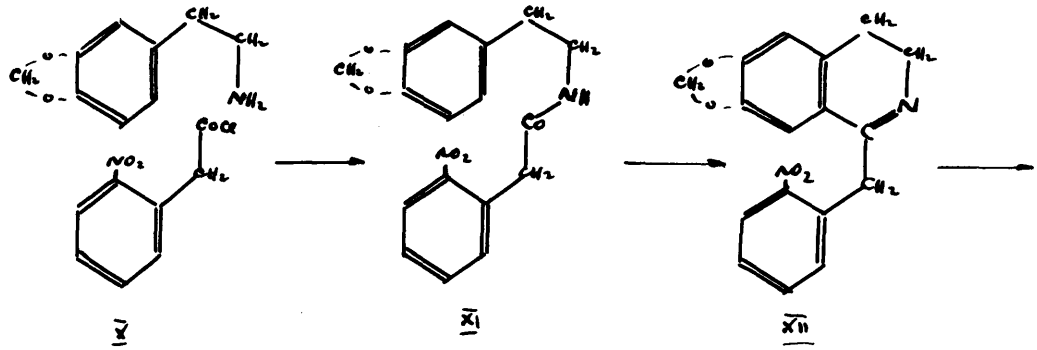
o-nitro-phenyl-acetic acid was synthesised as follows:



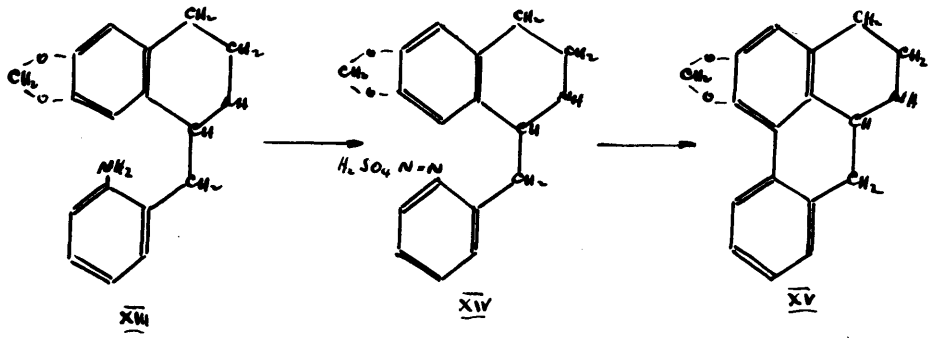
VII VIII IX

o-nitro-toluene was condensed with ethyloxalate to form o-nitro-phenyl-pyruvic acid which was oxydized with H_2O_2 to o-nitro-phenyl-acetic acid.

The synthesis of anonaine was then carried out as follows:



X XI XII



XIII XIV XV

From homopiperonylamine we obtained (3,4-methylenedioxyphenyl)-ethyl-o-nitro-phenylacetamide.

To accomplish the ringclosure to the corresponding isoquinoline derivative, P_2O_5 (Bischler, Pictet, Spaeth), PCl_5 (Haworth, Gulland) and $POCl_3$ have been used in the synthesis of isoquinoline alkaloids.

Various dehydrating agents and solvents were used but although the time and temperature of the reaction were varied also little or no yield was obtained. A very good yield was however obtained by allowing the amide to react with phosphorus oxychloride in chloroform solution at room temperature for some days. The advantage of $POCl_3$ over other dehydrating agents (e.g. P_2O_5 or PCl_5) lies in its rather mild reactivity so that the chances of its decomposing the amide are minimised.

On the other hand this method allowed the reaction to be carried out on a larger scale.

The isoquinoline compound was reduced with zinc dust and hydrochloric acid to 2'-amino-6,7-methylene-dioxy-I-benzyl-tetrahydro-isoquinoline.

In the

In the reduction with zinc and HCl not only the nitrogroup was reduced to the amino group but also $\geq C=N-CH_2-$ was reduced to $\geq CH-NH-CH_2-$. This was proved by the formation of a neutral diacetyl compound on treating the reduced base with acetic anhydride.

The tetrahydroisoquinoline compound is an oil and was diazotised in a 2n sulphuric acid solution with the calculated amount of sodium nitrite. The ringclosure to the phenanthrenederivative was accomplished on heating the diazonium solution. If only the correct amount of $NaNO_2$ necessary for diazotisation of the primary amino group is used, the formation of the nitroso compound of the secundary amino group is avoided. Since sodium nitrite first reacts with the primary amino group. No phenolic by-products were obtained, but various other basic compounds were produced, which however were not investigated. The synthetic d,l-anonaine was isolatedas the hydrochloride, which was then purified. The free racemic base was obtained crystalline only with difficulty.

Attempts to resolve d,l-anonaine with d- and l-tartaric acid and with d-α-bromocamphersulphonic acid have hetherto been unsuccessful.

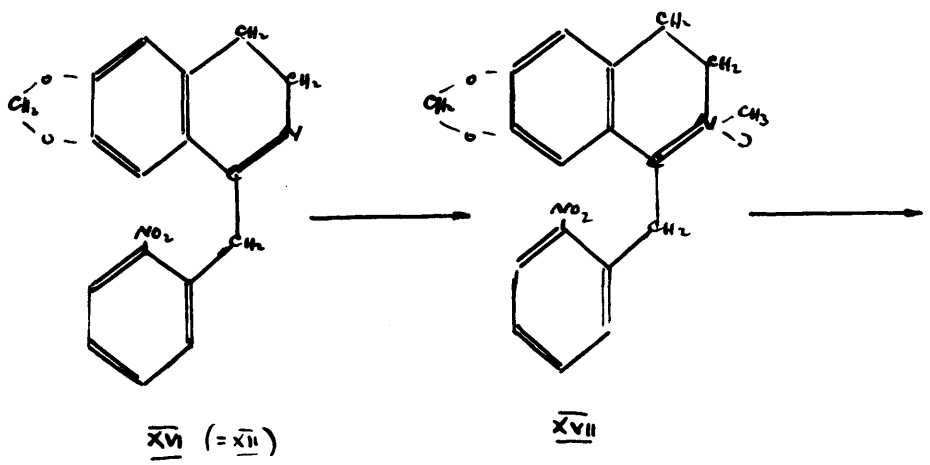
To

To confirm the constitution of the synthetic alkaloid and to prove its identity with natural anonaine, the centre of asymmetry was destroyed by a Hofmann degradation of the synthetic alkaloid and the products thus obtained proved identical with the corresponding degradation compounds of the natural alkaloids.

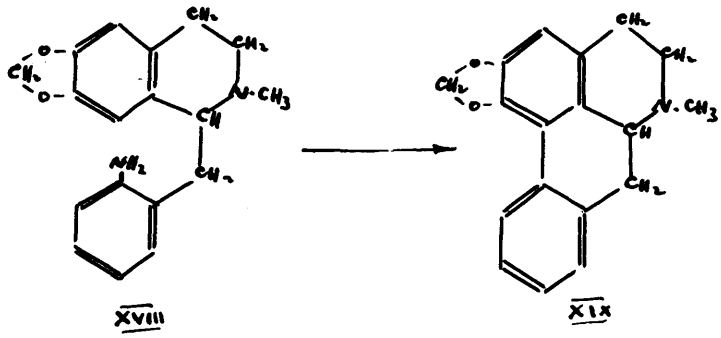
Synthetic d,l-anonaine gave the same colour reactions as natural anonaine.

We further synthesised the d,l-N-methyl-anonaine in the hope that it might be more easily resolved than the d,l-anonaine. Experiments in this direction are still being persued.

The synthesis of the N-methyl-anonaine starting from product XII (page 48) was carried out as follows:



XVI (= XII) XVII



XVIII XIX

Synthetic d,l-N-methylanonaine like the natural product could not be crystallized.

The synthetic N-CH_3-anonaine was isolated and purified as hydriodide.

From this synthetic rac.N.CH_3-anonaine the methiodide was prepared. It was identical with the corresponding compound obtained from synthetic d,l-anonaine.

C. Experimental.

1. Preparation of Homopiperonylamine.

a. Piperonyl-acrylic acid. (33)

235 g piperonal and 350 g malonic acid in 700 cc pyridine were heated with 11 cc piperidine on the water bath for 1 ½ hours. After the evolution of carbon dioxyde had ceased the solution was boiled for 5 minutes over a naked flame. The mixture was poured into 2 l water acidified with hydrochloric acid. The crystalline precipitate thus obtained was recrystallized from ethyl alcohol. m.p. 237°. Yield 88%.

b. 3,4-methylenedioxy-phenyl-propionic acid. (34)

This acid was obtained by reduction of the piperonyl-acrylic acid with 3% sodium amalgam.

Needles from ligroin. m.p. 86°. Yield 70%.

c. 3,4-methylenedioxy-propionamide. (35)

30 g of the above acid were dissolved in 100 cc chloroform, 23 cc thionylchloride were carefully added and the solution allowed to stand overnight at room temperature. 280 cc conc. ammonia (s.g. = 0.88) containing

taining 12 g solid sodium hydroxyde were poured very carefully into the acid chloride solution. The chloroform was then destilled off. Sufficient water was added to dissolve the whole precipitate, and the solution was filtered hot to remove small resinous impurities. On cooling the amide crystallized out in fine needles which after recrystallisation from water melted at 122°. Yield 79%.

d. Homopiperonylamine. (36)

The Hofmann degradation was carried out with the calculated amount of sodium hypochlorite under the conditions prescribed by Decker. It is not advisable to work on to large scale. By the degradation of 20-30 g propionamide an average yield of 60% was obtained. Homopiperonylamine was purified by destillation under high vaccum. The hydrochloride of the base melted at 210°.

2. Preparation of o-nitro-phenyl-acetic acid.

a. o-nitro-phenyl-pyruvic acid. (37)

46 g sodium were dissolved in 920 g absolute ethylalcohol and a mixture of 146 g diethyl-oxalate and 137 g o-nitro-toluene were added and the mixture digested for 3 days at 36°. The resulting viscous dark-red mass

was

was mixed with 187.5 g 20% hydrochloric acid, care being taken to prevent a rise of temperature. The alcohol was then removed under reduced pressure. The residue was repeatedly extracted with ether. The acid was extracted from the ethereal solution with small amounts of 5% NaOH until the caustic soda solution was only faintly coloured. The greater part of the acid was precipitated with hydrochloric acid as an oil which on standing became crystalline. The remainder of the acid was obtained by extracting with ether.

105 g of the acid were obtained. Yellow needles from benzene. m.p. 120°.

b. o-nitro-phenylacetic acid. (38)

100 g o-nitro-phenylpyruvic acid were dissolved in 2000 cc dil. NaOH and treated with small portions of 3% hydrogen peroxyde solution, until the red colour of the solution disappeared. By acidifying the solution with hydrochloric acid the free acid was precipitated. This was filtered off and the remainder of the acid extracted with ether. The acid was recrystallized from water. Yellow needles. m.p. 138°. 78 g of o-nitro-phenyl-acetic acid were obtained (90% yield).

Synthesis

3. Synthesis of d,l-anonaine.

a. β(3,4-methylenedioxy-phenyl)-ethyl-o-nitro-phenyl-acetamide.

18,1 g ($\frac{1}{10}$ mol) o-nitro-phenyl acetic acid were dissolved in 100 cc chloroform and mixed with 60 cc thionyl-chloride and heated at 40° till the evolution of HCl ceased (approx. 30 minutes). The chloroform and excess of thionylchloride were destilled off under reduced pressure and the last traces of thionylchloride removed in a vacuum desiccator over KOH. The acid chloride was then dissolved in 30 cc benzene and the solution added drop by drop to a solution of 31 g ($\frac{2}{10}$ mol) of homopiperonylamine in 40 cc benzene which was kept cool with running water.

The amide which is almost insoluble in benzene soon began to separate out and the solution was left overnight at room temperature. The amide was filtered off washed with a little ether and dried. The finely powdered amide was extracted twice with boiling dil. acetic acid and filtered on cooling, thus removing the homopiperonylamine-hydrochloride formed along with the amide. The amide was washed with water, dil. sodium carbonate solution and again with water and dried. The amide thus obtained was fairly pure. A small sample for analysis was recrystallized form acetone and water and again from methylalcohol

methylalcohol.

m.p. II9°. 30.6 g of the amide were obtained. (85% yield).

Analysis.

	%C	%H	% N
Calculated for $C_{I7}H_{I6}N_2$	62.2	4.9	8.5
found	62.I	5.I	8.5

b. 2'-nitro-6,7-methylenedioxy-I-benzyl-3,4-dihydro-isoquinoline.

5 g of the amide were dissolved in 20 cc chloroform and I5 cc phosphorus oxychloride in a flask fitted with a calciumchloride-tube and left at room temperature for 5 days. The chloroform and the excess of $POCl_3$ were distilled off under reduced pressure. The remaining dark-brown oily cake was dissolved in a little acetone and poured into I00 cc dil. hydrochloric acid. The insoluble residue was filtered off, dissolved in a little acetone, poured into I00 cc dil. hydrochloric acid and again filtered off. The combined acid filtrates, orange-yellow in colour, were made alkaline with caustic soda and repeatedly extracted with a mixture of ether and chloroform. This orange solution was washed with water and extracted with dil. hydrochloric acid. On making alkaline the isoquinoline base separated out first as a white turbidity and

and and later as an orange-yellow crystalline precipitate. This was filtered off, washed with water and dried. A small sample for analysis was recrystallized from methyl-alcohol. Prisms m.p. 165° 3.75 g were obtained (79% yield).

Analysis.

	% C	% H	% N
Calc. for $C_{17}H_{14}O_4N_2$	65.8	4.5	9.0
Found	65.8	4.3	9.3

c. 2'-amino-6,7-methylenedioxy-I-benzyl-tetra-hydro-isoquinoline.

8.64 g of the above isoquinoline compound were dissolvedin 90 cc conc. hydrochloric acid and 80 cc water and heated on the water bath. 25 g zincdust were added over a period of half an hour. The orange-brown colour of the solution soon turned light yellow. After one hour the solution was filtered hot, cooled and made strongly alkaline with caustic soda. The alkaline solution was extracted with ether until a sample of the ethereal solution extracted with dil. hydrochloric acid no longer gave a positive test with Mayer's reagent. The combined ether extractions were washed with water and extracted with dil. hydrochloric acid. The base was precipitated by the addition of sodium hydroxyde and again redissolved in ether. The ether solution was washed with water and dried over sodium

sulphate

sulphate. The solution fluoresced with a blue-yellow colour. After evaporation of the ether the base was obtained as an yellow-green oil which was used without further purification. (6.68 g - 75% yield).

The dihydrochloride of the base was obtained by passing dry hydrogen chloride into a solution of the base in ether. It was recrystallized twice from methyl-alcohol. White needles m.p. 257 (dec.)

Analysis.

		% C	% H	% N
Calculated for $C_{17}H_{19}O_2N_2Cl_2$		57.6	5.4	7.9
	found	57.0	5.6	7.5

The di-acetyl compound of the base was also prepared, by heating the base with an excess of acetic anhydride at 100° for half an hour. The excess acetic anhydride was destroyed with water and the acid solution extracted with ether. After evaporation of the ether the residue was recrystallized from 20% alcohol. On cooling the diacetyl compound appeared as a white turbidity which after standing 24 hours became crystalline. Rhomboidal crystals. m.p. 199°.

Analysis.	% C	% H
Calc. for $C_{21}H_{22}O_4N_2$	68.8	6.0
Found	68.7	6.5

The base

The base, diazotised with the calculated amount of sodium nitrite and coupled with β-naphthol, gave an orange-red dyestuff.

d. d,l-anonaine.

6.68 g of the above base were dissolved in 180 cc 2n sulphuric acid and diazotised by the dropwise addition of the calculated amount of freshly standardized 0,5 n sodium nitrite solution.

The original light yellow colour of the solution turned brown after the addition of few drops sodium nitrite. The diazotised solution was heated for 30 minutes on the water bath. A vigorous evolution of nitrogen took place and the solution turned very dark brown. 8 cc conc. hydrochloric acid and approx. 3 g zincdust were then added and the solution heated for a further half an hour by which time it had assumed a much lighter colour. It was filtered hot, cooled, extracted several times with ether, made strongly alkaline with caustic soda, and again extracted with ether. The racemic anonaine was precipitated from the ether solution as the hydrochloride by shaking with small portions of dil. hydrochloric acid, the hydrochloride being almost unsoluble in hydrochloric acid. It was obtained in long white

white needles by recrystallisation from 95% alcohol. m.p. 285.5° (with decompostion).

1.41 g of d,l-anonaine hydrochloride were obtained (22% yield).

Analysis.	% C	% H	% N
Calculated for $C_{17}H_{15}O_2N.HCl$	67.7	5.3	4.6
Found	67.7	5.4	4.8

Acetyl derivative of the synthetic alkaloid.

The acetylderivative was prepared as previously described for the natural alkaloid. White needles. m-p- 217°.

Analysis.	% C	% H	% N
Calculated for $C_{19}H_{17}O_3N$	74.3	5.5	4.6
Found	74.4	6.0	4.6

Compound formed by the action of chloroethyl-carbonate upon synthetic anonaine.

The reaction was carried out as previously described for natural l-anonaine. White needles from 20% alcohol. m-p. 140°.

Analysis.	% C	% H	% N
Calculated for $C_{2o}H_{19}O_4N$	71.1	6.2	4.5
Found	71.1	6.4	4.9

Colour

Colour reactions of synthetic d,l-anonaine.

The synthetic recemic anonaine gave the same colour reactions as natural anonaine.

Hofmann degradation of synthetic d,l-anonaine.

The Hofmann degradation of the synthetic d,l-anonaine was carried out under the same conditions as already described for the degradation of the natural alkaloid. (Page 35)

200 mg recemic anonainehydrochloride were used for the whole degradation.

The quaternary methiodide of the recemic alkaloid was obtained in white needles from water. m.p. 210°.

The compound was degraded to the methine base and this characterized as its methiodide. The methiodide of the methine base crystallized in long plates from alcohol. m.p. 269.5 - 270.5° (dec), corresponding product from natural anonaine. m.p. 270.5°(dec)

mixed m.p. 270.0-270.5°.

This methiodide derivative yielded the vinyl-compound on further degradation. Long white needles from alcohol and water of exactly the same crystalline form as those of the corresponding natural product.

m.p. 87°

m.p.

m.p. of the vinylcompound obtained by degradation of the natural alkaloid : 87°.

mixed m.p. 87°.

Analysis.

	% C	% H
Calculated for $C_{17}H_{12}O_2$	82.3	4.8
Found	82.3	4.8

4. Synthesis of d,l-N-methyl-anonaine.

a. 2'-nitro-6,7-methylenedioxy-I-benzyl-3,4-dihydro-isoquinoline-methiodide.

3,6 g of 2'-nitro-6,7-methylenedioxy-I-benzyl-3,4-dihydroisoquinoline (page 57) were heated with 10 cc CH_3J at 100° for half an hour in a sealed tube. After cooling, the contents of the tube were washed out with a little acetone and recrystallized from water. Long yellow plates m.p. 243° (dec). 4.86 g were obtained (93% yield)

Analysis.

	% C	% H	% N
Calculated for $C_{18}H_{16}O_4N_2J$	47.9	3.8	6.2
found	47.9	4.0	6.1.

2'-amino

b. 2'-amino-6,7-methylenedioxy-I-benzyl-2-methyl-tetrahydro-isoquinoline.

4.86 g of the above compound were heated with 15 cc conc hydrochloric acid and 40 cc water on the water bath and reduced by adding 5 g of zincdust over a period of 30 minutes. The almost colourless solution thus obtained was filtered hot, cooled, made strongly alkaline with KOH and extracted repeatedly with ether. The pink coloured ether solution was shaken up with dil. hydrochloric acid and the greenish grey coloured acid solution made alkaline. The base separated out as a light oil which was redissolved in ether. The ethereal solution was washed with water and dried over sodium sulphate. It had a red violet fluorescence. 2.86 (90% yield) of the reduced base were obtained.

The dihydrochloride of the base was precipitated from its ethereal solution by passing in dry hydrogen chloride, and was recrystallized from methylalcohol. Rhomboidal crystals m.p. 258-260°(dec).

Analysis.

	% C	% H
Calculated for $C_{18}H_{21}O_2N_2Cl_2$	58.7	5.7
Found	58.7	6.0

The solution obtained by adding the calculated amount of sodium nitrite to the solution of the dihydro-

chloride

chloride in water gave an orange-red dyestuff with β-naphthol.

c. d,l-N-methyl-anonaine.

1.43 g of the above base were dissolved in 25 cc methylalcohol and 25 cc 0,5 n sulphuric acid and diazotised by the dropwise addition of the calculated amount of a freshly standardized 0.5 n sodium nitrite solution over a period of one hour. The original light yellow colour of the solution soon became brown-red. The solution was then heated on the water bath for 30 minutes, nitrogen being given off vigorously. 2 cc conc. hydrochloric acid and 0.7 g zincdust were added and the solution heated for a further 15 minutes on the water bath, by which time the solution had assumed a bright orange colour. It was filtered hot, cooled, extracted with ether, made strongly alkaline with caustic soda and again extracted with ether. The base was extracted from the ethereal solution with the smallest possible amount of 2n hydrochloric acid. To this solution a large excess of a saturated solution of KJ in water was added. The hydriodide of the base separated out as a darkbrown oil. When the oil had settled, the clear mother liquor was decanted. The oily residue was rubbed with a little methylalcohol causing crystallisation.

The

The hydriodide of the rac. N.CH_3 anonaine thus obtained was recrystallized from water and afterwards from alcohol. Prisms, slightly greyish. m.p. 244°(dec).

Analysis.

	% C	% H	% N.
Calculated for $C_{18}H_{18}O_2NJ$	53.0	4.4	3.4
Found	53.3	5.0	3.2

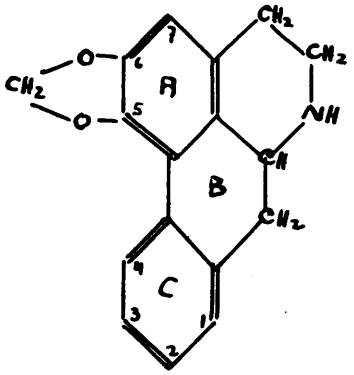
The methiodide of the synthetic d,l-N.CH_3-anonaine was obtained by heating under reflux an alcoholic solution of the hydriodide of the base with CH_3J in presence of Na_2CO_3.

White needles from water. m-p, 210-211°. The mixed melting point with the corresponding compound obtained from synthetic d,l-anonaine was also 210°.

D. Summary.

The constitution of the alkaloid anonaine has been investigated.

The following structural formula was suggested:



It is based chiefly on the following experimental results:

1. Empirical formula for anonaine $C_{17}H_{15}O_2N$.
2. Proof a methylenedioxy and a secundary amino-group.
3. Negative tests for methoxy, carbonyl, phenolic and alcoholic hydroxy groups.
4. The details of the Hofmann degradation as well as the effect of chloroethylcarbonate upon N.methyl-anonaine proved the isoquinoline structure of anonaine.
5. The formation of phthalic acid in the oxydation of anonaine proved that anonaine does not possess a papaverine structure.

It

It showed further, that ring C is unsubstituted.

By analogy the methylenedioxy group was assumed to be in position 5,6.

The correctness of the suggested formula was proved by the synthesis of the alkaloid.

d,l-anonaine and also d,l-N-methyl-anonaine were synthesised.

These synthetic alkaloids were deprived of their asymmetric centres by a Hofmann degradationand the products thus obtained were proved to be identical with the corresponding degradation compounds of natural anonaine.

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