

THE FORMATION OF TROPANONE AND N-HOMOLOGS

By

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degree of Doctor of Philosophy**

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INTRODUCTION ON PLANT SYNTHESIS AND TROPANONE

It is well established that in many, perhaps in most, plant as well as in animal cells the processes are directed and governed by enzymes. The question arises whether in all chemical processes of the living cell enzymes are necessary. Are there not some in which the reactions proceed spontaneously without the aid of enzymes?

In the animal cell no evidence for such a spontaneous synthesis or degradation has been observed. In the plant conditions are different (1). There is the abundance of the metabolic products of the cell which appear in the tissues, such as the carbohydrates, the aminoacids and the lipoids. The large number of alkaloids in plants stands out in contrast to the limited number in the animal cell. In animal alkaloids, that is, organic bases of animal origin, it is almost a question exclusively of the aminoacid precursor. Another striking thing about the natural substances of the plant kingdom is the fact that frequently a natural product, e.g., a certain alkaloid, is found only in a single species, whereas in closely related species different alkaloids or none at all are found; or, an alkaloid may be found in a limited number of related plants. One example from the many available is lupinin, found in Lupinus luteus and niger (leguminosae) and found only in these two Lupinus, and it is also found in Anabasis aphylla (Chenopodiaceae).

It is natural to conclude that a certain degree of fortuitousness applies here, that in just one plant there should be found the sum of all the conditions which lead to the formation of a definite substance, whereas in related species one or more of these conditions should be missing, so that there is a change in the direction, or even complete

absence of synthesis. Thus, one comes to the conclusion that at least for the plant cell it is possible to distinguish between two types of chemical processes, namely, those which are vital and catalyzed in their several stages by specific enzymes and those which are fortuitously produced. The latter may also be influenced by enzymes. But it is also reasonable that a natural product should arise from intermediates which are formed in cell metabolism, that these intermediates are so reactive that from the view of the organic chemist, and in the mild reaction conditions of the cell, they react readily to form a condensation product. This condensation product must then be slowly changed by the cell so that it accumulates and thus becomes isolable.

The opinion concerning the synthesis of alkaloids under physiological conditions was expressed in a paper "The Synthesis of Alkaloids in and Outside the Plant" (Entrance in Communications of the German Pharmaceutical Society 5, 93 (1928) given before the German Pharmaceutical Society at Berlin, by Carl Mannich. He said:

"Man wird milde Methoden suchen müssen, welche ohne Anwendung brutaler Reaktionen von einfachen Grundstoffen zu komplizierteren Basen führen. Es scheint mir nicht richtig, die erstaunlichen chemischen Künste der Pflanze nur durch die wundertätige Wirkung der Enzyme erklären zu wollen. Mindestens muss man versuchen, chemische Prozesse aufzufinden, welche auch ohne Enzyme die Alkaloidbildung verständlich machen."

The question of the physiological conditions and how the reactions proceed which account for the biogenesis of natural plant products, especially the alkaloids, will now be considered. If one would detect the formation of a product which appears momentarily in the cell, then he cannot proceed as in the fermentation process, in the isolation of the enzyme. Even if the formation of natural products could be observed in the expressed juices (which has not been observed thus far), the method would be impractical because the quantities of transition material available at

any given moment are relatively small, as they are involved in further syntheses.

There remains, then, the indirect method. Considerations which come into view are three:

1. The constitution of the natural product.

2. The fact that these products are formed in the cell without the aid of strenuous conditions such as strong alkalies, acids, elevated temperatures, etc., which are frequently relied on in the laboratory. The formation takes place at moderately low temperature, at high dilution, and at a pH which does not deviate far from 7. These are called the "physiological conditions."

3. Our knowledge of the metabolic processes in the cell, i.e., the degradation of aminoacids, fatty acids, etc., give us indication of which organic compounds may be expected in the various parts of the cell and thus may be considered as intermediates in the synthesis of natural products.

With these assumptions it becomes possible to set up hypotheses as to the biogenesis of the substance studied. From the constitution of a single substance, generally, no extensive valid conclusions may be drawn as to natural intermediates. But from numerous substances of related structure it becomes possible to establish certain conditions.

Once the hypothesis is established it must be proved. It is not permissible to assume any reaction as possible in the cell for the biogenesis of a natural substance; it must take place under physiological conditions. If it is assumed that a natural product is formed from the reactive intermediates in the cell, then it must be shown that under physiological conditions the natural product is actually formed from such

hypothetical intermediates.

If the intermediates of postulated constitution do not react with one another under biological conditions, one may perhaps postulate that an enzyme initiates the reaction. But no advantage is gained by this assumption, not until such a biocatalyst is isolated.

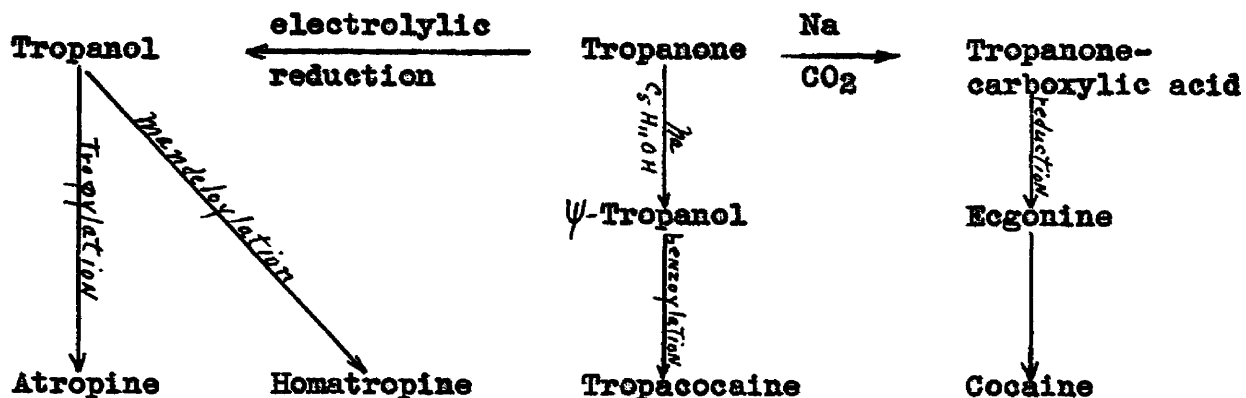
Finally, one must be sure that the intermediates for biosynthesis are capable of existing in the cell, but it is not necessary that the intermediates be isolated as natural products. One must anticipate that the actual building blocks for the biogenesis of natural products are so reactive that they themselves accumulate in only rare instances.

One of the most striking characteristics of an alkaloid-bearing plant is its capacity to produce a number of closely related bases. Examination of any series of alkaloids inevitably suggests that the plant, with its preeminent synthetic ability, has built up such a series from common parent substances through condensation, methylation, decarboxylation, and oxidation and reduction reactions. This idea was first suggested early in this century by Pictet (2) and by Willstätter (3). The aminoacids, or their transformation products, the amino aldehydes and amines, with formaldehyde, formic acid, and methanol, undoubtedly are the chief building units for the synthesis of alkaloids.

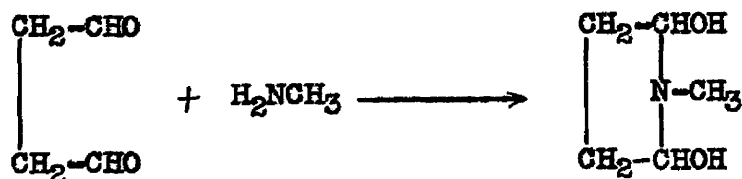
The first experimental demonstration of the simplicity of method by which the plant may synthesize alkaloids was Robinson's synthesis of tropanone from succindialdehyde, methylamine, and acetonedicarboxylic acid (4).

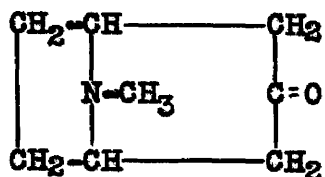
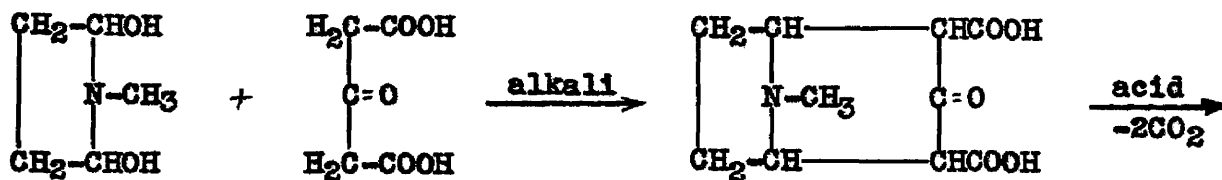
Tropanone, originally obtained by the oxidation of tropine (tropanol) (5, 6) and from ecgonine (7), whose structure was established by the brilliant work of Willstätter, has become the key compound in postulating the biosynthesis of the atropine group of alkaloids. As shown below, it may be regarded as the natural starting point in the synthetic preparation

of a number of bases of great value to medicine and surgery.



Numerous plant alkaloids are structurally derived from tropanone. Tropanone does not appear as such in nature. Rather, the natural products are derived from reduced tropanone; esters of both stereoisomeric alcohols, tropanol and pseudo-tropanol, occur naturally. Since the reduction of the carbonyl group and esterification of the resulting hydroxyl group are possible in the cell and, perhaps, catalyzed by enzymes, the biogenesis of these alkaloids may be referred to that of tropanone. For this Robinson gave the answer in 1917. He showed that by bringing together succindialdehyde and acetonedicarboxylic acid in the presence of excess methylamine, the aldehyde-amine reacts with the acid to form tropanonedicarboxylic acid and that this beta-keto-acid readily loses two molecules of carbon dioxide with the formation of tropanone (8).





Tropanone

Since the indicated intermediates are hypothetical building blocks of the living cell, Robinson concluded that this synthesis is also that used by the cell (8).

According to Schöpf (9), synthesis in the plant cell may take place with participation of specific enzyme systems, adapted to the production of one definite substance, as for example, the synthesis of starch from carbon dioxide; or unspecific enzymes may take part, e.g., enzymes as have a general function, as decarboxylation, hydrogenation, dehydrogenation, and oxidation; or finally, natural products, or the intermediates from which they are derived, may be formed without the participation of enzymes, when sufficiently reactive units occur simultaneously in the course of cell metabolism. This last case is susceptible of study in the laboratory. Essential conditions to be observed are proper hydrogen-ion concentrations and temperatures comparable to those under which the plant operates, and the use of starting materials which the plant may be expected to have available.

There can be no doubt as to the ability of the plant to reduce ketone groups and to accomplish esterification, so that the question of

the photochemical synthesis of the alkaloids of the belladonna group, the tropane derivatives, is largely that of the synthesis of tropanone. Although succindialdehyde (from degradation of ornithine), methylamine, and acetonedicarboxylic acid are all cell-possible substances, Robinson's synthesis, as confirmation of the hypothesis, is open to objections, because his condensation leading to tropanonedicarboxylic acid was carried out in strongly alkaline solution, and the subsequent decarboxylation required physiologically impossible conditions with respect to temperature and hydrogen-ion concentration. When, however, the condensation was carried out in a buffered solution between pH 3 and pH 11 at 25°, spontaneous decarboxylation took place, and tropanone was obtained directly in excellent yields. At pH 13, in agreement with Robinson's results, the dicarboxylic acid was obtained.

The experiments and results on the preparation of tropanone by Schöpf and Lehmann (10) support the theory of biosynthesis as their results given in Table I show.

TABLE I. Tropanone from Succindialdehyde (A) Methylamine Hydrochloride (B) and Acetonedicarboxylic Acid (C)

Reaction Series

I. M/45A, m/25B, m/20C, m/10 buffer; 25° C., time of reaction, 3 days.							
II. M/45A, m/25B, m/25C, m/12 buffer; 20-22° C., time of reaction 3 days.							
pH at beginning of experiment		3.0	5.0	7.0	9.0	11.0	13.0
pH at end of experiment	I	3.0	5.1	7.0	8.6	11.0	12.6
	II	3.3	6.0	7.0	8.2	10.7	12.6
m.p. of tropanone picrate	I	205	211	211	213	214	200
	II	215	212	210	205	204	210
per cent yield of picrate	I	47	54	65	66	86	3
	II	68	83	78	61	64	5

It is seen that at pH range 3-11 tropanone is immediately and directly obtained. At pH 13, in agreement with Robinson's results, the dicarboxylic acid is obtained. Thus, Robinson's theory of the biogenesis, with small modifications is substantiated, not that the dicarboxylic acid is formed first but tropanone is obtained directly.

If one of the intermediates were the monoester of acetonedicarboxylic acid, the expected condensation product would be the ketone corresponding to methylecgonine. Reduction of the ketone and esterification of the resulting carbinol would lead to compounds like cocaine and the truxillines.

Except for benzoylecgonine all are esterified with methyl alcohol. It has been shown experimentally that the monomethylester of the dicarboxylic acid condenses with methylamine and succindialdehyde at pH 5 to form carbomethoxytropanone. Benzoylecgonine might then result from a

secondary reaction in which the carbomethoxy group is hydrolyzed and the keto group reduced before the hydroxyl group is benzoylated. In vitro the hydrolysis of the $-COOCH_3$ proceeds faster than that of the $-O-CO-C_6H_5-$ group.

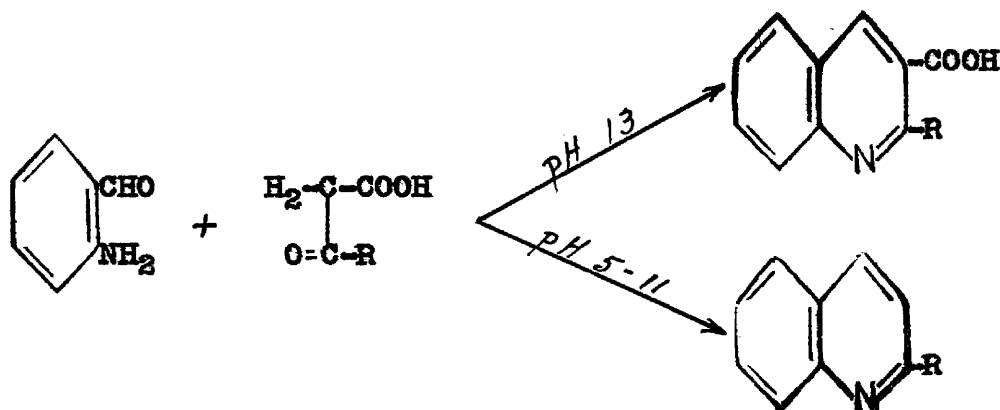
The results in the tropane series may be applied without modification to pseudo-pelletierine, a ring homolog of tropanone, which appears as such in nature. Robinson (11) obtained pseudo-pelletierine from glutardialdehyde, methylamine, and acetonedicarboxylic acid, and Schöpf (12) was able to prepare the same compound, using solutions buffered at pH 7 at 25°, in nearly quantitative yield.

In the bark of the South American Galipea officinalis are found a series of alkaloids which have been investigated by Späth and co-workers (13). They are the following: quinoline, quinaldine, α -n-amylquinoline, 4-methoxy-2-n-amylquinoline, galipine, cusparine, and galipoline. All of these are quinoline derivatives with substituents in the 2- and the 4-positions. The quinoline nucleus is not further changed, but in the 2-position are found the substituents, H-, CH_3- , $CH_3(CH_2)_4-$, and $C_6H_3(OH)_2-CH_2CH_2-$. This regularity leads to the assumption that the quinoline portion of the alkaloids is always formed from the same building blocks and that these combine with different other intermediates to form the remainder of the molecule.

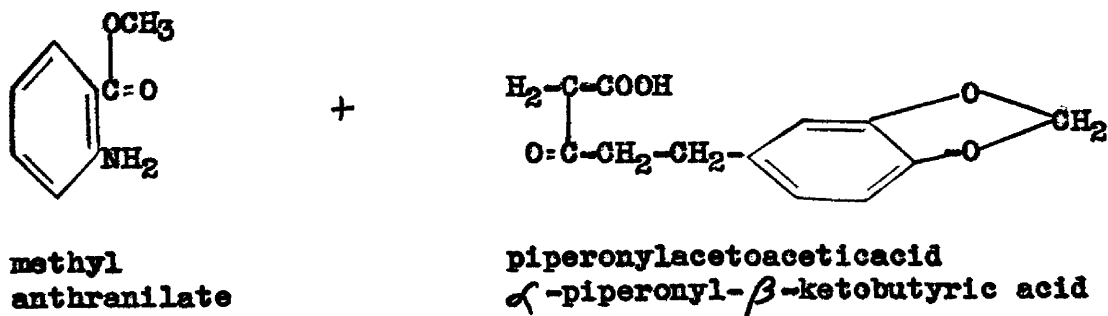
The alkaloids containing a quinoline nucleus could reasonably be supposed to be formed through a Friedländer type of synthesis, the condensation of o-aminobenzaldehyde with ketones. The oxidation product of o-aminobenzaldehyde, namely anthranilic acid, is found frequently in nature, and is observed as a degradation product from tryptophan. Methyl ketones are present in many ethereal oils. The biogenesis of the quinoline group appears to have its starting point in substances that may be

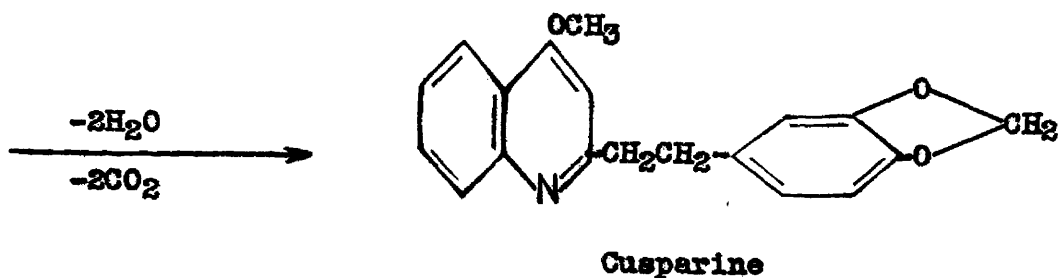
regarded as the progenitors of the methyl ketones, namely the β -keto-acids.

If o-aminobenzaldehyde is allowed to react, in dilute solutions, with acetoacetic acid or caproylacetic acid at various pH conditions, it is found that at a pH 13 the 3-carboxy compound is formed, but in the pH range 5-11 excellent yields of the 2-alkylquinoline are obtained (14).

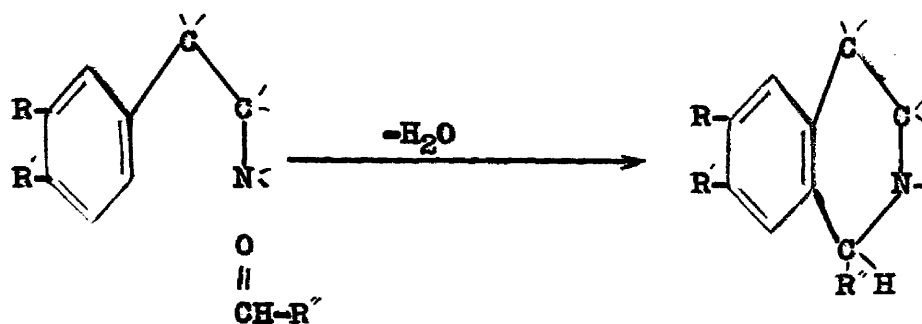


Schöpf and Lehman (14) advance the opinion that some of the angostura alkaloids are synthesized in the plant from methyl anthranilate, or anthranilic acid, and a β -ketoacid. Thus the biosynthesis of cusparine would involve methyl anthranilate and an acid, a condensation with a simultaneous decarboxylation in the following manner:



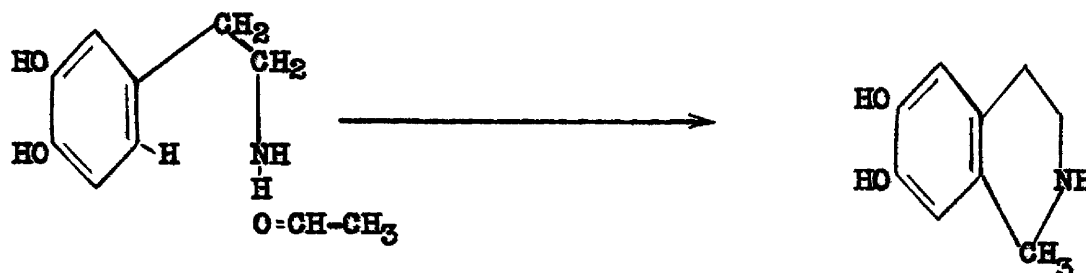


The manner of the biogenesis of the isoquinoline alkaloids has not been determined, but speculations in this respect are not lacking. A general mechanism would involve a condensation somewhat as follows:

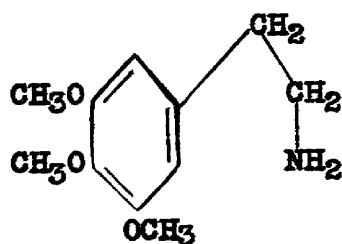


This followed by biological processes such as oxidation, reduction, etc., would account reasonably for the formation of the bases such as the mescaline compounds or the benzylisoquinoline derivatives. Aldehydes are known natural products and hence are readily explained. The necessary phenethylamine intermediate may very well be derived by biological degradation, oxidation, etc., from phenylalanine. Evidence for such a mechanism in nature may be presumed in the Bischler-Napieralski reaction. Here, however, the conditions are so drastic that biological conditions cannot duplicate them. Therefore, to check the hypothesis under conditions approximating nature with respect to pH range and temperature, Schöpf and Bayerle (15) allowed a solution of M/25 3,4-dihydroxyphenylethylamine and M/12.5 acetaldehyde to stand for three days at 25° at

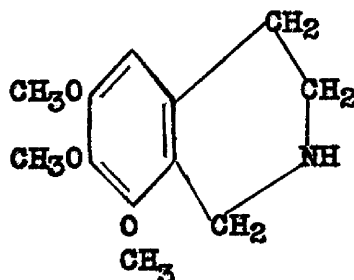
pH 5; at the end of that time they reported excellent yields of 1-methyl-6,7-dihydroxytetrahydroisoquinoline.



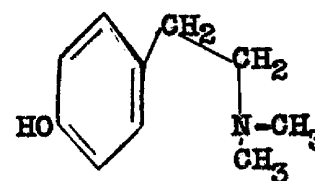
This reaction took place spontaneously and without the aid of enzymes or catalysts. It is not impossible that many natural products are prepared in quite an analogous manner. The methylation of hydroxyl groups or of a nitrogen atom is a possible cell reaction, and, therefore, the above mentioned isoquinoline derivative may be looked upon as the precursor of the natural bases Carnegine, Salsoline, and the anhalonium alkaloids which have been isolated from the mescal button, Anhalonium lewinii. The structures of these natural bases are:



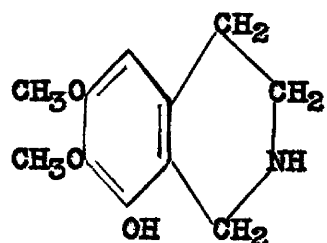
Mescaline



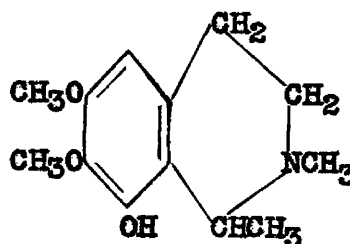
Anhalinine



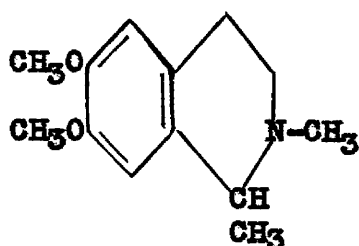
Anhaline



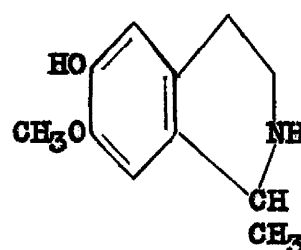
Anhalamine



Pelletine



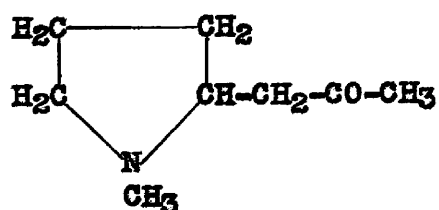
Carnegine



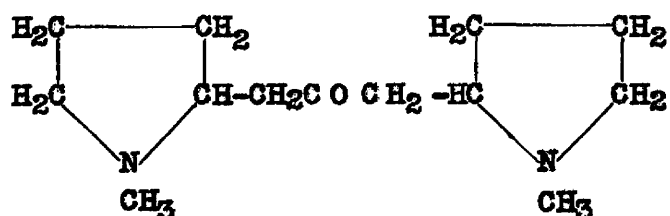
Salsoline

These closely related cactus alkaloids serve as an excellent illustration of the principle that the products of biosynthesis in the plant are structurally very similar. This holds true often not only for a single species, but also for closely related or allied species.

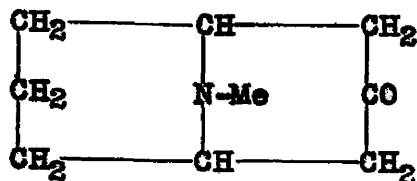
If one were to assume the six-membered ring of tropanone opened by the addition of two atoms of hydrogen, then one obtains the formula for hygrine, isolated from Peruvian cocoa. In a similar manner methylsalsoline corresponds to pseudopelletierine. Further, closely related to hygrine is cuskohygrine.



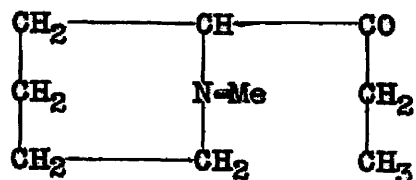
hygrine



cuskohygrine

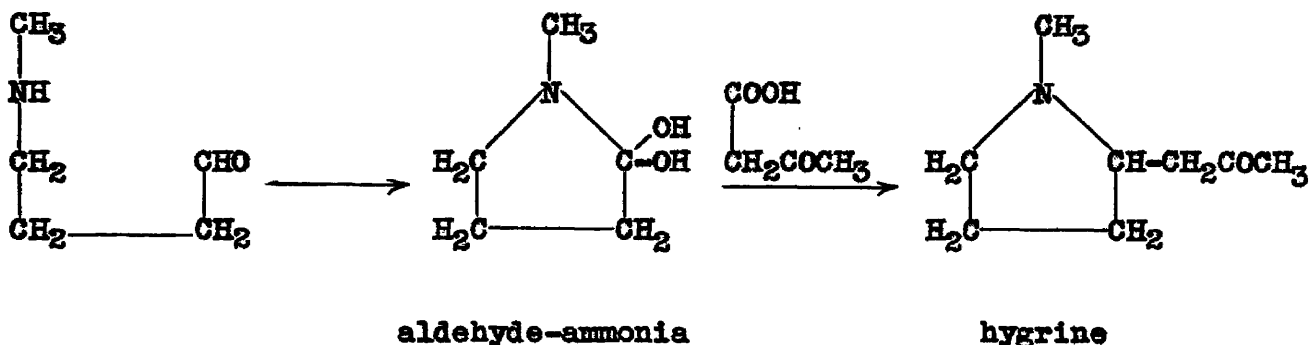


pseudopelletierine



methyloisopelletierine

It is natural to assume for these alkaloids an origin in the cell just as for tropanone and pseudopelletierine. Actually, Robinson (16) advanced the hypothesis that hygrine is obtained from γ -methylaminobutyraldehyde and acetoacetic acid.



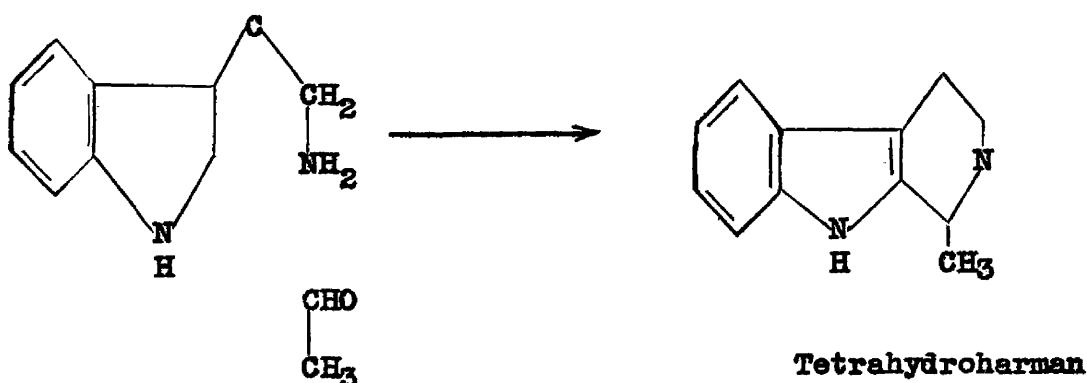
of γ -methylaminobutyraldehyde and acetonedicarboxylic acid. Methyloisopelletierine would then derive from δ -methylaminovaleraldehyde and pelletierine would then derive from β -methylaminovaleraldehyde and acetoacetic acid.

There can hardly be any doubt that the indicated synthesis will take place smoothly. The difficulties in carrying out the experimental tests, however, lie in the inability to obtain the necessary ω -methylaminoaldehydes. Robinson (17) overcame this difficulty by using

γ -aminobutyraldehyde, obtained by the oxidation of ornithine, $\text{NH}_2\text{---}(\text{CH}_2)_3\text{CH}(\text{NH}_2)\text{---COOH}$, with acetoacetic acid and obtained nor-hygrine. Schöpf (18) attempted to prepare the comparatively readily synthesizable diethylacetal of γ -aminobutyraldehyde, but the hydrolysis of the acetal did not form the aldehyde in appreciable amounts. Therefore, the acetal

was hydrolyzed at pH 5 in the presence of acetoacetic acid, with the hope that the liberated aldehyde would react as soon as it formed, but the desired reaction product could not be isolated. Success was achieved only when the comparatively unstable acetoacetic acid was replaced with the more stable benzoylacetic acid. Under these conditions the formation of the ketone $C_4H_4N-CH_2-CO-C_6H_5$ was proved, which fundamentally establishes the possibility for biogenesis according to the indicated reaction.

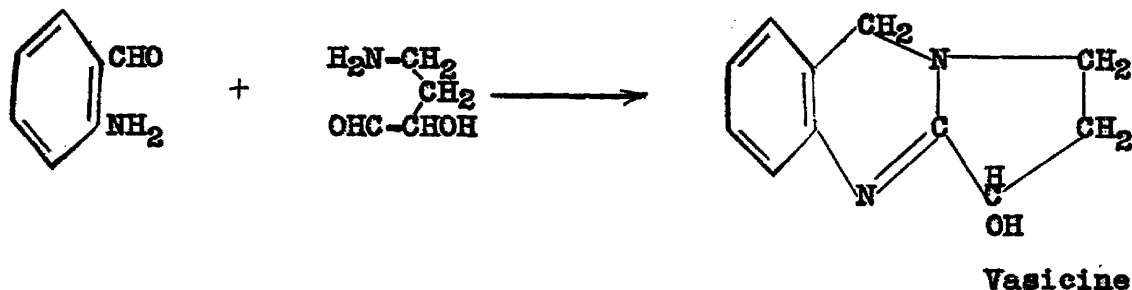
Structurally related to the alkaloids carnegine and salsoline, already discussed, are the harmala alkaloids, -harmaline, harmine and harman. By analogy for the biogenesis of the tetrahydroisoquinolines, the building unit must be tryptamine, derived from tryptophan by decarboxylation, or its 6-hydroxy or 6-methoxy derivatives. In this series, too, the mechanism has been subjected to direct investigation. Schöpf (19) condensed tryptamine with acetaldehyde under physiological conditions and obtained tetrahydroharman. Hahn (20) independently showed that tryptamine (M/14) condensed with acetaldehyde (M/7) at pH 5 and 25° to form tetrahydroharman, and then by loss of hydrogen forms dehydrogenated products.



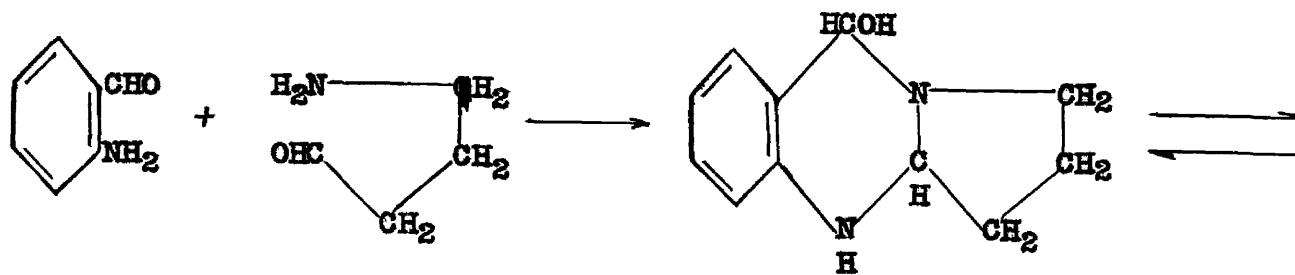
The reaction does not proceed satisfactorily with more complicated aldehydes, but succeeds with α -keto acids, which are probably the biochemical progenitors of the aldehydes (20). Thus, the possibility of the

reaction taking place within the cell was demonstrated, and this might well be the reaction for the biogenesis of the harmala alkaloids.

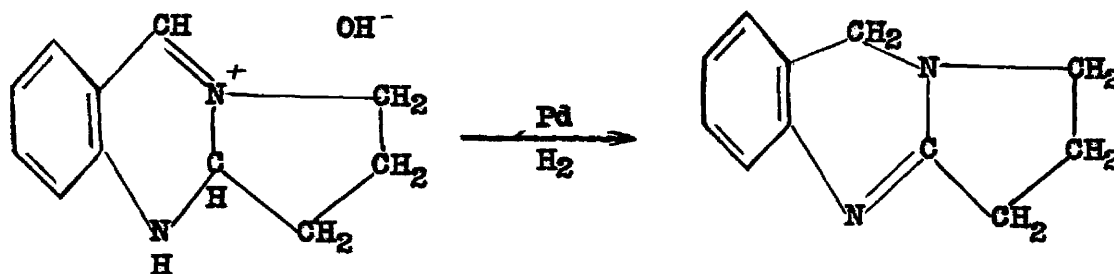
In numerous works, especially those of Späth and his co-workers (21), the constitution of vasicine, or peganine, has been confirmed by synthesis. It is seen that the molecule may be composed of two building blocks, namely, *o*-aminobenzaldehyde and α -hydroxy- γ -aminobutyraldehyde.



Unfortunately, α -hydroxy- γ -aminobutyraldehyde is not known, but γ -aminobutyraldehyde, in the form of the diethylacetal, is available, and the synthesis of desoxyvasicine by the use of this aminoaldehyde makes the above hypothesis of the biogenesis of vasicine seem reasonable. Schopf (18) found that in dilute solution, at pH 5, γ -aminobutyraldehyde-diethylacetal undergoes rapid hydrolysis and the liberated aldehyde condenses with *o*-aminobenzaldehyde to the pseudo-base I. The pseudo-base isomerizes to the colored quaternary ammonium base II, in which a shift of two hydrogen atoms takes place under the influence of palladium and hydrogen to form desoxyvasicine.



I. Pseudo-base



II. Ammonium base

Desoxyvasicine

This shows that a structure such as found in the ammonium configuration possesses the tendency to go over readily into the more stable configuration of desoxyvasicine, provided there is present in the plant a catalyst to aid the hydrogen shift.

What appears certain in the investigations described is the principle of aldehyde-ammonia formation and the condensation of aldehydes and aldehyde-ammonias with beta-keto-acids in manifold manners for the synthesis, under the mildest conditions, of numerous alkaloids, or their precursors. There may be a diversity of opinion on the question of the extent to which the plant employs the synthesis tried in the laboratory. In view of the fact that the assumed building blocks are cell-possible compounds and often yield practically quantitative amounts of product, and further, since the reaction takes place rapidly and may take place concurrently with other transformations of the building blocks, such as oxidation and reduction, there should be no particular objection to the

view that the syntheses described take place in the plant. A definite indication for the correctness of this assumption does not otherwise appear. Final proof will require controlled experiments in the living cell. Such experiments would be difficult and perhaps impossible.

The methods of synthesis under biological conditions may in time displace the synthetic methods used up to the present. They cannot do so now because the prerequisite starting materials are today still relatively unavailable. They will, however, be provided, especially when it is a question of synthesizing organic compounds which may be difficult to prepare by the usual procedures.

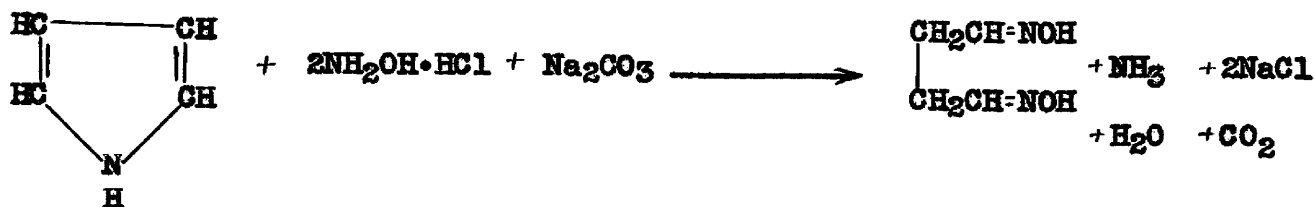
In spite of present disappointments, the success of the biosynthetic methods described is inspiring. It can be predicted that with refinements of technique and choice of more suitable reactants, syntheses of this type will be extended to afford a great deal of additional information on the probable mechanism of formation of the alkaloids in the plant.

METHODS OF PREPARING SUCCINDIALDEHYDE

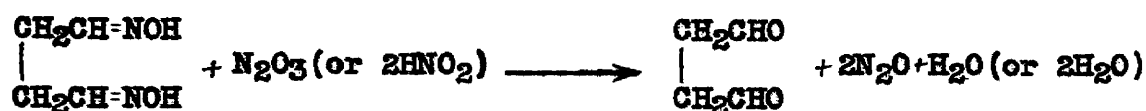
Following the work of Robinson (4) and Schöpf (12) on the synthesis of tropanone and related alkaloids, interest in the preparation of succindialdehyde has greatly increased.

The first mention of succindialdehyde is that by Soytzeff (22) in 1873, who claimed to have prepared it by the reduction of succinyl chloride with sodium amalgam. It was shown later, however, by Wislicenus (23) that Soytzeff did not have the dialdehyde but γ -butyrolactone.

In 1884 Ciamician and Dennstedt (24) prepared succindialdoxime by prolonged heating of an alcoholic solution of pyrrole, hydroxylamine hydrochloride, and sodium carbonate.



In 1901 Harries and co-workers (25, 26) converted the dioxime to the dialdehyde by allowing nitrous acid to act on the oxime after the method used by Claisen and Manasse (27) to convert isonitrosocamphor to camphor quinone.



Nitrogen trioxide for the preparation was generated by arsenic and nitric acid (Sp. Gr. 1.3) (28). The gas was bubbled rapidly through a well-cooled suspension of the oxime in water until fumes of N_2O were no longer evolved (29). The solution was neutralized with precipitated calcium carbonate and filtered. The filtrate was concentrated at reduced pressure in a stream of carbon dioxide at 30°C . The residue was transferred to another flask and the contents distilled rapidly at low pressure on an oil bath until the temperature reached 120°C . The fore-run contained some dialdehyde which was partly recovered by repeated fractionation (30). The aldehyde thus obtained was a glassy polymer. The monomer was later obtained by distilling the polymer at atmospheric pressure and fractionating the middle fraction at reduced pressure.

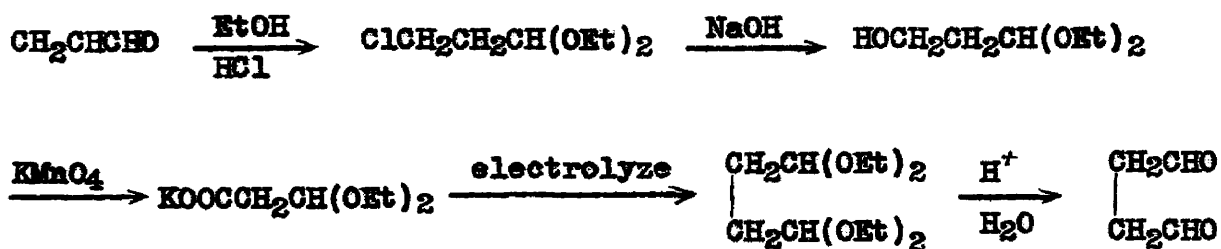
The yield of dialdehyde from pyrrole was increased by Willstätter and Heubner (31) and by Mannich and Budde (32). The former were able to obtain the dioxime from pyrrole in greater yield by increasing the quantity of hydroxylamine hydrochloride to the theoretical amount; the

latter obtained the dialdehyde from the oxime using ethyl nitrite instead of nitrous acid. This method of preparation removes the hazard of explosions in the use of nitrous acid with the oxime.

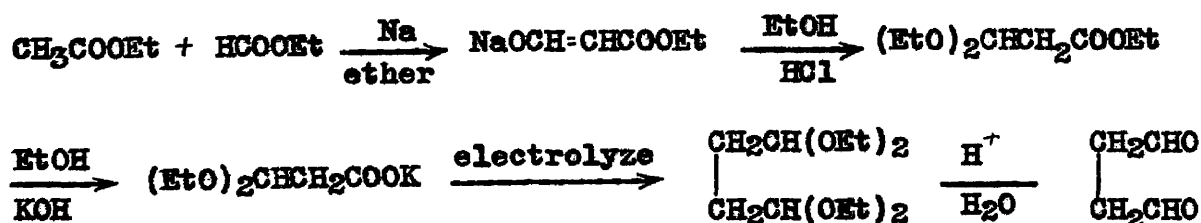
Succindialdoxime has been obtained from N-ethylpyrrole and hydroxylamine (33) and from the reduction of 1,4-dinitrobutane (34).

Harries (35) has presented some evidence that furan reacts with a methanolic hydrogen chloride solution to give succindialdehyde tetramethylacetal.

In 1906 Wohl and Schweitzer (36) electrolyzed the potassium salt of malonic semialdehyde diethylacetal to obtain succindialdehyde tetraethylacetal which was hydrolyzed to the free aldehyde:

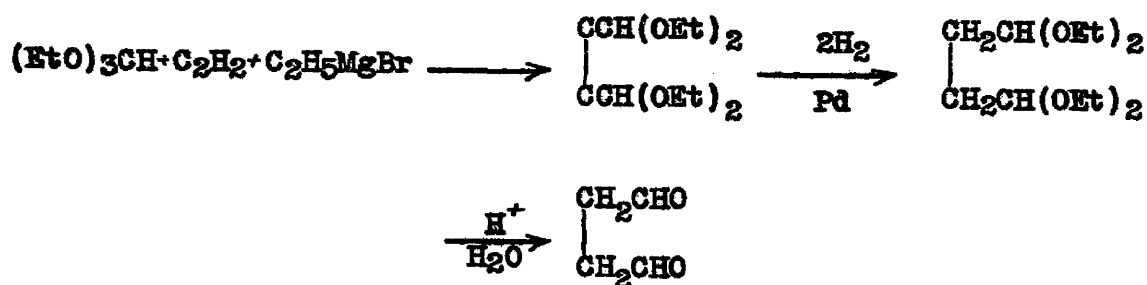


Sugasawa (37) in 1927 obtained the dialdehyde by the method of Wohl and Schweitzer (36) but prepared the intermediate potassium salt of malonic semiacetal by a different procedure:



Keimatsu and Yokota (38) in 1927 used acetylene, orthoformic ester, and ethylmagnesium bromide followed by the reduction of the substituted acetylene obtained to get the tetraethylacetal of succindialdehyde and

hydrolyzed the product to the dialdehyde:



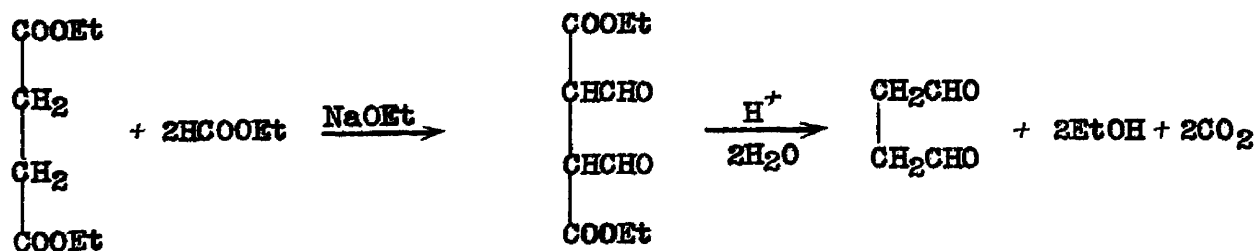
Marcilly and Blaise (39) in 1904 isolated a small amount of succin-dialdehyde among the oxidation products of certain unsaturated acids.

Turk (40) in 1905 prepared the dialdehyde by hydrolysis of diallyl diozonide.

Harries (41) in 1908 obtained it by the hydrolysis of cyclooctadiene 1,5 diozonide and in 1912 by the hydrolysis of the ozonides of certain butadiene polymers in the course of proof of structure (42).

A poor yield of the dialdehyde has been isolated from dehydrogena-tion products of 1,4 butandiol, but γ -butyrolactone is the chief product of the reaction (43).

In 1943 Yourtee (44) at the University of Maryland obtained succin-dialdehyde in 7-10% yield by the condensation of ethyl succinate with ethyl formate followed by hydrolysis and decarboxylation of the inter-mediate α,α' -diformylsuccinic ester which could not be isolated from the condensation reaction mixture:



The dialdehyde prepared was distilled in vacuo under dry nitrogen gas and the fraction boiling 61-65° at 10-12 mm was collected. The yield was 9.5% based on ethyl succinate used.

In addition to monomeric succindialdehyde, at least four polymeric forms have been described in the literature (45, 25). The monomer is a light, mobile liquid of sweetish but stinging odor; b.p./760 169-70° (sl.d.); b.p./11 65-70°; d_4^{18} 1.069; n_D^{18} 1.42397, n_D^{21} 1.42617, n_D^{30} 1.42667 (28, 46). It is easily soluble in all the common solvents, unstable in dilute acid solution and exceedingly unstable in dilute alkaline solution, and its vapors are corrosive to the skin and mucous membranes (25). It polymerizes readily on standing, especially under the influence of moisture, to a glassy form but will remain liquid for a long time in the dry, cold state in a well-stoppered container (28). It gives an intense blue color with Schiff's reagent (25), reduces Fehling's solution even in the cold (25), and yields derivatives with all the usual aldehyde reagents (45). Oxidation by $KMnO_4$ destroys the dialdehyde (26), HNO_2 yields succinic acid (29), and HNO_3 yields oxalic acid (26). Sodium amalgam in moist ether reduces the dialdehyde to tetramethylene glycol (26).

With water in a sealed tube at 180°, furane is formed; with phosphorous trisulfide, thiophene is formed; and with ammonia and acetic acid, pyrrole is the product (25).

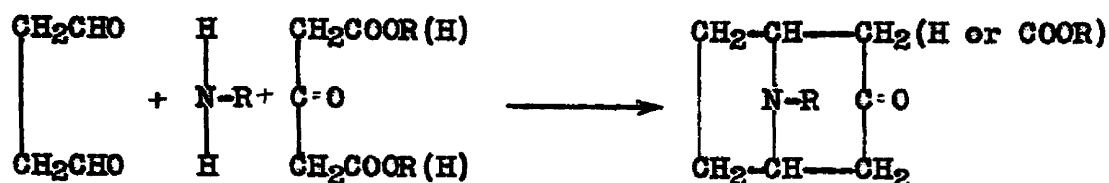
The so-called "glassy" form (probably pentameric) is a tough sticky substance with biting odor. It liquifies at 65° and boils at 169-70° at 760mm pressure to yield the monomer. It dissolves readily in alcohol but difficultly in water, ether, or benzene yielding a solution of the monomer. Its d^{19} 1.23 and n_D^{20} 1.47849 (25, 26, 28).

Three other polymeric forms (26) are solids. One, m.p. 64°, is prepared by dropping the "melted" glassy form into water at 50°. Evapora-

tion of a benzene solution of the monomer yields another form melting at 130-40°. An amorphous form, termed parasuccindialdehyde, is produced when an acetone solution of the aldehyde is allowed to stand with anhydrous oxalic acid. This is a white powder decomposing at 90-100°.

RESEARCH AIM

The success of Schöpf in proving the biogenesis of the tropane alkaloids, particularly the biosynthesis of the intermediate ketone, tropanone, is very inspiring. His work gave promise that homologs of tropanone might be synthesized according to the following equation:



The primary aim of this investigation was first, to duplicate Schöpf's results and, second, to extend the investigation to the preparation of tropanone homologs with the view in mind of synthesizing compounds related to atropine, cocaine, and tropacocaine, and testing them pharmacologically. It at once becomes apparent that such an investigation must be concerned first with the appropriate intermediate which may be converted into the desired alcohol or hydroxy ester, and then esterification studies may be undertaken.

The necessary starting materials are readily available with the exception of succindialdehyde. Since no satisfactory synthesis to date is available for the preparation of the dialdehyde, considerable time was spent in attempting to find a new method of synthesis.

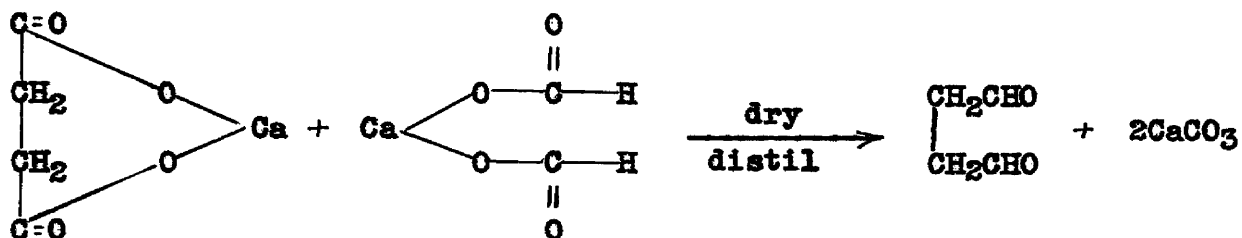
This dissertation describes:

- (a) Experimental work dealing with the attempted synthesis of succindialdehyde.
- (b) Condensation experiments leading to the formation of several tropanone homologs.
- (c) A catalytic method for the reduction of tropanone to tropanol.

EXPERIMENTALSUCCINDIALDEHYDE:

In view of the difficulty of preparing succindialdehyde by known procedures, as previously described, it was felt that new methods deserved consideration. The following hypothetical reactions were carefully considered and some of them were tried in the laboratory.

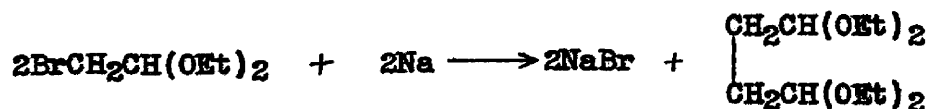
1. Dry distillation of mixed calcium succinate and calcium formate:



Since the distillation of the calcium or barium salts of higher acids with the same salts of formic acid is one general method for the preparation of aldehydes, it was thought that the above reaction might yield the desired dialdehyde.

When the mixed calcium salts, prepared in the usual manner from equimolar quantities of succinic and formic acids were heated in a distillation flask, copious quantities of carbon dioxide were evolved and no distillate was obtained in the receiver. The contents of the flask became very black and were very difficult to remove. This reaction was repeated twice without success and was not further investigated.

2. The Fittig reaction on bromoacetal to yield the tetraethylacetal of succindialdehyde:

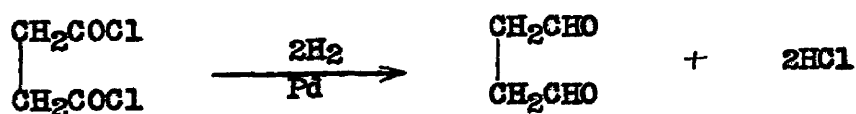


Diethylacetal was prepared according to the directions of Organic

Syntheses (47), and was converted into the α -bromo derivative by the method of Hartung and Adkins (48).

Into a 250 cc. flask fitted with a reflux condenser were placed 75-100 cc. of anhydrous toluene and 5 gm. of sodium wire. 40 gm. of bromoacetal was added slowly through the condenser, and when the addition was complete effervescence was noticed, the reaction mixture becoming light green in color. The reaction flask was heated on a hot water bath and the mixture allowed to reflux for three hours. At the end of this time the mixture was brown in color and a precipitate settled in the bottom of the flask. The contents were filtered and the filtrate fractionated using a long column. A small quantity of product distilling at 34-36° was obtained and identified as vinyl ethyl ether. This result was unexpected, but after consulting the chemical literature it was found that this reaction had already been tried and that, instead of succindialdehyde tetraethylacetal, the product was vinyl ethyl ether (49, 50).

3. A Rosenmund type of reduction of succinyl chloride:

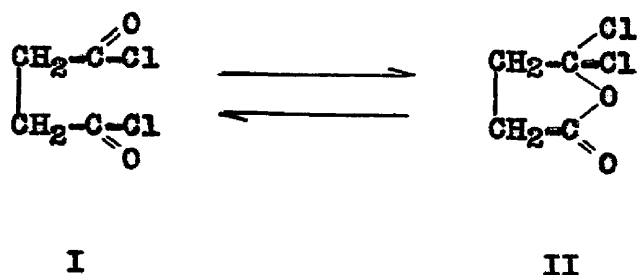


One of the general methods for the preparation of aldehydes described in text books consists of the reduction of acid chlorides, using palladium as a catalyst, according to the general equation:



Although this reaction is generally applicable for the acid chlorides of monocarboxylic acids, the reduction of succinyl chloride might be expected to take place in a similar manner.

However, two structures have been proposed for succinyl chloride:



Since formula I is the most widely accepted structure, and since this is the structure ascribed to the succinyl chloride available from the Eastman Kodak Company, it seemed reasonable to assume that the reduction of this substance, using palladium as a catalyst, might yield the corresponding aldehyde.

Succinyl chloride was prepared by the directions of Hartman (51) according to the following reaction.



using 1 mole of succinic acid and 2 moles of phosphorus pentachloride.

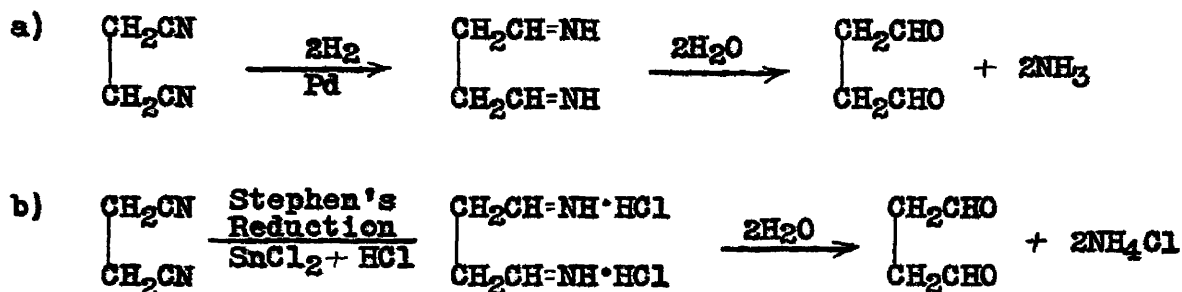
The yield of product distilling at 82-85°/15 mm. was 0.665 mole (103 gm.)

The palladium catalyst was prepared according to the directions of Hartung (52, 53). To 3 gm. Norite or blood charcoal was added 0.3 gm. palladium chloride crystals. This mixture was placed in a 250 cc. flask with 100 cc. distilled water and shaken in an atmosphere of hydrogen until saturated. The solution was filtered and the palladinized charcoal washed successively with distilled water and ethyl alcohol. The catalyst was dried in a vacuum desiccator over H₂SO₄ before use.

To 7.75 gm. (.05 mole) of succinyl chloride were added the palladium catalyst and 100 cc. of anhydrous benzene and the mixture hydrogenated in

a pressure bomb of the American Instrument Company at 10 atmospheres. The rate of absorption was followed by observing the fall in pressure on a gauge, previously calibrated. The expected hydrogenation did not take place and after several unsuccessful attempts was not further investigated.

4. The partial hydrogenation of succinonitrile to the di-imine which on hydrolysis should yield the dialdehyde:



It is known that benzyloxyamide may, under proper conditions, be reduced to the corresponding imine from which excellent yields of phenylacetaldehyde may be isolated (54). Analogous reactions with the dinitrile of succinic acid should then yield the corresponding dialdehyde.

Succinonitrile was prepared according to the method described in Organic Syntheses (55) for the preparation of trimethylene cyanide. The product distilled at 142-147°/12 mm., the yield being 70-75% of the theoretical. The nitrile is reported to distil at 185°/60 mm., and 158-60°/20 mm. (56).

To 2 gm. (.025 mole) of succinonitrile were added freshly prepared palladium catalyst, prepared as already described, and 100 cc. of commercial absolute ethyl alcohol. About 18 cc. of absolute alcoholic HCl, corresponding to 2 equivalents of HCl per mole, was added and the mixture hydrogenated in the pressure bomb at 10 atmospheres. Almost the theoretical amount of hydrogen was taken up in about 5 hours. Shaking was

continued for an additional 2 hours with no further fall in pressure. The mixture was then removed from the bomb and filtered by suction, the catalyst washed with a small quantity of commercial absolute ethyl alcohol, and the filtrate distilled at reduced pressure to remove almost all the solvent. The residue was taken up with a small quantity of absolute alcohol, saturated with ethyl ether, with the intention of isolating the imine-hydrochloride, and allowed to crystallize in the ice-box. Approximately 1.3 gm. of yellow crystalline material, melting at $168-9^{\circ}$ d, was obtained. A nitrogen determination using the Kjeldahl procedure was carried out, and the product was found to contain 18.14% nitrogen, whereas the calculated value is 17.83%. Using the Volhard procedure the compound was found to contain 77.85% chlorine, whereas the calculated value is only 41.40%. It did not reduce Fehling's solution but a strong, amine-like, disagreeable odor was evolved. When the hydrogenation was carried out in 70% ethyl alcohol without the presence of HCl, using Raney nickel in place of the palladium catalyst, the theoretical amount of hydrogen was absorbed in 4 hours. After filtering off the catalyst and washing it with 70% ethyl alcohol, the filtrate was found to be strongly basic and have a pungent amine-like odor. Since no trace of succindialdehyde resulted from the hydrogenation procedures, the method of synthesis was abandoned.

In 1925 Stephen (57) reported a new method for the synthesis of aldehydes the basis of which is the conversion of a nitrile through the imino-chloride (which need not be isolated) into an aldehyde with the same number of carbon atoms. The most suitable reducing agent is anhydrous stannous chloride dissolved in ether saturated with hydrogen chloride.

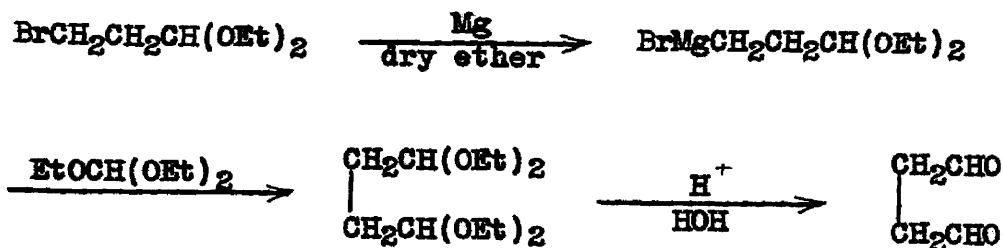
A simple method of preparing anhydrous stannous chloride is that of

Stephen (58) by treating $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (1 mole) with acetic anhydride (2 moles). The dehydration is almost instantaneous, much heat is evolved, and the anhydrous salt separates immediately. After being washed free from acetic acid with dry ether, it can be preserved indefinitely in a desiccator.

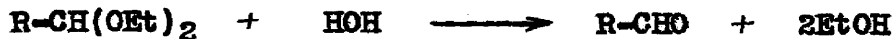
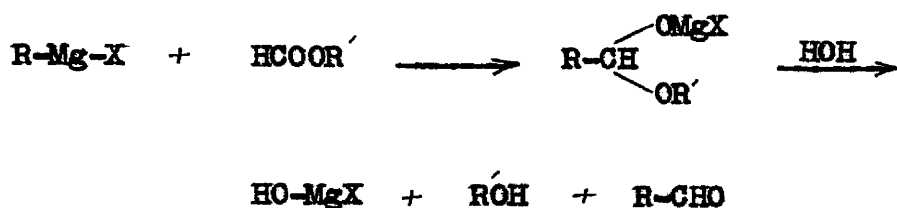
Since the reported method is applicable to aliphatic and aromatic nitriles and the yields usually almost quantitative, it was thought that this method of reduction should be tried on succinonitrile.

Into a 500 cc. round bottom flask containing 200 cc. of dry ether was suspended 35.6 gm. (.1875 mole) of the finely powdered anhydrous SnCl_2 . The mixture was saturated with dry HCl until two layers formed, the lower viscous layer consisting of SnCl_2 dissolved in ethereal HCl . Then 10 gm. (.125 mole) of succinonitrile dissolved in 25 cc. of chloroform was added and the mixture shaken vigorously. After a few minutes the mixture became quite warm, the ether layer began to boil, the lower layer became deep yellow in color, and after 10 minutes solidified to a gummy mass. Attempted hydrolysis of the resulting product did not produce any trace of succindialdehyde. Repeated attempts gave similar results. Inasmuch as a reaction, similar to that described by Stephen, did occur, lack of time prevented a thorough investigation of this reaction. The possibility of using this reaction for the synthesis of succindialdehyde was not ruled out by these negative results; the proper conditions for the reaction deserve to be more thoroughly investigated.

5. The formation of the tetraethylacetal by the reaction of ethyl orthoformate with the Grignard reagent from the acetal of β -bromopropionaldehyde:



Since another general method for the preparation of aldehydes is the reaction of the Grignard reagent with an alkyl formate, or with orthoformic ester,



it was thought that the indicated reaction might yield succindialdehyde.

β -Bromopropionaldehyde diethylacetal was prepared according to the general directions of Nef (59) using acrolein and alcoholic HBr. Into a 500 cc. three-neck flask, surrounded by an ice-salt bath kept at 0° C., and fitted with a mechanical stirrer, reflux condenser, and a separatory funnel, was placed 212 gm. saturated ethanolic HBr; to it was added through the separatory funnel, over a period of 30 minutes, 100 gm. acrolein (E. K. & Co.). A short time after all the acrolein had been added the mixture became very dark brown in color. The stirring was continued for an additional hour, after which time an oily mixture was obtained. This was neutralized first with anhydrous sodium carbonate; then approximately 250 cc. of ether was added and the solution transferred to a separatory funnel and washed with a saturated sodium bicarbonate solution.

The organic layer was dried over a mixture of anhydrous sodium sulfate and potassium carbonate for 12 hours. It was filtered into a Claisen flask and after removal of the ether was distilled under reduced pressure. Because a large amount of decomposition accompanied the distillation, only 20 gm. of the acetal of β -bromopropionaldehyde distilling at 50-60°/5 mm. was obtained. The product, slightly acid to litmus, was neutralized with anhydrous potassium carbonate. Several attempts to form the Grignard reagent in the usual manner with magnesium turnings were unsuccessful.

Before abandoning this approach, the acetal of β -Chloropropionaldehyde was prepared by the method of Witzeman (60) and of Evans and Hass (61), but it proved equally unreactive with metallic magnesium.

This non-reactivity of the β -halogeno derivatives of propionaldehyde is surprising, for ordinarily such halogen atoms are considered labile and quite reactive.

Since the proposed methods for the preparation of succindialdehyde from available intermediates and by adaptation of established procedures proved disappointing, attention was next turned to the most attractive synthesis described in the chemical literature, namely, the conversion of pyrrole into the dialdehyde, via the dioxime. The dioxime was prepared according to the method of Willstätter and Hübner (62), whose directions were also followed by Schöpf (12). These investigators converted the dioxime into the dialdehyde by means of N_2O_3 . It was found, during the present investigation, more advantageous to use HNO_2 rather than its so-called anhydride.

Preparation of succindialdioxime. Into a 2 liter three neck flask, fitted with a mechanical stirrer and reflux condenser were placed 1 liter of 95% ethyl alcohol, 67 gm. (1 mole) freshly distilled pyrrole (Eastman's practical grade), and 141 gm. (2 mole + excess) of hydroxylamine hydro-

chloride. A water bath, heated on a hot plate, was placed under the reaction flask and the stirring begun. As soon as the hydroxylamine hydrochloride was completely dissolved, 106 gm. (1 mole) of anhydrous sodium carbonate was added, in small portions, to the colorless solution as rapidly as possible, and the mixture was refluxed for 24 hours. During this time the solution turned from colorless to light brown. The hot alcoholic mixture was filtered through a sintered glass funnel and the filtrate concentrated to dryness under diminished pressure. The light brown residue was removed from the distilling flask with the smallest quantity of cold water and filtered. The product was dissolved in the minimum quantity of boiling water, decolorized with charcoal, and allowed to crystallize in the ice-box overnight. After filtering and concentrating the filtrate, 40-44 gm. (35-38%) of succindialdoxime was obtained, melting at 171-172°.

Numerous attempts were made to increase the yield. The time of refluxing was varied from 18 to 30 hours; freshly distilled synthetic pyrrole (Eastman) was used in place of the practical grade; the time of addition of sodium carbonate was varied from 15 minutes to over a period of 8 hours; and in all cases the yield of product was not appreciably affected. However, when hydroxylamine sulfate was used as the source of hydroxylamine, only a few grams of succindialdoxime was obtained.

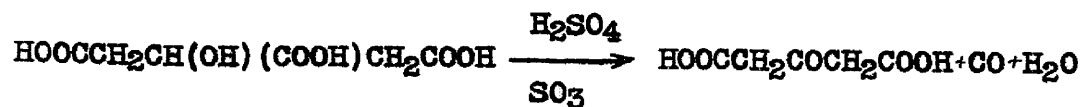
Preparation of succindialdehyde from succindialdoxime. 5.8 gm. (.05 mole) of succindialdoxime was placed into a 250 cc. beaker, 54 cc. of 10% H_2SO_4 was added, and the mixture cooled to 0° C by means of an ice-salt bath. Then 7 gm. (0.1 mole + 0.1 gm. excess) of sodium nitrite was added in small portions, the temperature of the mixture being kept at 0° C. Brown fumes of NO_2 indicate a too rapid addition of $NaNO_2$. The dioxime was completely dissolved after all the $NaNO_2$ was added. The

temperature was allowed to rise gradually to 15-20° until effervescence ceased. The solution was a lemon-yellow color at this point. It was then neutralized to litmus by the addition of small portions of BaCO₃, the mixture filtered with suction, and the residue washed with a small quantity of water. The theoretical yield of succindialdehyde is 4.3 gm. (.05 mole). In order to determine the yield of dialdehyde by this procedure, a portion of the aqueous filtrate corresponding to .01 mole of dialdehyde was used to prepare the 2,4-dinitrophenylhydrazone, according to the procedure described by Shriner and Fuson (63). The yield of crude product after washing with alcohol and drying was 4.01 gm. (90%) and melted at 268-270° (dec.) The reported melting point of the derivative is 278-80° (dec.) (64). This substance exhibited unusual electrical properties. When freshly rubbed, the yellow crystals would cling to the walls of a glass vessel and it was difficult to get them into a melting point tube. When spread on a piece of paper under which rubbed ebony was moved the crystals acted as do iron filings in a magnetic field. The semicarbazone, phenylhydrazone and sodium bisulfite addition product were prepared by the method of Harries (65, 66), and the melting points for the semicarbazone (187-8°) and the diphenylhydrazone (125-6°) agreed with those reported.

In his work on the synthesis of tropanone Schöpf presumably used the pure dialdehyde. However, in this investigation, the aqueous solution of the dialdehyde, resulting from the action of HNO₂ on the dioxime, was used.

ACETONEDICARBOXYLIC ACID:

This material is prepared from citric acid, using fuming sulfuric acid, according to the equation:



Satisfactory quantities were synthesized using the directions of Organic Syntheses (67). The yield of light gray to white product was 75-80%. As the acid itself is unstable, the material was used as quickly as possible in the synthesis of tropanone and its homologs. However, Wiig (68) observed that if the acid is purified by recrystallization from ethyl acetate three times and thoroughly dried it undergoes no decomposition, at least over a period of seven months, when kept at room temperature in a desiccator. In this investigation the acid mixture was filtered through a large sintered glass funnel, and after the suction and pressing had removed practically all of the sulfuric acid, the crystals were stirred in the funnel with sufficient cold ethyl acetate to make a thick paste, and then sucked dry. This washing with ethyl acetate was repeated twice, then once with petroleum ether, followed by two washings with absolute ether. The product was thoroughly dried and was kept without noticeable decomposition for several weeks in an evacuated desiccator (1 mm.) over H_2SO_4 . Even though the washings decreased the yield somewhat, the product could be kept satisfactorily until used. When Wiig's method of recrystallization from ethyl acetate was tried, a large amount of the acid could not be recovered.

CONDENSATION REACTIONS:

Since succindialdehyde may be obtained in 90% yields or better from the dioxime, as already described, solutions of known concentrations may thus be obtained directly. In trial condensations, aqueous solutions of

the dialdehyde were prepared. A typical reaction was carried out as follows:

A twentieth mole (5.8 gm.) succindialdoxime, placed in a 250 cc. beaker, was treated with 54 cc. of 10% sulfuric acid; to the mixture, cooled to 0°, was slowly added, over the period of about an hour, 7.0 gm. crystalline sodium nitrite (0.1 mole + 0.1 gm. excess), the temperature being kept at 0°. The temperature was then allowed to rise slowly to room temperature, and after effervescence had ceased, the solution was made neutral to litmus by the addition of BaCO₃ in small portions until carbon dioxide was no longer given off. The precipitated BaSO₄ was then removed by suction and washed with a small amount of water. The volume of the filtrate and washings was then adjusted to 100 cc. An aliquot portion, or 20 cc., representing 0.01 mole of the original dioxime, was withdrawn, treated with 2,4-dinitrophenylhydrazine, and a yield of bis 2,4-dinitrophenylhydrazone of 0.009 mole was obtained. It was assumed, therefore, that the remaining 80 cc. of solution contained 0.036 mole succindialdoxime.

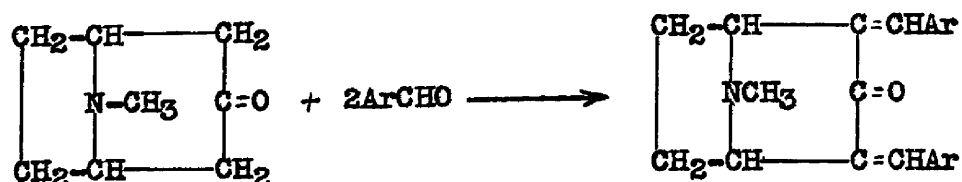
Fifty cc. of the aldehyde solution, corresponding to 0.0225 mole or 1.94 gm. of succindialdehyde, was diluted with about 200 cc. of water and placed in a liter flask. To this was added 7.3 gm. (0.05 mole) acetonedicarboxylic acid and 2.7 gm. (0.04 mole) methylamine hydrochloride (previously recrystallized from ethanol). Then a saturated solution of Na₂HPO₄ was added until the pH, as measured on a Beckman pH meter, was 7. The volume of the solution was then made up to a liter, without appreciable change in the pH. At this point the solution was clear amber color, and effervescence was observed. It was allowed to stand at room temperature for three days.

Since tropanone is very soluble in water, and since the yield, even

if theoretical, would at best be 0.0225 mole or 3.1 gm., it would be difficult to isolate all of the product from so dilute a solution. Consequently, in the preliminary condensation reactions, the yield of tropanone was determined by its conversion into an insoluble derivative whose quantitative formation and precipitation could be relied on, either the picrate or the dipiperonylidene derivative.

After completion of the reaction, 100 cc. of the solution was cooled to 5°, saturated with K_2CO_3 , and repeatedly extracted with ether. The combined ethereal extracts were dried over anhydrous Na_2SO_4 and the solvent volatilized on a steam bath, to leave a residue of about 25 cc. To this was added a solution of ether saturated with anhydrous picric acid; a yellow precipitate formed immediately. After an hour the solid was removed on a tared sintered glass funnel, washed with anhydrous ether and dried. The solid weighed 0.511 gm. representing 5.11 gm. for the total reaction. Since the molecular formula for the picrate is $C_{14}H_{16}O_8N_4$ (m.w. 368) (12) this corresponds to 0.014 mole, or a yield of 62.4%. The picrate, after recrystallization from water, melted at 220°. This agrees with the figure quoted by Schöpf (10).

A second condensation using 1.94 gm. succindialdehyde (prepared in solution as described above), 7.3 gm. acetonedicarboxylic acid, and 2.7 gm. methylamine hydrochloride, in a liter of solution, was carried out as before. The extractive from 100 cc. of the solution was converted into the dipiperonylidene, derivative according to the following equation (4):



The insoluble, crystalline product was removed, weighing 0.50 gm., corresponding to 5.0 gm. for the total reaction. Theory 9.1 gm., or 55% yield.

These reactions showed that it was possible to determine the extent of condensation, at least for comparative purposes, by isolating a tropanone derivative rather than the highly soluble tropanone itself.

Dipiperonylidene tropanone was prepared by the method of Robinson (4) and its properties agreed with those given by him. An aliquot portion representing 0.00225 mole of theoretical tropanone from a condensation mixture was extracted with ether. To the extractive was added 1 gm. piperonal in 25 cc. ethanol and 0.8 gm. KOH in 5 cc. water. The solution was refluxed for 15 minutes, turning reddish-brown almost immediately, and the yellow derivative separated during this time. After the addition of water and cooling, the solid was collected in a sintered glass funnel, washed with water and alcohol, and crystallized from ethyl acetate. Robinson reported that a practically quantitative yield may be expected, an observation that was confirmed when pure tropanone later became available.

Dipiperonylidene tropanone separates from ethyl acetate in bright yellow needles melting at 214° , and is sparingly soluble in most organic solvents. If it is rubbed on the side of a test tube and H_2SO_4 added, the substance acquires a coppery lustre and then passes into an intense royal-blue solution. This becomes green and finally yellow on dilution with water.

Since one of the aims of this investigation was to repeat and check Schöpf's results on the synthesis of tropanone under biological conditions, this task was next undertaken. It was necessary to spend considerable

time investigating his synthesis of tropanone and setting up "standard" conditions, because he did not publish full experimental details of the reaction.

The following were the "standard" conditions adopted for the synthesis of tropanone from succindialdehyde, methylamine hydrochloride, and acetonedicarboxylic acid in aqueous solution: Succindialdehyde solution obtained from 5.8 gm. dioxime, as already described, was made up to a known exact volume and divided into two equal portions. One portion, containing 1.94 gm. dialdehyde based on an established conversion of 90% from the dioxime, was placed into a liter flask containing approximately 200 cc. of distilled water. Then 7.3 gm. (.05 mole) or 5.84 gm. (.04 mole) of acetonedicarboxylic acid and 2.7 gm. (.04 mole) of methylamine hydrochloride were added, followed by the addition of a saturated solution of Na_2HPO_4 until the desired pH of the solution, determined by the Beckman pH meter, was obtained. After adjusting the volume to one liter and to pH between 5 and 7, the clear amber solution was allowed to stand for 3 days at room temperature. The yield of product was determined by isolating from an aliquot portion either the picrate or the dipiperonylidene derivative. These conditions consistently gave yields of tropanone that agreed favorably with those reported by Schöpf (10).

The difference in yields when the condensation was carried out at pH 5 to pH 11 was not as great as Schöpf recorded, as shown in Table II.

TABLE II. Influence of pH on Yield of Tropanone

pH of Exp't.		yield observed	yield by Schöpf
at beginning	at end		
5.0*	5.1		54%
5.20	5.71	58.1%	
7.0	7.0		65%
7.05	7.46	62.4%	
11.0	10.7		64%
11.02	9.85	60.3%	

*Schopf did not explain how he adjusted the pH with the accuracy that his figures indicate.

It was early found that for 0.0225 mole succindialdehyde, the acetonedicarboxylic acid may be varied from 0.04 to 0.05 mole without affecting the yield of tropanone.

Under the "standard" conditions the yield of tropanone, even at 100%, would be 3.1 gm. From the manipulative angle it would be desirable to work with smaller volumes, i.e., higher concentrations. A series of experiments showed that this is possible. By keeping the ratio of reagents constant, namely,

0.0225 mole succindialdehyde
 0.04 mole acetonedicarboxylic acid
 0.04 mole methylamine hydrochloride

the yield of tropanone from more concentrated reaction solutions are shown in Table III.

TABLE III. Effect of Concentration on Yield of Tropanone

Volume	pH	Gms. Picrate	% Yield
1000 cc.	7.1	5.17	62.4
500 cc.	11.02	5.0	60.3
250 cc.	10.9	4.15	50.0*

*This figure is too low because some of the product was lost before precipitation as the picrate. Time did not permit a repetition of these conditions, but it is believed that the actual yield would be very nearly that obtained in the higher dilutions.

When 23.2 gm. (0.2 mole) of succindialdoxime was converted into the dialdehyde by the described procedure, using 28 gm. of NaNO_2 and 216 cc. of 10% H_2SO_4 , the aqueous solution obtained, corresponding theoretically to 0.2 mole succindialdehyde, or actually 0.18 mole, was allowed to react with 21.6 gm. (0.32 mole) methylamine hydrochloride and 46.72 gm. (0.32 mole) acetonedicarboxylic acid. The pH was adjusted to 5.5 to 6 with a saturated solution of Na_2HPO_4 in the usual manner, and the volume of the solution was made up to 2 liters. A second reaction was carried out using the same quantities and conditions described above. The crude tropanone, obtained by combining the extractives from the two reactions, was distilled under diminished pressure, and the product distilling at $113^\circ/25$ mm. was collected. The white crystalline material was removed from the receiving flask with petroleum ether, the solution transferred to a crystallizing dish, and the solvent allowed to evaporate, whereupon the white crystals reappeared. The last traces of petroleum ether were removed in an evacuated desiccator, and the product was found to weigh 27 gm.

The theoretical yield of tropanone, assuming 90% conversion of succindialdoxime to the dialdehyde, was 0.36 mole or 50 gm. The yield, based on aldehyde, therefore, was 54%. On the basis of 60 to 65% yields of tropanone, 30 to 32.5 gm. to be expected, 83 to 90% of the available tropanone was isolated in pure form.

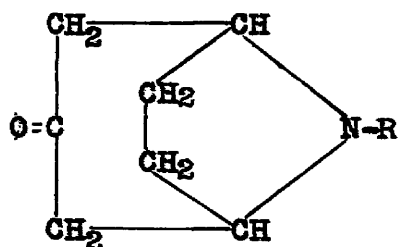
HOMOLOGS AND ANALOGS OF TROPANONE:

A further aim in this investigation was to determine whether tropanone with the N-methyl replaced by other alkyl groups may be obtained. That is, in these condensations is it possible to replace the methylamine with other primary amines to obtain the corresponding N-substituted tropanone homologs or analogs? Accordingly, the "standard" conditions for condensation were repeated but the methylamine replaced by the following:

- 1) ethylamine
- 2) isopropylamine
- 3) benzylamine
- 4) ethanolamine

The products of the respective condensation reactions were isolated as the dipiperonylidene derivatives except for the isopropyl compound, which was isolated as the picrate. The data are summarized in Table IV.

TABLE IV. N-Homologs and Analogs of Tropanone

Dipiperonylidene Derivative

R=	Mol. Form.	m.p.	% Yield	Analysis	
				Calc. N	Found N
-C ₂ H ₅	C ₂₅ H ₂₃ O ₅ N	184-5°	71.9	3.34	3.18 3.12
-CH ₂ C ₆ H ₅	C ₃₀ H ₂₅ O ₅ N	194-5°	30.0	2.89	2.89 2.85
-CH ₂ CH ₂ OH	C ₂₅ H ₂₃ O ₆ N	230-1°	63.4	3.23	3.06 2.98
-CH(CH ₃) ₂ *			51.6		

*Product isolated as the picrate and not analyzed. However, the behavior of the condensation reaction and the nature of the product encourage the belief that N-isopropyl-nor-tropanone was formed.

The appearance of the condensation reaction as it progressed with these other primary amines was quite like that when methylamine was used. Although the tropanones themselves were not isolated, their derivatives behaved quite as was expected. The analyses confirm the formation of the anticipated products. Time did not permit the further study of these reactions, but it is confidently believed that they do take place, and there is no reason to doubt that the corresponding tropanones may be obtained in satisfactory yields and that the ketones may be converted into the corresponding tropanols. It may, however, be necessary, with high molec-

ular weight or insoluble amines to modify somewhat the conditions to facilitate the proper condensation. For example, a single experiment with phenylethanolamine, $C_6H_5CHOHCH_2NH_2$, was unsuccessful. Since only a small amount of this aminoalcohol intermediate was available, it could not be determined whether the poor results were due to the physical or chemical character of the amine.

REDUCTION OF TROPANONE:

The reduction of tropanone to either or both of the stereoisomeric tropanols, in which the hydroxyl group may be cis or trans with respect to the nitrogen bridge, has been mentioned. Given tropanone, the technical preparation of homatropine and tropacocaine would be a comparatively simple matter, if the reduction of tropanone to tropanol or pseudo-tropanol could be accomplished. Willstätter (70) found that when tropanone was reduced electrolytically or by zinc dust in hydriodic acid, a mixture of tropanol and pseudo-tropanol was produced and could be separated by fractional precipitation of the picrates, tropanol picrate being the less soluble.

Since a catalytic method for the reduction of tropanone apparently has not been reported, this type of reduction was investigated.

A twentieth mole, 6.95 gm., of pure tropanone was dissolved in 150 cc. of benzene, 3 gm. of activated palladium catalyst, made with sodium acetate (71), was added and the mixture shaken in hydrogen at atmospheric pressure. Only a very small quantity of hydrogen was absorbed in 2 hours, so the catalyst was filtered off, 0.1 gm. of PtO_2 was added to the filtrate, and the mixture hydrogenated again. Over a period of 9 hours, approximately one-half of the theoretical amount of hydrogen was absorbed. The reduction mixture was then transferred to the bomb and

the hydrogenation completed under 10 atmospheres in 45 minutes. The mixture was removed from the bomb and the benzene taken off under diminished pressure. The residue was taken up with a small quantity of ether and 200 cc. of saturated solution of picric acid in ether was added. The picrate obtained was found to weigh 4.0 gm. and melted at $275-6^{\circ}$ (dec.). The reported decomposition point for tropanol picrate is 275° (72). Upon addition of more ethereal picric acid, 13 gm. of picrate was obtained and found to melt at $215-8^{\circ}$ (dec.). Since the reported decomposition point for pseudo-tropanol picrate is $258-9^{\circ}$ (72), and since the picrate decomposed at the same temperature after recrystallization from water, a mixture of tropanol and pseudo-tropanol was indicated.

The observation that the absorption of hydrogen was rapid when PtO_2 was used under pressure suggested the use of this catalyst for the reduction of tropanone.

A second reduction of 6.95 gm. (.05 mole) of pure tropanone was carried out. The ketone was dissolved in 150 cc. of commercial absolute alcohol, 0.1 gm. PtO_2 was added, and the mixture hydrogenated in the bomb at 10 atmospheres. The theoretical amount of hydrogen was absorbed in one hour. Shaking was continued for an additional hour. The mixture was then removed from the bomb, filtered by suction, and the filtrate distilled under reduced pressure to remove the alcohol. The residue was distilled and the fraction distilling at $120-5^{\circ}/15$ mm. collected. The distillate was a colorless syrupy liquid, but on being transferred to a beaker and cooled by an ice-bath, it solidified. The hygroscopic crystals weighed 6 gm. A portion of the material was converted into the picrate which, after recrystallization from water, was found to melt at 275° (dec.), indicating that the reduction product was entirely tropanol. Since fur-

ther evidence was desired, the remainder of the reduction product was converted into tropanyl benzoate hydrochloride according to the method of Cliff and Tutin (73) by adding an excess of benzoyl chloride to the base and heating the mixture to the boiling point. An additive compound of the base and acid chloride appeared first to be formed, but when the temperature was raised, this soon redissolved, whereupon the hydrochloride of the benzoylated base rapidly separated. The cooled mixture was then diluted with ether and the hydrochloride collected. After being once crystallized from commercial absolute alcohol, it melted and decomposed at $267-8^{\circ}$ in agreement with the product described by Cliff and Tutin.

Discussion of Results

The suggestion by Willstätter and Robinson, more fully developed by Schöpf, that many products may form naturally if the appropriate intermediates occur simultaneously within the cell is philosophically intriguing. Schöpf's work shows that this idea is amenable to laboratory proof. The implications are numerous.

In the course of the present investigation the experimental conclusions of Schöpf have been substantially verified so far as the biogenesis of the tropanone alkaloids is concerned. Not only does this confirmation shed light on the possible mechanisms employed by the plant, but it also suggests new approaches for the chemist's consideration in synthesizing natural products or related compounds.

For example, could succindialdehyde be obtained in satisfactory amounts, and at a reasonable cost, the synthesis of tropanone should prove practicable and economical. The reduction to tropanol, or to ψ -tropanol, and esterification of the alcohol will then give new sources

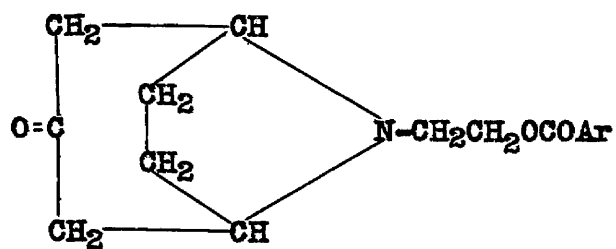
of medicinally important products.

Again, Schöpf's suggestion that cocaine arises from a similar condensation, where the monomethyl ester of acetonedicarboxylic acid is employed, promises also to become a practicable synthetic source for that alkaloid. In this instance, assuming that a good source of succindialdehyde becomes available, the key intermediate will probably be the monomethyl acetonedicarboxylate, for the conversion of the condensation product to methylecgonine should offer no difficulty, and the benzylation of methylecgonine to form cocaine is an established reaction.

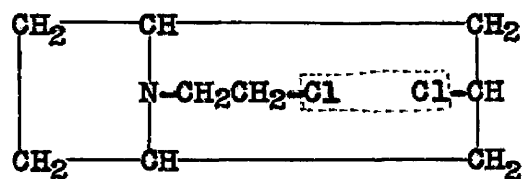
It has been established that a nine-fold increase in the "biological" concentration employed by Schöpf does not appreciably affect the yield of tropanone. It is not presumed that even this is the highest concentration. A series of experiments should be undertaken to determine the best conditions for optimum yields of tropanone.

It has also been established that not only methylamine will condense under these conditions employed. Other primary amines react quite as well to give the higher homologs or analogs of tropanone. It requires no imagination to see that these may also be reduced to the corresponding tropanol or ψ -tropanol compounds, which on proper esterification may be converted into atropine-like or tropacocaine-like compounds. Or, if in the condensation acetonedicarboxylic acid is replaced by its monoalkylester, the analogous cocaine-like compounds may be expected. The physiological properties of such compounds merit investigation.

The use of an alkanolamine, as shown by the results with ethanolamine, leads to a tropanone in which the alkyl group on the N-atom bears an alcoholic hydroxyl. Esterification with an aromatic acid will introduce a new anesthesiophore structure in a cocaine-like molecule, for example,



Or if in such a tropanone, the ketone is reduced to the carbinol and both hydroxyl groups are replaced by halogen atoms, the prospect of forming a substituted quinuclidene appears, as follows:



SUMMARY

1. The possibility of synthesizing succindialdehyde was investigated. The reactions tried were:
 - a. The dry distillation of mixed calcium succinate and calcium formate.
 - b. The Fittig reaction on bromoacetal to yield the tetraethylacetal of succindialdehyde.
 - c. A Rosenmund type of reduction of succinyl chloride.
 - d. The partial hydrogenation of succinonitrile, either catalytically or by the Stephen Method, to the di-imine which on hydrolysis should yield the dialdehyde.
 - e. The formation of the tetraethylacetal by the reaction of ethyl orthoformate with the Grignard reagent from the acetal of β -bromopropionaldehyde.

All results were negative. However, the Stephen reduction of succinonitrile may merit further attention.

2. The dioxime of succindialdehyde was obtained in yields of 35 to 38% from pyrrole.

3. The dioxime was converted into the dialdehyde in yields of at least 90%, and for use in these investigations, the aqueous solution, as obtained, proved entirely satisfactory. This obviated the necessity for isolating an elusive and unstable intermediate.

4. The spontaneous condensation of succindialdehyde, acetonedicarboxylic acid, and methylamine to form tropanone was investigated. The yield of tropanone varied from 60 to 65% when

- a. The pH limitations and concentrations employed by Schöpf

were followed.

- b. The concentration employed by Schöpf was multiplied as much as nine-fold.
- c. The pH of the reaction solution was varied from 5 to 11.

It was possible to prepare tropanone in large amounts by these procedures.

5. Homologs and analogs of tropanone may be prepared similarly, replacing methylamine with an equivalent portion of another primary amine.

In this investigation the following were prepared and characterized:

- a. N-ethylnortropanone as the dipiperonylidene derivative.
- b. N-isopropylnortropanone as the picrate.
- c. N-benzylnortropanone as the dipiperonylidene derivative.
- d. N- β -hydroxyethylnortropanone as the dipiperonylidene derivative.

6. Tropanone was reduced catalytically, using platonic oxide, to tropanol. No trace of the isomeric pseudo-tropanol was found.

7. The possible application of these results for the synthesis of compounds having medicinal interest is discussed.

LITERATURE CITED

- (1) Schöpf, *Angew. Chem.* 50, 779-787; 797-805 (1937)
- (2) Pictet, *Arch. sci. phys. nat.* 19, 329 (1905)
- (3) Willstätter, *Ber.* 33, 1160 (1900)
- (4) Robinson, *J. Chem. Soc.* 111, 762 (1917)
- (5) Willstätter, *Ber.* 29, 396 (1896)
- (6) Ciamician and Silber, *Ber.* 29, 490 (1896)
- (7) Willstätter and Müller, *Ber.* 31, 2655 (1898)
- (8) Robinson, *J. Chem. Soc.* 111, 876 (1917)
- (9) Schöpf, *Ann.* 497, 1 (1932)
- (10) Schöpf and Lehmann, *Ann.* 518, 5, (1935)
- (11) Robinson and Menzies, *J. Chem. Soc.* 125, 2163 (1924)
- (12) Schöpf and Lehmann, *Ann.* 518, 1-37 (1935)
- (13) Spath and co-workers, *Ber.* 57, 1243, 1687 (1924);
Monatsh. 52, 129 (1929); 55, 352 (1930); *Ber.* 62, 2244 (1929)
- (14) Schöpf and Lehmann, *Ann.* 497, 7 (1932)
- (15) Schöpf and Bayerle, *Ann.* 513, 190 (1934)
- (16) Robinson, *J. Chem. Soc.* 111, 876 (1917)
- (17) Robinson, *J. Chem. Soc.* 1082 (1936)
- (18) Schöpf, *Ann.* 523, 1 (1936)
- (19) Schöpf, *Ann.* 513, 190 (1934)
- (20) Hahn and Ludwig, *Ber.* 67, 2031 (1934)
- (21) Spath and Kuffner, and Platzner, *Ber.* 68, 497, 699 (1935);
69, 255 (1936)
- (22) Soytzeff, *Ber.* 6 1255 (1873); 13, 1061 (1880)
- (23) Wislicenus, *Ber.* 27, 3186 (1894)
- (24) Ciamician and Dennstedt, *Ber.* 17, 533 (1884)
- (25) Harries and co-workers, *Ber.* 34, 1488-98 (1901)

- (26) Harries, Ber. 35, 1183-9 (1902)
- (27) Claisen and Manasse, Ber. 22, 530-3 (1889)
- (28) Harries and Hohenemser, Ber. 41, 255-60 (1908)
- (29) Harries and Krutzfeld, Ber. 39, 3670-7 (1906)
- (30) Harries, Ber. 35, 1183-9 (1902)
- (31) Willstätter and Heuber, Ber. 40, 3871 (1907)
- (32) Mannich and Budde, Arch. Phar. 270, 283-90 (1932)
- (33) Ciamician and Zanetti, Ber. 23, 1788 (1890)
- (34) Braun and Sobocki, Ber. 44, 2534 (1911)
- (35) Harries, Ber. 31, 37 (1898); 34, 1496 (1901)
- (36) Wohl and Schweitzer, Ber. 39, 890 (1906)
- (37) Sugawara, J. Phar. Soc. Japan, No. 545, 551-7 (1927)
- (38) Keimatsu and Yokota, J. Pharm. Soc. Japan, No. 542, 284-90 (1927)
- (39) Marcilly and Blaise, Bull. soc. chim. (3) 31, 161 (1904)
- (40) Türk, Ann. 343, 361 (1905)
- (41) Harries, Ber. 41, 674 (1908)
- (42) Harries, Angew. Chem. 25, 1459 (1912)
- (43) Reppe, Kröper, and Schmidt. (to I. G. Farbenindustrie Act-Ges.)
Ger. 699, 945, Nov. 14, 1940; Chem. Abst. 35, 6977 (1941)
- (44) Yourtee, Ph. D. Thesis, University of Maryland (1943)
- (45) Beilstein's "Handbuch der Organischen Chemie", 4th. ed., Vol. I,
p. 767
- (46) Harries, Ber. 41, 909-10 (1908)
- (47) Adkins and Nissen, Org. Syntheses, Vol. 3, 1, (1923)
- (48) Hartung and Adkins, J. Am. Chem. Soc. 49, 2510 (1927)
- (49) Wislicenus, Ann. 192, 106 (1878)
- (50) Freundler, Ledru, Compt. rend. 140, 795; Bull. soc. chim. (4) 1, 72
- (51) Hartman, Private communication, Dep't. Syn. Chem. (E. K. & Co.)
- (52) Hartung, J. Am. Chem. Soc. 50, 3370-4 (1928)

- (53) Hartung and Munch, J. Am. Chem. Soc. 51, 2262-6 (1929)
- (54) Hartung, Private Communication
- (55) Marvel and McColm, Org. Syntheses, Coll. Vol. I p. 536 (1941)
- (56) Fauconnier, Bull. soc. chim. 50 214 (1888)
- (57) Stephen, J. Chem. Soc. 127, 1874 (1925)
- (58) Stephen, J. Chem. Soc. p. 2786 (1930)
- (59) Nef, Ann. 335, 263 (1904)
- (60) Witzeman, J. Am. Chem. Soc. 36, 1909 (1914)
- (61) Evans and Hass, J. Am. Chem. Soc. 48, 2703 (1926)
- (62) Willstätter["], and Heubner, Ber. 40, 3871 (1907)
- (63) Shriner and Fuson, "The Systematic Identification of Organic Compounds",
2nd. Ed. p. 143
- (64) Matthieson and Hagedorn, Mikro chemie, ver Mikr. Octa 29, 55-61
(1941); Chem. Abst. 35, 5923 (1941)
- (65) Harries, Ber. 34, 1488-98 (1901); 35, 1188 (1902)
- (66) Harries and Krutzfeld, Ber. 39, 3671 (1906)
- (67) Adams, Chiles, and Rassweiler, Org. Syntheses, Coll. Vol I, 2nd. Ed.
p. 10
- (68) Wiig, J. Phys. Chem. 32, 961 (1928)
- (69) Willstätter["], Ann. 317, 204 (1901); 326, 1, (1903)
- (70) Willstätter["] and Iglauer, Ber. 33, 1170 (1900)
- (71) Iwamoto and Hartung, J. Org. Chem. In press
- (72) Willstätter["], Ber. 33, 1173 (1900)
- (73) Cliff and Tutin, J. Chem. Soc. 95, 1970 (1909)

EPILOGUE

Because of impending induction into the Armed Forces of my Country on November 30, 1944, it is impossible to carry out the experiments which so logically suggest themselves from the results of the investigation here recorded. It is regrettable that time does not permit the completion of the following intriguing prospects:

1. The esterification of N-(β -hydroxyethyl)-nortropanone with aromatic acids to yield compounds containing the anesthesiophoric structure.
2. The preparation of the N-homologs and their conversion into atropine- and tropacocaine-like compounds for pharmacological testing.
3. The synthesis of N-(β -chloroethyl)-3-chlorotropane and its possible conversion, by means of the Wurtz reaction, into a quinuclidene derivative.

LeRoy Curtis Keagle

Baltimore, Maryland

November 21, 1944