

CIS- AND TRANS-TROPANOL AND HOMOLOGS

By

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fulfilment of the requirements for the
degree of Doctor of Philosophy

1947

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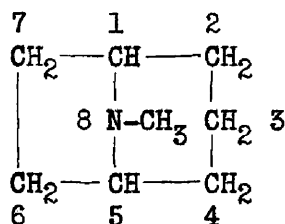
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INTRODUCTION ON TROPANE ALKALOIDS

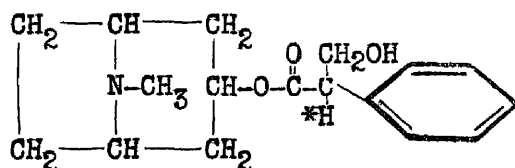
The tropane nucleus merits a great deal of consideration since it is present in two of the important groups of alkaloids in the medical armamentarium; namely, the alkaloids of the Solanacea and the Erythroxyllacea. Among the chief solanaceous alkaloids are atropine, hyoscyamine, and scopol-



Tropane

amine (hyoscine); of lesser value are apoatropine, belladonnine, nor-hyoscine, nor-atropine, and meteloidine.

Atropine, tropanyl tropate*, is found primarily in Atropa belladonna, Hyoscyamus niger, and Datura stramonium (1). The presence of an asymmetric carbon atom, denoted by an asterisk (*) in the formula below, makes it possi-

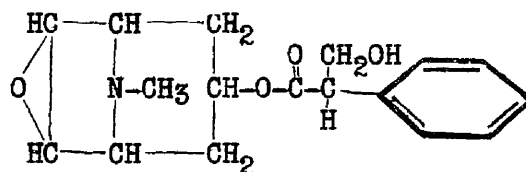


Atropine

ble to have an optically active compound. Such a compound when levo-rotatory is called (-)hyoscyamine, and as such is the chief constituent of the previously mentioned sources of atropine. During extraction, hyoscyamine readily racemizes to dl-hyoscyamine (atropine). The levo isomer is much more mydriatic than the dextro.

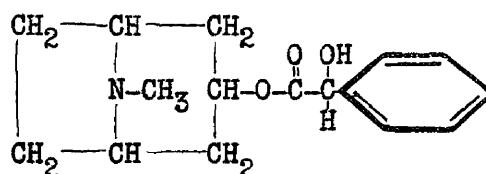
*For the sake of uniformity, tropanol, corresponding to the earlier name, tropine, will be the designation in this paper for 3-hydroxytropane. In a similar manner, all esters of 3-hydroxytropane will be referred to as tropanyl esters, corresponding to the tropéines in previous literature; for example, atropine, which is the tropic acid ester of tropanol, would be tropanyl tropate.

Scopolamine (hyoscine) is the (-)-tropic acid ester of scopine. It occurs chiefly in Datura metel, Datura arborea, and Scopolia carniolica (1). It is chiefly a central nervous system depressant (2).



Scopolamine

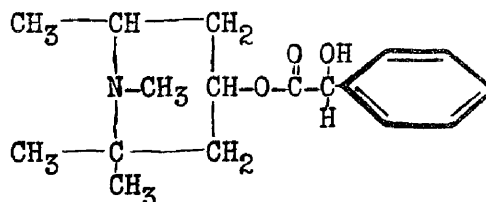
A number of synthetic atropine-like substitutes have been developed. Homatropine, a racemic tropanyl mandelate, gives rise to a much shorter period of mydriasis than atropine.



Homatropine

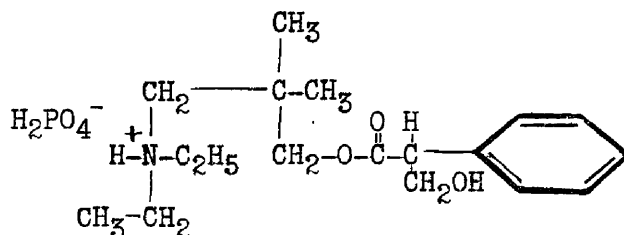
Eumydrine, another mydriatic of much shorter duration than atropine, is the quaternary salt formed by adding methyl nitrate to atropine.

Eucatropine, euthalmine, no longer contains the intact tropane nucleus, the pyrrolidine fraction being split. This synthetic alkaloid, the mandelic acid ester of 1,2,2,6-tetramethyl-4-hydroxypiperidine, is used as the hydrochloride to induce a relatively short period of mydriasis.



Eucatropine

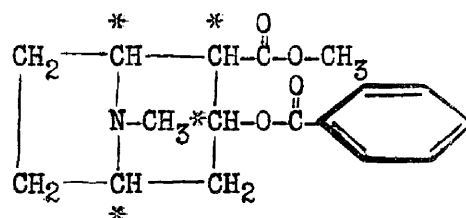
Syntropan has only the fragments of the tropane nucleus; it is the phosphate of the dl-tropic acid ester of 3-diethylamino-2,2-dimethyl-1-propanol. It is used chiefly as an antispasmodic since it possesses very little mydriatic properties (5).



Syntropan

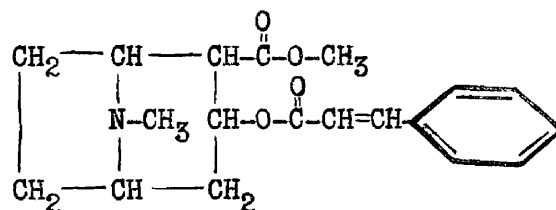
The more important Erythroxyton alkaloids include cocaine, cinnamyl cocaine and α - and β -truxillines. The chief sources are the leaves of Erythroxyton coca and other species. Tropacocaine, isolated from Javanese coca and Peruvian coca leaves is not a true cocaine-type alkaloid nor are the lesser ones including acylecgonines, hydroxytropane and hydrines.

Cocaine is the methyl ester of the benzoylated aminocarboxyalcohol, (-)ecgonine, which is 2-carboxy-3-tropanol (1). It is a strong local anesthetic and is also mydriatic.



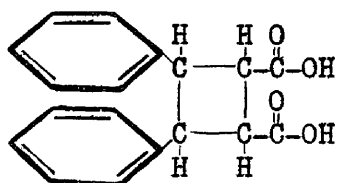
Cocaine

Cinnamyl cocaine is the cinnamoyl ester of methyl (-)ecgonine.

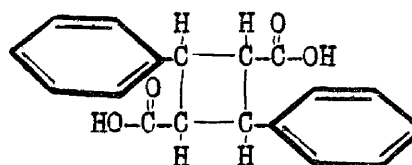


Cinnamyl Cocaine

The α - and β -truxillines are analogous to cocaine in that α - and β -truxillic acids, respectively, esterify two molecules of methyl (-)ecgonine.



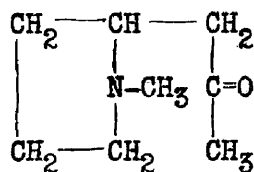
α -Truxillic Acid



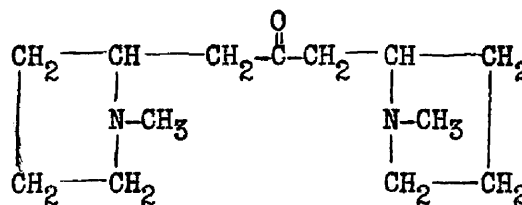
β -Truxillic Acid

Tropacocaine is the benzoic acid ester of pseudo-tropanol, which is a stereoisomer of tropanol, the two bearing a cis-trans relationship to each other.

The other Erythroxyton alkaloids of interest to the chemist are the hygrines which are obtained from Peruvian coca leaves and which may be considered as containing an incompletely formed tropane nucleus. Presented herewith are the formulae for dl-hygrine (8) and cuscohygrine (9).

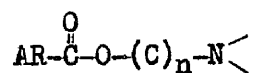


dl-Hygrine



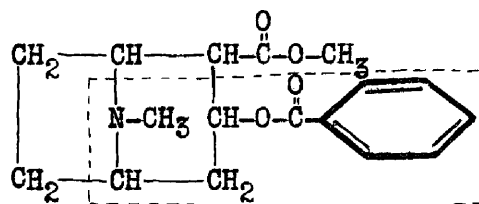
Cuscohygrine

Synthetic cocaine substitutes are very numerous and compare most favorably with cocaine. The earlier substitutes had structures similar to cocaine, i.e., they had a whole or partially ruptured tropane nucleus. Later ones contained only the so-called anesthesiophoric group, which is essentially the aromatic acid ester of an alkanolamine.

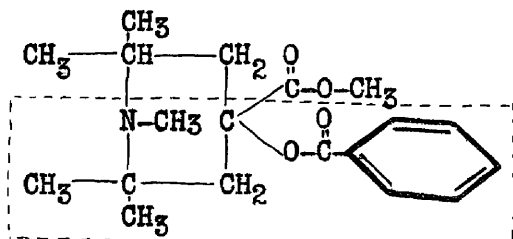


Anesthesiophoric Group

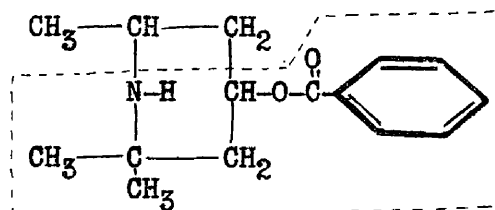
As seen in the following formulae, cocaine, as well as various synthetic agents, has this characteristic group



Anesthesiophoric Group in Cocaine

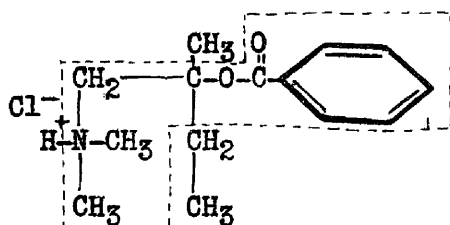


α -Eucaine

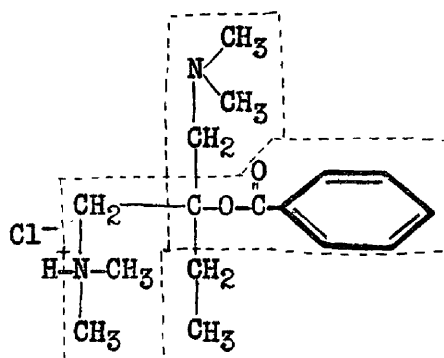


β -Eucaine
(Benzamine)

The split piperidine cycle of tropane is all that remains in stovaine (amylocaine) and amydricaine.

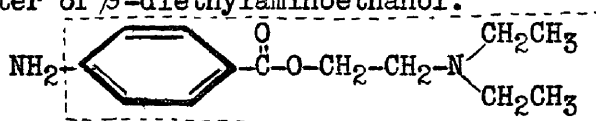


Stovaine
(Amylocaine)



Alypin Hydrochloride
(Amydricaine Hydrochloride)

Other useful substitutes do not have even the broken tropane nucleus but they do have innumerable modifications of the anesthesiophoric group; the most well-known, of course, is procaine (novocaine), the para-amino-benzoic acid ester of β -diethylaminoethanol.



Procaine

PHARMACOLOGICAL ASPECTS

Pharmacologically, atropine may be considered representative of the solanaceous alkaloids. As for the mechanism of its effect on the central nervous system little is known. More important, or at least better understood, is its effect on smooth muscles and secretory glands. It is an autonomic blocking agent to those cells innervated by the postganglionic cholinergic nerves. It does not affect the nicotinic action of acetylcholine, which refers to the stimulation of ganglia and voluntary muscle; however, it does block the muscarinic action of acetylcholine, which refers to the stimulation of smooth muscle and glands (2).

The central effects of different solanaceous alkaloids vary considerably but the peripheral effects are more uniform, as is expected from the similarity of chemical structure. Atropine quickens the heart, paralyzes the sphincter pupillae and ciliary muscles causing mydriasis and cycloplegia, suppresses salivary, nasal, bronchial and gastric secretions, is inhibitory to bronchial muscles, lowers the tone of the intestinal muscles and also suppresses the secretion of the sweat glands, which are innervated by the sympathetic nervous system but stimulated by acetylcholine (4).

Recently atropine has come into physiological importance in the determination of the mode of propagation of nerve impulses in the central nervous system. Diisopropylfluoro phosphate (DFP) when injected into laboratory test animals causes an inactivation of cholinesterase and among the symptoms observed are central convulsions. These convulsions can be relieved long before the natural regeneration of cholinesterase or the elimination of DFP, by the injection of atropine, which seemingly exerts some effect on the central nervous system in relieving the central effects of the excess acetylcholine in the animal body (4).

The effects of cocaine and other natural and synthetic local anesthetics of analogous structure suggest a similarity in their mode of action. However, little is known of this mode. It is suggested that cocaine is analgesic due to protoplasmic poisoning, a concept invalidated by the quick recovery of the nerve tissue (5).

Cocaine exhibits a complexity of pharmacological effects. Locally it is a powerful anesthetic and acts more rapidly on Erlanger's and Gasser's C group (slow pain-conducting fibres) than on the B group (rapid pain-conducting fibres) (6). It causes mydriasis without affecting accommodation (7). The main objection to the drug is its stimulation of the central nervous system giving the sensation of relief of fatigue in the skeletal muscle. It is this same stimulation which the cocaine addict enjoys. Fortunately most of the cocaine-like substitutes do not produce as serious side effects.

STRUCTURAL CONSIDERATIONS

The correlation of chemical structure to activity is well shown by the great number of variations that have been wrought on the tropanol nucleus. A cursory glance at the structural formula does not immediately reveal the fact that it can exist in cis and trans modifications. Willstätter postulated that tropanol and pseudo-tropanol bore such a stereoisomeric relationship to each other (10) and he was corroborated by Barrowcliffe and Tutin, who also showed that each of the cis and trans forms could not yield optical isomers (11). Figures 1 and 2 show this relationship. Carbon atoms, numbers 1 and 5, are asymmetric but are made to behave as a unit by the nitrogen bridge, which makes the molecule assume a meso or internally compensated form of no optical activity. These free bases do not exert any great mydriatic effect except in large doses (12, 13). Nevertheless tropanol has been found to lower blood pressure and depress the heart and pseudo-tropanol to elevate blood pressure and excite the heart. Tropanol and pseudo-tropanol are generally depressive on the parasympathetic system but the effect of the latter compound is preceded by a fleeting parasympathomimetic action (14). The actual demonstrable effect of the two isomeric bases is correlated with the type of acid esterifying the amino alcohol. Pseudo-tropanyl tropate is not mydriatic and tropanyl benzoate is a poor local anesthetic, whereas pseudo-tropanyl benzoate (tropacocaine) is a stronger local anesthetic than cocaine and tropanyl tropate (atropine) is a powerful mydriatic (15). It is evident that the tropanol configuration is more prevalent in the majority of mydriatic alkaloids while the pseudo-tropanol configuration is present in those alkaloids of more potent local anesthetic properties.

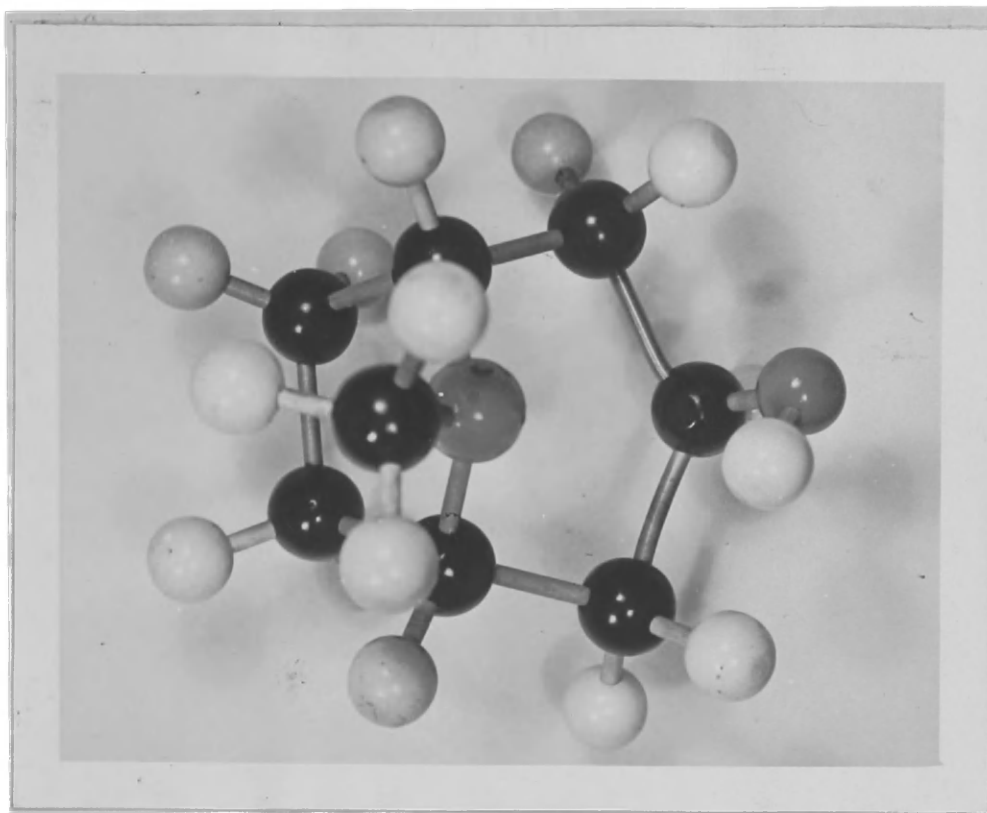


Figure 1. cis-Tropanol

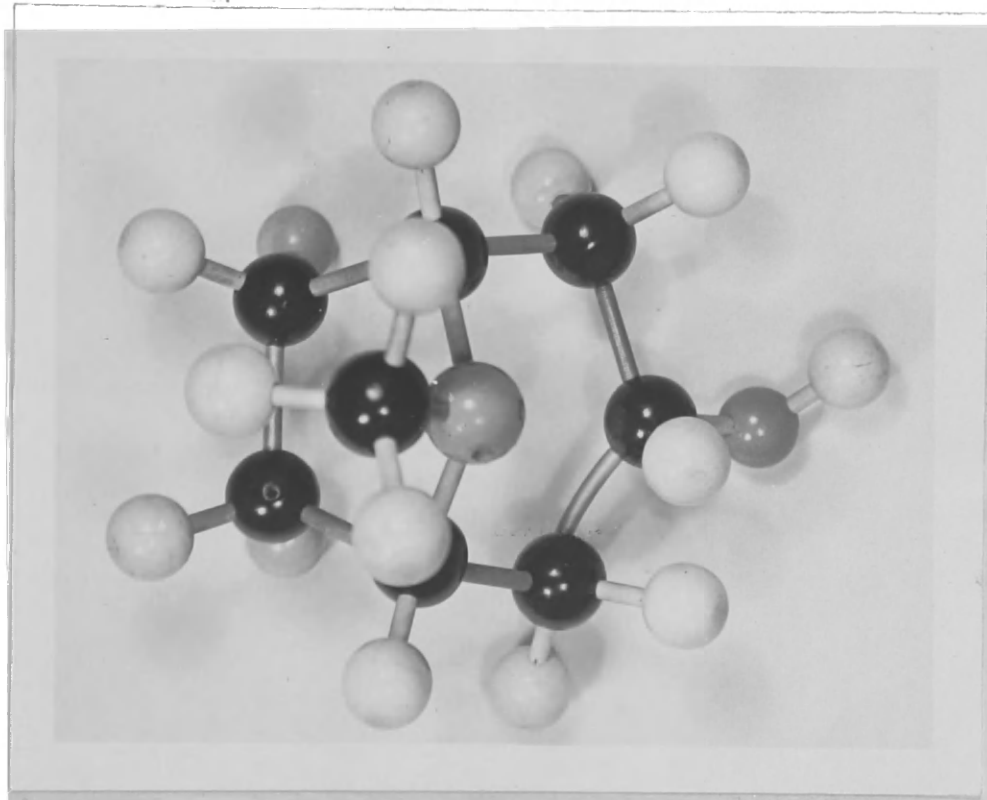
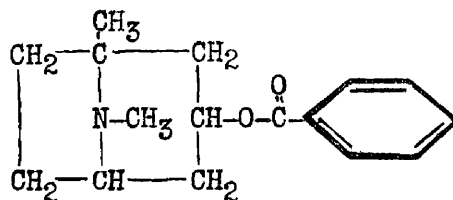


Figure 2. trans-Tropanol

The type of acid esterifying the tropanol base is of paramount importance in conferring mydriatic properties. Tropanol esters of aliphatic acids produce no mydriasis. The benzene portion of an aromatic esterifying acid can be replaced by a pyridine nucleus with retention of mydriatic activity. A para-disubstituted benzene ring in the aromatic acid nucleus is least mydriatic; ortho- and meta-disubstituted analogs such as ortho- and meta-hydroxybenzoic acid ester of tropanol are active. Unfortunately, no generalization can be made in the correlation of the chemical composition of tropanyl esters with mydriatic activity in keeping with all the observed facts (16). Cushny has shown that maximum mydriasis can be expected of those esters containing a levorotatory hydroxyaromatic residue as exemplified by (-)hyoscyamine (tropanyl (-)-tropate) (17) or (-)homatropine (tropanyl (-)-mandelate). Recently the diphenylacetic acid ester of tropanol has been reported as a powerful intestinal paralyzant (20).

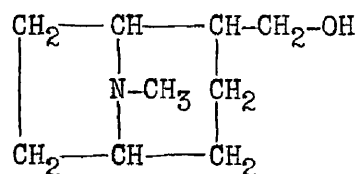
There is greater latitude in the type of aromatic acid used to esterify the amino alkanol nucleus of local anesthetics. The acyl group may be a substituted or unsubstituted benzoyl residue (18).

A great deal of useful information can be inferred from a study of the various homologs of the tropanol nucleus. The homologs are of three general types; namely, external expansion on the tropane ring, internal expansion of the ring itself, and expansion of the alkyl substituent on the nitrogen atom. The last modification will be discussed under variations on the nitrogen atom. 1-Methyltropacocaine produces local



1-Methyltropacocaine

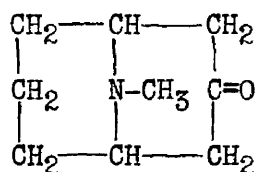
anesthesia of a longer duration than tropacocaine (19). Homotropine is another external expansion homolog of tropanol with the position of the hydroxyl group changed to give 2-hydroxymethyltropane; the tropanyl ester



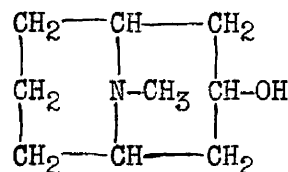
Homotropine

is an atropine-like mydriatic and the benzoyl ester is a tropacocaine-like local anesthetic (21).

The ring expansion of the tropane nucleus appears in the pyrrolidine or piperidine cycle with differing results. Pseudo-pelletierine, which may be considered as tropanone with the pyrrolidine ring enlarged by one methylene group, yields upon reduction, two granatolines, un-

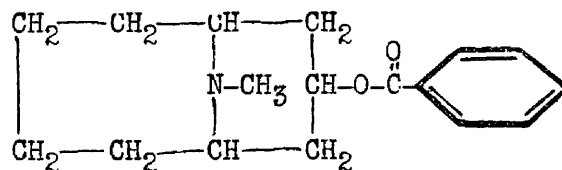


Pseudopelletierine



Methyl-Granatoline

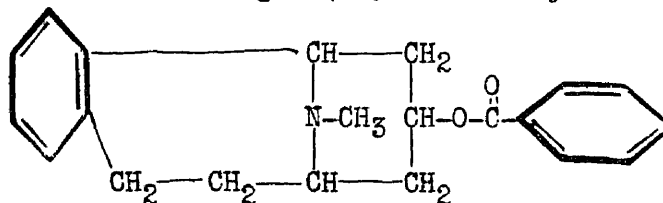
doubtedly corresponding to tropanol and pseudo-tropanol. One of these two possible products when esterified with tropic or mandelic acid yields a mydriatic (22). Esterification of either of these bases with benzoic acid or some of its derivatives produces compounds which are local anesthetics (23). Benzoyl-N-methylhomogranatoline does produce local anesthesia of a longer period than tropacocaine (24). An inter-



Benzoyl-N-methylhomogranatoline

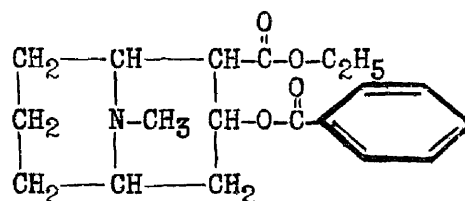
esting unsaturated analog of tropanol is the benzoic acid ester of

pseudo-8:9-benz- $\Delta^{8:9}$ -homogranaten-3-ol which has been shown to be slower in producing local anesthesia than tropacocaine, however the period of effectiveness is longer (25). The ethyl ester of benzoyl-



Benzoic acid ester of ps-8:9-benz- $\Delta^{8:9}$ -homogranaten-3-ol

homoecgonine is less anesthetic and more toxic than cocaine (26). From



Ethylbenzoylhomoecgonine

the above examples of ring expansion in the pyrrolidine fragment of the rudimentary tropane nucleus, it can be seen that no fundamental change occurs in the pharmacological properties except for the speed of action and the effective duration time of the local anesthetic-type compounds. There is insufficient experimental evidence to generalize on the effect of enlarging the piperidine fragment of tropane drugs. However, it does not seem to be any more essential than the pyrrolidine fragment as evidenced by its absence in synthetic mydriatics like syntropan or synthetic local anesthetics like procaine.

Starting with tropanol as a hypothetical building block for mydriatics and local anesthetics, it is well to review the effect of functional group substitution. The most striking contrast is shown by scopolamine and atropine. The former may be considered as 6,7-epoxy-atropine. As would be expected, both compounds are mydriatics but

scopolamine is chiefly depressant in its central actions and atropine chiefly stimulant to the medulla and higher cerebral centers.

The insertion of a carboxylic group on the tropanol nucleus in the 2-position gives ecgonine. The mydriatic properties of this nucleus are subordinated and the local anesthetic properties enhanced upon esterification of the carboxylic group with methyl alcohol and the benzylation of the hydroxyl group. It is suggested that the esterifying group in cocaine acts only to insure neutrality (15). Replacement by an ethyl group produces little change in activity whereas replacement by a benzyl, phenethyl or some of the hydroxy derivatives improves the anesthetic properties of the cocaine structure (27). It must be noted here again that the tropane configuration is not essential for local anesthetics as evidenced by the preponderance of those synthetic agents which have only an anesthesiophoric group but no tropane nucleus.

The relative ease of introducing into the tropane nucleus a nitrogen atom bearing groups different from the original N-methyl group has given a variety of compounds with some alterations in pharmacological activity. The simplest variations are those embodied in the ability of amino-nitrogen to form quaternary salts. Atropine methobromide and atropine methonitrate (eumydrin) are atropine substitutes. The fixation of oxygen on the nitrogen atom of tropanol or pseudo-tropanol practically eliminates all characteristic properties of these two compounds (14).

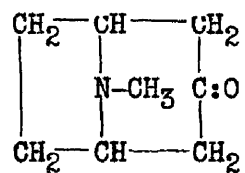
The effect of hydroxyalkyl substitution on the bicyclic nitrogen atom of tropane has been investigated rather thoroughly. The tropanyl esters and the benzoyl esters of these compounds are found to be respectively atropine-like and cocaine-like in their activity (21). In passing, one may note that here, as in other examples, the hydroxyl group

of the tropane compound need not be directly attached to the bicyclic ring for mydriasis or local anesthesia. Optimum mydriatic activity can be obtained by placing the hydroxyl group on the beta carbon atom of the N-alkyl chain and optimum anesthetic activity, on the gamma carbon atom. The alpha placement of the hydroxyl group produces no great change in properties. The beta and gamma relationships were found to be consistent for many other hydroxyalkamines (28). Analogous investigations have been made on numerous synthetic agents containing the anesthesiophoric group.

The stereoisomeric configuration of tropanol and pseudo-tropanol exerts a profound influence on the pharmacological activity of compounds containing this nucleus. The tropanol configuration seems essential to atropine-like peripheral activity and the pseudo-tropanol configuration seems to confer optimal local anesthetic activity. Atropine, scopolamine, hyoscyamine, and homatropine contain the former configuration. Cocaine, itself, contains the tropanol configuration which seems an obvious explanation for the mydriatic side effects; nonetheless, it is not due to a depression of the parasympathetic system as with atropine but an increasing of response of certain organs such as the iris to sympathetic impulses (5). The pseudo-cocaines, i.e., the alkyl arylacyl esters of pseudo-ecgonine, which contains the pseudo-tropanol configuration, are less toxic and more potent than the analogous cocaines derived from (-)ecgonine which contains the tropanol configuration (29). Further, tropacocaine is admittedly a faster local anesthetic than cocaine, without any mydriatic side effects (1). It will be recalled that pseudo-tropanyl tropate is not mydriatic and tropanyl benzoate is weakly anesthetic. Generalizing, one can say that the

tropanol configuration tends to confer mydriatic activity supplemented by some anesthetic activity and that the pseudo-tropanol configuration tends to confer local anesthetic activity with little or no mydriatic activity.

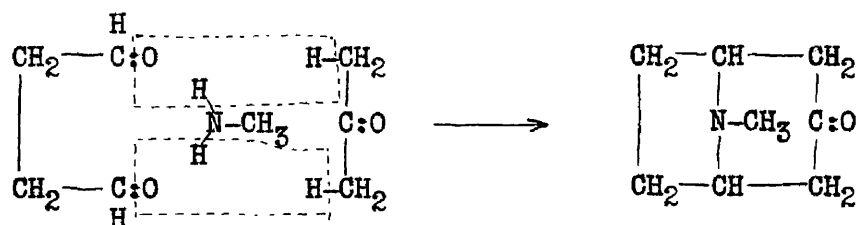
Tropanone may be considered as the first stage in the oxidation of either tropanol or pseudo-tropanol. Its activity is closely akin to that of pseudo-tropanol (14).



Tropanone

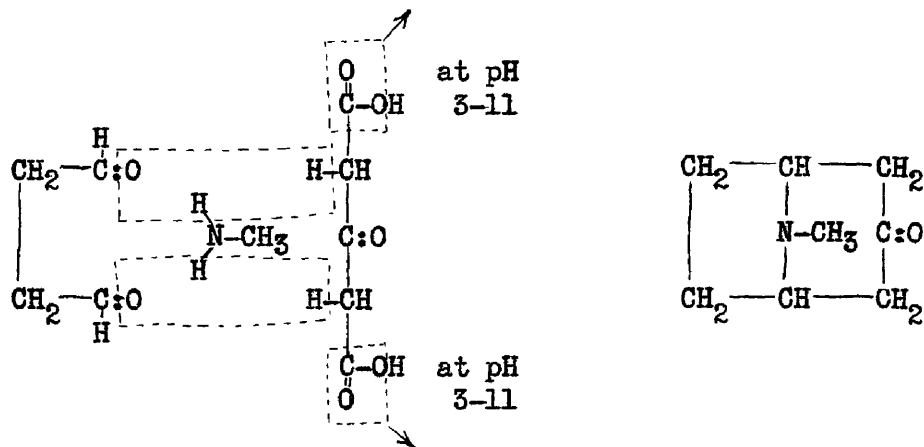
TROPANONE

Tropanone has been of interest to the alkaloidal chemist from three standpoints: various solanaceous and coca alkaloids ultimately yield tropanone upon hydrolysis and mild oxidation; conceivably, it is a plant intermediate; and conversely, a readily available source of tropanone is desirable from a viewpoint of synthesis of alkaloids. In 1901, Willstätter synthesized tropanone from suberone in over 20 steps (30). Certainly the structure was proved beyond a doubt. It remained for Robinson to synthesize the same compound in one step from succindialdehyde, methylamine, and acetone:

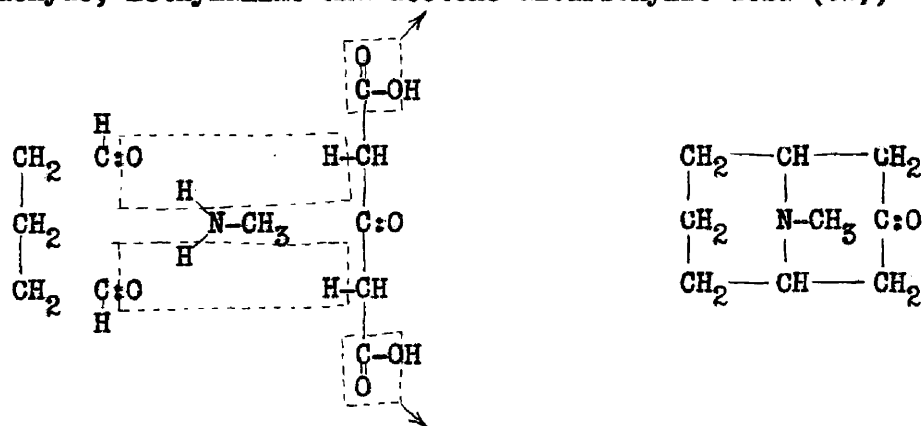


The yield was very low and subsequently use was made of ethyl acetone-dicarboxylate and of calcium acetonedicarboxylate in lieu of acetone under alkaline conditions of excess calcium carbonate. The yield of tropanone isolated as the dipiperonylidene derivative was 42% (31). The influence of pH and concentration on the course of reaction were investigated by Schöpf and Lehman who found that within pH ranges of 3 to 11, tropanone could be formed in excellent yields with 1/45th molar succindialdehyde, 1/25th molar methylamine hydrochloride, and 1/20th molar acetonedicarboxylic acid, and 1/10th molar buffer at room temperature after standing three days. Here the tropanone was isolated as the picrate (32). The results confirmed Robinson's phytochemical theory of tropanone's being synthesized under biological conditions of temperature, concentration, and pH in the plant. Schöpf obtained chiefly tropanone dicarboxylate at a pH greater than 13,

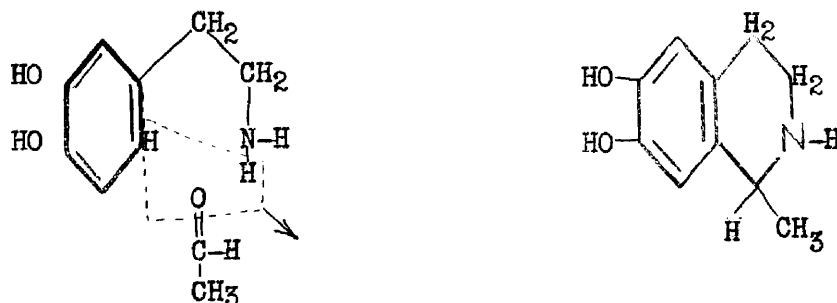
suggesting thereby that spontaneous decarboxylation took place during the formation of the hypothetical plant intermediate, tropanone, under biological conditions of pH in agreement with the following equation:



This proposed method of biosynthesis has also been employed under similar conditions for the preparation of pseudopelletierine from glutar-dialdehyde, methylamine and acetone dicarboxylic acid (32),



and for the preparation of 1-methyl-6,7-dihydroxytetrahydroisoquinoline (33),



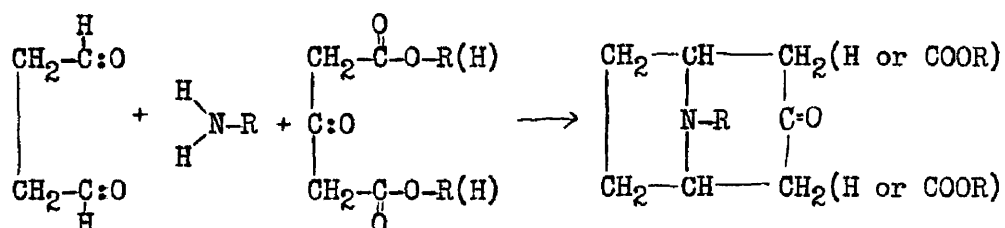
The synthesis of tropanone under phytochemical conditions is indeed a monument to the workers in the field of alkaloidal chemistry. Its elegant versatility is shown by the variants of tropanone made by this method. Methylamine may be replaced by a number of primary aliphatic amines to yield N-ethylnortropanone, N-2-hydroxyethylnortropanone, N-n-propylnortropanone, N-isopropylnortropanone, and N-benzyl-nortropanone (34, 35). Similarly, the acetonedicarboxylic acid may be replaced by different esters, half esters and salts of the same acid. The succindialdehyde may be replaced by other aldehydes such as glutar-dialdehyde (32) or laevulinaldehyde, $\text{CH}_3\text{-}\overset{\text{O}}{\text{C}}\text{-(CH}_2\text{)}_2\text{CHO}$, (36) but analogous diketones are not utilizable (36).

The chief objection to this type of synthesis is the bulky high dilutions of the condensation mixtures, which makes difficult the practical isolation of the desired tropanone intermediate for further investigation. The compounds required for the synthesis of tropanone are, with the obvious exception of methylamine, not easily obtained in a pure state or do not keep well under ideal storage conditions.

Tropanone exhibits the expected properties of an amino ketone; it is a strong base; it forms an oxime, a semicarbazone, quaternary salts, and salts of acids (1). Reduction with sodium in alcohol or with sodium amalgam yields pseudo-tropanol (37) and reduction with hydrogen over platonic oxide (Adams' catalyst) yields tropanol (34). The ketonic group activates the hydrogen atoms on the two adjoining methylene groups, making possible the formation of compounds with aldehydes, e.g., the formation of the dipiperonylidene derivative with piperonal (31). Tropanone, being rather reactive, taxes the ingenuity of the chemist to harness all of its chemical potentialities.

RESEARCH AIM

The presence of the tropane nucleus in many of the mydriatics and local anesthetics logically suggests that a further study be made of those compounds which can be made from tropanone or its N-alkyl homologs. At present the most promising method of making these tropanones is Schöpf's synthesis carried out under biological conditions of pH, concentration, and temperature according to the following equation:



The profound pharmacological differences imparted to a compound by the presence of a tropanol or pseudo-tropanol, i.e., cis or trans, configuration naturally raises the question as to which is the cis and which is the trans stereoisomer.

The purpose of this investigation was threefold: first, to study the different physical and chemical properties of tropanol and pseudo-tropanol with the hope of being able to assign the proper cis or trans configuration to each of these stereoisomers; second, to study the reaction of tropanone with methyl magnesium iodide and methyl lithium in an effort to prepare 3-methyl tropanol, a tertiary alcohol; and third, to subject some homologous tropanones to catalytic hydrogenation.

This dissertation includes:

- (a) Experimental work concerning the synthesis of tropanone, its homologs, and the intermediates required therefor.

- (b) The observed differences of tropanol and pseudo-tropanol regarding their density as liquids at the same temperature, the pH of equivalent strength aqueous solution thereof, their esterification, and the correlation of the foregoing observations with Fisher-Hirschfelder atomic radii models of cis- and trans-tropanol.
- (c) The reaction of tropanone with methylmagnesium iodide and with methyllithium.
- (d) The catalytic reduction of tropanone and its homologs.

EXPERIMENTAL

Of the three compounds, methylamine, acetonedicarboxylic acid, and succindialdehyde, required for the synthesis of tropanone, the latter is the most difficult to obtain. Since the aldehyde is used in an aqueous condensation mixture, it is permissible or even desirable to produce it directly in aqueous solution. The method used was the conversion of an acidic aqueous suspension of succindialdoxime to the aldehyde by the action of nitrous acid generated in situ (34). It was necessary, first of all, to prepare succindialdoxime, because it is not readily available.

Prior to the production of succindialdehyde by the above-mentioned manner, several attempts to convert pyrrole directly to succindialdehyde were undertaken. Acid hydrolysis of pyrrole is known to give a red polymer. Accordingly, those conditions of acid hydrolysis were modified with the hope of preventing polymerization by using acidified alcohol to form the tetraacetal.

1. One ml. of pyrrole in 10 ml. of alcohol was allowed to react with 1 ml. of 10% sulfuric acid. Upon heating, a dark green solution resulted which gave no evidence for the formation of aldehyde or the corresponding acetal.

2. One ml. of pyrrole in 5 ml. of alcohol was allowed to react with 1 ml. of concentrated hydrochloric acid. A red polymer developed upon prolonged heating on a steam bath.

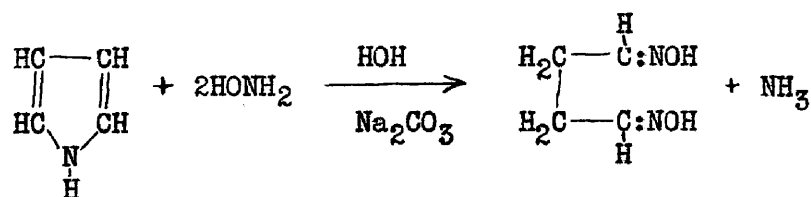
3. One ml. of pyrrole was allowed to react with 5 ml. of 10% hydrogen peroxide. Upon boiling, a dark brown solution developed which had an aldehyde odor. Similar treatment with 15% and 30% hydrogen peroxide yielded the same results. The aldehyde, if present, was formed in negligible amounts.

4. One ml. of pyrrole was allowed to react with 5 ml. of 10% hydrogen peroxide and 1 ml. of 10% sulfuric acid. A dark green solution with no aldehyde odor developed upon heating. Similar treatment with 15% and 30% hydrogen peroxide yielded the same results.

Since a noticeable aldehyde-like odor developed upon treatment of pyrrole with 30% hydrogen peroxide, it was decided to use larger quantities to facilitate isolation and characterization of the desired aldehyde. Fifty-four gm. of 30% hydrogen peroxide was mixed with 33.5 gm. of pyrrole under reflux. A mildly exothermic reaction was initiated by the application of a small flame. After the exothermic reaction ceased, sufficient heat was applied to keep the solution refluxing for 2 hours. All attempts to isolate or characterize succindialdehyde failed.

SUCCINDIALDOXIME:

Succindialdoxime was prepared according to the method of Willstätter and Heubner (38) in which pyrrole was converted to the dioxime by the action of hydroxylammonium salts in the presence of sodium carbonate. The overall reaction is indicated in the following equation:



The most satisfactory procedure for preparing optimum yields of succindialdoxime are as follows. Into a 2 liter, three neck flask, equipped with a mechanical stirrer and reflux condenser, were placed 1 liter of 95% ethyl alcohol and 141 gm. (2 moles) of hydroxylammonium chloride, C. P., which was recrystallized from 95% ethyl alcohol. The mixture was stirred and heated to refluxing on a water bath.

Sixty-seven gm. (1 mole) of pyrrole, freshly distilled at 129° , was then added and the stirring and heating continued until a very pale green color developed. Since almost all of the hydroxylammonium chloride was dissolved, 106 gm. (1 mole) of anhydrous sodium carbonate was added at such a rate as to avoid excessive frothing. Refluxing and stirring were continued for a total period of 24 hours. The sublimate of ammonium chloride which occasionally collected in the condenser had to be broken loose to avoid clogging. The reaction mixture, while still hot, was then filtered, preferably through a sintered glass funnel, to remove suspended inorganic material. The precipitate on the funnel was washed with three 25 ml. portions of hot 95% alcohol. The filtrate, combined with the washings, was treated with 10 gm. of Norite, heated to boiling, and stirred very rapidly with a mechanical stirrer. The boiling suspension was filtered through paper, yielding a clear amber solution. This was concentrated at reduced pressure to one-fifth of its original volume. The concentrate, containing yellow solid, was cooled to 0° and filtered rapidly. The crystalline material thus obtained was redissolved in a minimum amount of boiling water and decolorized with 5 gm. of Norite, and then allowed to stand overnight in a refrigerator. The pale straw-colored crystals which developed were filtered off, dried, and found to weigh 46.5 gm. (40%), melting at 170° (unc.). A small portion of the crystals upon recrystallization from water was found to melt at 171° (unc.). Reworking of the original mother liquor proved futile.

It should be emphasized that the pyrrole must be freshly distilled and the hydroxylammonium chloride be of the highest purity. The time of addition of the sodium carbonate is equally important; it must be

added while the mixture is pale green and before the faintest amber tinge develops. Any deviations from the above precautions resulted in greatly lowered yields.

A number of modifications of the above method were carried out with the desire of improving the yield or lowering the expense of producing succindialdoxime and are described below.

1. An equivalent amount of sodium bicarbonate, 84 gm. (1 mole) was used to replace 53 gm. ($\frac{1}{2}$ mole) of sodium carbonate in a half quantity run of the aldoxime. The salt was added to the hydroxylammonium chloride in refluxing alcohol before the addition of pyrrole. The mixture, which assumed a flesh-pink color, was allowed to reflux with stirring for $32\frac{1}{2}$ hours. Negligible amounts of the aldoxime were obtained after working up in the usual manner.

2. Fifty-six gm. of potassium hydroxide was dissolved in a minimum amount of boiling 95% ethyl alcohol. This solution was then added to a half run of aldoxime in the usual manner. Refluxing was continued for 25 hours whereupon a strong pyrrole odor was still detectable. No aldoxime could be isolated from the mixture.

3. Forty and five-tenths gm. ($\frac{1}{4}$ mole) of hydroxylammonium sulfate, equivalent to $\frac{1}{2}$ mole of hydroxylammonium chloride, was used to replace the latter in a typical half quantity run. Negligible amounts of succindialdoxime were isolated. The hydroxylammonium sulfate used here was of practical grade, 95%. It proved less desirable than the practical grade of the chloride.

4. Six and seven-tenths gm. ($\frac{1}{10}$ mole) of pyrrole, 14.1 gm. ($\frac{1}{5}$ mole) of hydroxylammonium chloride, and 50 ml. of pyridine were allowed to reflux in a 250 ml. Erlenmeyer flask for 5 hours. A dark

brown color developed in the clear solution and crystals of ammonium chloride separated out but no dialdoxime could be isolated.

SUCCINDIALDEHYDE:

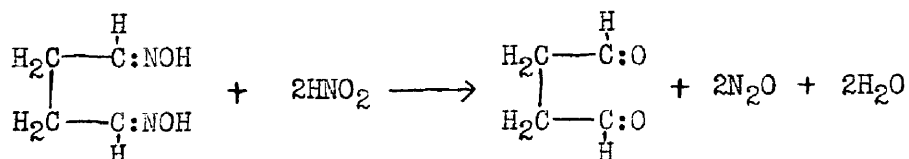
Succindialdehyde may be prepared from the dioxime by three methods which are closely related:

1. Reaction with nitrogen trioxide (N_2O_3) (39).
2. Reaction with nitrous acid (HNO_2) (40).
3. Reaction with an alkyl nitrite ($RONO$) (41).

It was hoped to use succindialdehyde in the pure monomeric state for maximum yields of tropanone. The method chosen for its preparation was that of Mannich and Budde (41), except that n-butyl nitrite was used in lieu of ethyl nitrite.

Fifteen gm. (0.13 mole) of succindialdoxime was dispersed in 30 ml. of dioxane; the resulting mixture was cooled to 0° and 33.5 ml. of n-butyl nitrite added over a period of one hour at such a rate that the temperature remained between 5° and 15° . After standing overnight, the mixture was fractionally distilled in an atmosphere of carbon dioxide. Eight gm. of a pungent, irritating, oily material was collected at $84-87^\circ/3.5$ mm. A slightly purplish hue developed in the distillate. The insolubility of this product in the aqueous condensation mixture for the preparation of tropanone, together with its positive fuchsin-aldehyde test, showed it to be a probable polymer of succindialdehyde.

In view of Keagle's success in the use of freshly prepared solutions of the aldehyde, the second method was used (34), i.e.,



Succindialdehyde from succindialdoxime. The following is a typical run which was carried out immediately before the use of the aldehyde in

a condensation reaction. Eleven and six-tenths gm. (0.10 mole) of succindialdoxime was finely triturated and suspended in 108 ml. of 10% sulfuric acid. The resulting suspension was cooled to 0° with rapid stirring in a 250 ml. beaker. Fourteen gm. (0.2 mole) of sodium nitrite was slowly added over a period of 1½ to 2 hours, care being taken not to generate brown fumes or to allow the temperature to rise above 0°. The amber solution was allowed to rise to room temperature. Effervescence and evolution of brown fumes occurred. The solution was neutralized by stirring in solid barium carbonate until effervescence ceased. The solid barium sulfate and excess barium carbonate were filtered off. A very strong pungent aldehyde odor was detected at this point. The residue on the filter was washed with sufficient water to bring the volume of the filtrate to approximately 110 ml. The aqueous citrine-colored filtrate was calculated to contain 0.09 mole of succindialdehyde as proved by Keagle (34) and was used as such in various tropanone condensations.

ACETONEDICARBOXYLIC ACID

This acid was successfully prepared by the action of fuming sulfuric acid on citric acid at 0° as described in Organic Synthesis (42) and modified by Keagle (34). Keagle's modification was the washing of the crude acetonedicarboxylic acid crystals, collected on a sintered glass funnel, with three portions of ice-cold ethyl acetate followed by two washings with ice-cold absolute ether and petroleum ether. It was found that the use of desiccated or anhydrous citric acid shortened the initial time of addition of the citric acid to the cold fuming sulfuric acid. Much better yields of very pure pale yellow crystals were obtained when the final cooling was carried out to -5° instead of the recommended 0°. The overall yield of washed and dried product was 80%.

TROPANONE AND HOMOLOGS

The general method for preparing tropanone and its homologs is very similar. One general method, successfully employed by Keagle (34), was used in the following cases. Any variations together with the results are herein described for various runs of tropanone and the N-alkyl substituted homologs.

Preparation of tropanone. Twenty-three and two-tenths gm. of succindialdoxime was allowed to react with nitrous acid from 28 gm. of sodium nitrite and 216 ml. of 10% sulfuric acid in the manner described under succindialdehyde. Based on 90% conversion, 0.18 mole of the aldehyde was calculated to be present. Twenty-one and six-tenths gm. (0.32 mole) of practical grade methylamine hydrochloride, recrystallized from 95% ethanol, was rapidly dissolved in the clear aqueous solution of the aldehyde. To this was slowly added 46.72 gm. (0.32 mole) of acetonedicarboxylic acid previously dissolved in 50 ml. of a cold saturated solution of trisodium phosphate. A saturated solution of trisodium phosphate was used to buffer the condensation mixture to pH 6 checked with a Beckman pH meter. The resulting solution was then adjusted to a volume of 2 liters and allowed to stand for 3 days. Slow evolution of carbon dioxide was observed during this time. The aqueous solution, having acquired a brownish, cloudy appearance, was cooled to 5° and saturated with sodium carbonate. Small amounts of a tarry oil separated out. The mixture was exhaustively extracted with diethyl ether, use being made of a saturated solution of picric acid in ether to indicate absence of amines, as evidenced by the lack of formation of a yellow precipitate with a 1 ml. portion of the last portions of ethereal extract. The various ethereal extracts were dried over

anhydrous magnesium sulfate or sodium sulfate and condensed to approximately 30 ml. over a steam bath. The condensed extract was placed in a 50 ml. Claisen flask and the ether removed by distillation under reduced pressure. The brown oil remaining was subjected to vacuum distillation whereupon 9.0 gm. of white crystalline distillate was collected at 77-80°/7 mm. (36% yield). The picrate derivative recrystallized from water or alcohol melted at 207-8° (unc.) with decomposition. The reported melting point of the derivative is 211° (35).

With the hope of increasing yields, several extraction steps were tried. The use of diisopropyl ether or chloroform as an immiscible solvent gave lowered yields. The aqueous condensation mixture was acidified with hydrochloric acid and concentrated on a steam bath to one-fifth the original volume. The inorganic material was filtered off and the filtrate was made alkaline with excess sodium carbonate. Extraction with ether yielded negligible amounts of tropanone.

N-Ethyl-nor-tropanone. This compound was prepared in the same manner as tropanone except that half the quantities of reactants were used. Thirteen and one-tenth gm. (0.16 mole) of ethylamine hydrochloride was used in place of 0.16 mole of methylamine hydrochloride. The crude brown oil obtained upon extraction and evaporation was subjected to vacuum distillation yielding 2 gm. of a light amber liquid at 70-80°/8 mm. This compound yielded a picrate which upon recrystallization from water melted at 183° (unc.). The reported melting point of the derivative is 189° (35).

N-Isopropyl-nor-tropanone. This compound was prepared in exactly the same manner as described above, 15.3 gm. of isopropylamine hydrochloride (0.16 mole) replacing 0.16 mole of methylamine hydrochloride.

Three gm. of a clear white liquid distilled over at $100^{\circ}/11$ mm. This compound yielded a picrate which upon recrystallization from water melted at 167° . The reported melting point is $115-116^{\circ}$ (35).

PSEUDO-TROPANOL:

Pseudo-tropanol can be easily prepared by the reduction of tropanone in alcohol with metallic sodium (37).

Nine gm. (0.065 mole) of freshly prepared tropanone was dissolved in 90 gm. of absolute ethanol. This solution was heated to boiling under a reflux condenser the upper end of which was protected by a soda lime tube. To the mixture was slowly added 9 gm. (0.39 mole) of clean sodium cut into small pieces. After all of the sodium globules disappeared from the mixture the alcohol was drawn off under reduced pressure while the mixture was heated on a steam bath. A brown mushy solid remained which was dissolved in water and exhaustively extracted with diethyl ether. The ethereal extracts were dried over anhydrous magnesium sulfate and concentrated on a steam bath to a dark brown oil which developed crude crystals upon cooling. This oil was transferred to a 15 ml. distilling flask. Residual alcohol and ether were removed by vacuum distillation. Five gm. of pseudo-tropanol was collected at $124-127^{\circ}/13$ mm. corresponding to 55.5% yield. This compound yielded a picrate which upon recrystallization from water melted at 268° (unc.). The reported melting point is $258-9^{\circ}$ (44).

TROPANOL AND HOMOLOGS:

Tropanol is best prepared by the catalytic hydrogenation of tropanone. Palladium, platinum (34), and nickel (43) have been used as catalysts.

Preparation of Tropanol. One and one-half gm. of tropanone was dissolved in 25 ml. of absolute alcohol. To this was added 0.3 gm. of Raney nickel catalyst. Reduction with hydrogen was carried out in a bomb shaker at a pressure of 200 lbs. per sq. in. No tropanol could be obtained from the alcoholic solution.

Keagle's reported selective reduction of tropanone to tropanol with platinic oxide catalyst (Adams catalyst) was confirmed in the following experiment.

One and fifteen hundredths gm. (0.0083 mole) of tropanone was dissolved in 25 ml. of absolute ethanol containing 15 mgm. of platinic oxide. The solution in the bomb shaker was subjected to a pressure of 200 lbs. per sq. in. with hydrogen. One-half of the calculated amount of hydrogen was taken up. A fresh charge of 30 mgm. of catalyst was added and shaking resumed whereupon the theoretical amount of hydrogen was taken up. The reduction mixture was taken from the bomb and the catalyst filtered off, care being taken not to dry the catalyst which was decidedly pyrophoric. The alcoholic solution was evaporated to dryness under reduced pressure. The white oily liquid was allowed to crystallize in a tightly stoppered flask stored in a refrigerator. A quantitative yield of white crystalline tropanol was obtained. This hygroscopic material yielded a picrate which upon recrystallization from water melted at 275° (unc.). The reported melting point is 275° (34).

N-Isopropyl-nor-tropanol. This compound was prepared in the same manner as tropanol, starting with 2 gm. of N-isopropyl-nor-tropanone, 20 mgm. of platinic oxide and 30 ml. of absolute ethanol. Reduction with hydrogen was carried out at a pressure of 300 lbs. per sq. in. The theoretical amount of hydrogen was taken up in $1\frac{1}{2}$ hours. The catalyst

was filtered off and the alcohol removed from the filtrate under reduced pressure. A clear syrupy liquid remained which yielded small hygroscopic white crystals when cooled in a bath of Dry Ice and ethanol. The compound yielded a picrate which upon recrystallization from water melted at $172-4^{\circ}$ (unc.).

N-Ethyl-nor-tropanol. This compound was prepared in exactly the same manner as above, starting with 0.5 gm. of N-ethyl-nor-tropanone, 15 mgm. of platinic oxide and 25 ml. of absolute ethanol. Reduction with hydrogen was carried out at a pressure of 300 lbs. per sq. in. The theoretical amount of hydrogen was taken up in $1\frac{1}{2}$ hours. The catalyst was filtered off and the alcohol removed under reduced pressure. A clear syrupy liquid remained which yielded hygroscopic white platelets when cooled in a bath of Dry Ice and ethanol. These crystals melted at room temperature. This compound yielded a picrate which upon recrystallization from water melted at 175° (unc.).

GRIGNARD TYPE REACTIONS

It was desired to prepare the tertiary alcohol, 3-methyl-3-tropanol, from tropanone by use of a typical Grignard reagent, such as methylmagnesium iodide.

Fifty-six hundredths gm. (0.023 mole) of dry, fat-free magnesium turnings was placed in a special Grignard flask*. A 25 ml. dropping funnel, which was connected to the reaction flask delivery tube, was protected on the top by a tube packed with calcium chloride and soda lime. The top of the reaction flask was similarly protected. Three and

*This flask was constructed from a 50 ml. Florence flask by sealing off the side arm, equipping the neck with a small water jacket, and sealing a bent glass delivery tube onto the upper surface of the sphere of the flask.

twenty-six hundredths gm. (0.023 mole) of freshly distilled methyl iodide dissolved in 15 ml. of absolute ether was then placed in the dropping funnel and added with shaking to the magnesium turnings. A reaction started immediately and was carried to completion by the moderate application of heat after 15 minutes. Shaking was continued throughout the entire course of this experiment. A solution of 3.203 gm. (0.023 mole) of tropanone in 10 ml. of absolute ether was placed in the dropping funnel and slowly added with agitation to the Grignard reagent. A white amorphous solid mass developed in about 20 minutes. The apparatus and contents were allowed to stand overnight. The reaction mixture was then shaken with water and filtered. The filtrate was exhaustively extracted with ether. The resulting ethereal solution was concentrated on a steam bath yielding approximately 1.5 gm. of light brown crystals. This compound yielded a picrate which upon recrystallization from water melted at 204.5° (unc.).

Further purification of the product was accomplished by vacuum sublimation*. Five different portions of snow-white material were collected. Each fraction melted at $42.5-43.5^{\circ}$ (unc.) and yielded a picrate which upon recrystallization from water melted at 205.2° (Anschutz). Since the melting point of the product corresponded to that of tropanone, and the various picrates melted at nearly the same temperature as tropanone picrate ($207-8^{\circ}$), a mixed melting point of the picrates of the product in question and tropanone was run. The resulting melting point was 204° , showing an insignificant depression. It was suspected that the product was tropanone and not the desired 3-methyl-3-tropanol. The

*The sublimation apparatus consisted of a 60 ml. side arm test tube with an inner 25 ml. test tube filled with Dry Ice and ethanol to function as a "cold finger" condensing surface.

hydrochloride of the product was prepared and the chloride content determined by a Volhard analysis. Chloride, calculated for $C_9H_{18}ONCl$, 18.5%; Chloride, calculated for $C_8H_{14}ONCl$, 20.2%; Chloride found, 20.0%.

The result of the above data showed tropanone to be the unchanged product. This result is not too surprising if one considers that tropanone, a cyclic ketone, can enolize giving rise to an active hydrogen which can then react with methylmagnesium iodide to yield methane and the magnesium iodide enolate of the ketone. Subsequent treatment with water would be expected to give the free enol which can then tautomerize back to the ketone. Similar results have been given for the reactions of menthone and pulegone with Grignard reagents (45).

With the hope of carrying out the original purpose of the Grignard reaction, further modifications were employed.

The first modification consisted of using five molar equivalents of magnesium and methyl iodide. The procedure was otherwise identical to the previous one. The product obtained was unchanged tropanone.

The other modification consisted of using an amount of freshly cut lithium wire exactly equivalent to the amount of magnesium used in the first procedure, i.e., a 2:1 molar ratio of lithium to the magnesium. The procedure was exactly the same as above with the exception that dry nitrogen gas was allowed to flow through the system. The product obtained was shown to be unchanged tropanone.

CIS- AND TRANS-TROPANOL:

As has been previously mentioned, it would be desirable to determine the actual spatial configuration of tropanol and pseudo-tropanol. It was thought some clues in solving this question could be obtained from a determination of the densities, a study of esterification, a

measurement of pH of equivalent strength aqueous solutions, and potentiometric titrations of the aqueous solutions of each base.

According to the rule of Auwers and Skita, the cis configuration of a compound usually possesses a greater density, a greater refractive index and a lower molecular refraction than the trans configuration (46). An inspection of the atomic models for cis- and trans-tropanol in Figure 3 does not reveal any appreciable difference in the volume occupied by each form. The most striking difference between the two models is

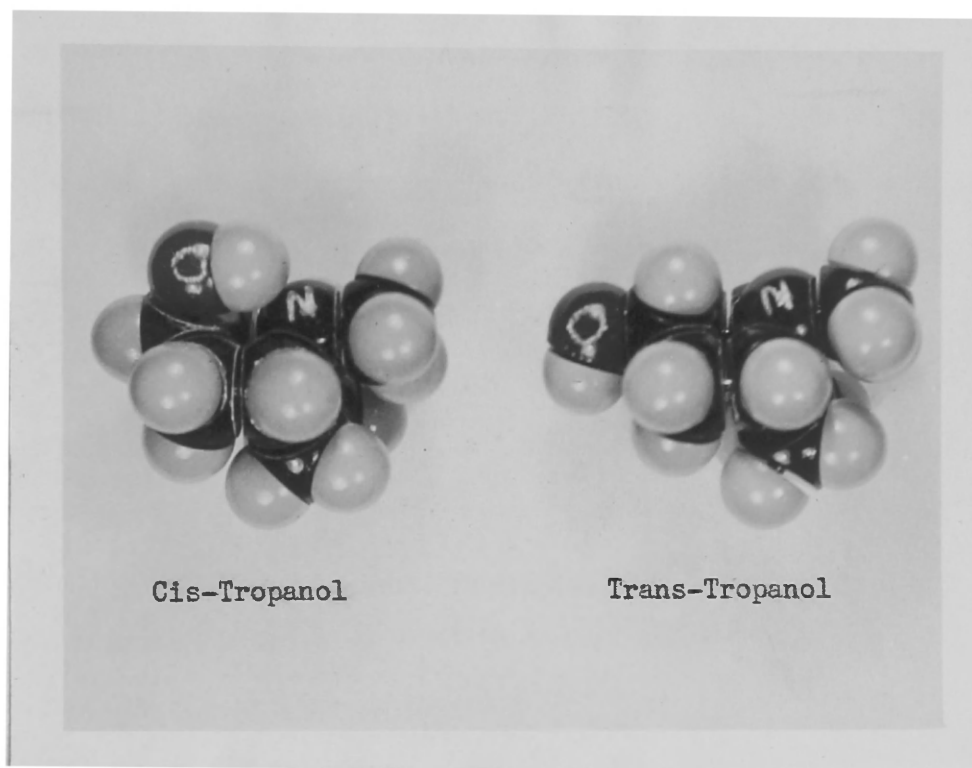


Figure 3. Cis- and Trans-Tropanol

evident in the cis form which shows partial blocking off of the nitrogen atom by the hydroxyl hydrogen giving rise to possible hydrogen bonding. It would then be expected that any reaction or property dependent on the amino nitrogen would be more hindered than appears likely in the trans

isomer. The effects of this structural difference may be expected to manifest themselves in such properties as the relative strength of the bases in water, the ease of picrate formation, and the hygroscopicity of the molecule, i.e., attraction for water. Similarly, one would expect reactions of the alcoholic hydroxyl group in the cis configuration to be impaired, e.g., ease of ester formation. With these considerations in mind, the following experiments were undertaken.

Density. Because of the limited amounts of material available, small flask-type pycnometers of approximately 0.5 ml. capacity were fabricated from 1 mm. Pyrex tubing. The volumes were determined by weighing the water contents at 22°. Tropanol and pseudo-tropanol were then melted, placed in the miniature flasks, and maintained at a temperature of 116° in a cottonseed oil bath. After the volumes were carefully adjusted, the respective flasks were cleaned on the surface, dried, and allowed to cool to room temperature. Weighings were then made. Corrections were made for the volumes of the pycnometers at 116° by employing a cubical expansion coefficient for Pyrex glass.

Data:

Weight of pycnometer I and water at 22°	1.7693 gm.
Weight of pycnometer I	1.2895 gm.
Weight of water in pycnometer I	0.4798 gm.
Volume of pycnometer I at 22°	0.4809 ml.
Volume of pycnometer I at 116°, allowing for cubical expansion of Pyrex	0.4814 ml.
Weight of pycnometer I and pseudo-tropanol	1.7698 gm.
Weight of pseudo-tropanol in pycnometer I	0.4803 gm.
Density of pseudo-tropanol at 116°	0.9979 gm./ml.
Weight of pycnometer II and water at 22°	1.7576 gm.
Weight of pycnometer II	1.2844 gm.
Weight of water in pycnometer II	0.4732 gm.
Volume of pycnometer II at 22°	0.4742 ml.
Volume of pycnometer II at 116°, allowing for cubical expansion of Pyrex	0.4747 ml.

Data (continued):

Weight of pycnometer II and tropanol	1.7596 gm.
Weight of tropanol in pycnometer II	0.4752 gm.
Density of tropanol at 116°	1.0012 gm./ml.

The observed density of tropanol at 116° was found to be 1.001(2)* gm. per ml. and pseudo-tropanol 0.997(9)* gm. per ml. Without further check, it is believed that these figures are not sufficiently significant to justify conclusions.

Esterification. Tropanol and pseudo-tropanol were esterified under the same conditions at the same time. Into a 25 ml. Erlenmeyer flask was placed 0.141 gm. (0.001 mole) of tropanol. Into a similar flask was placed the same amount of pseudo-tropanol. To each flask, 1.124 gm. (0.008 mole) of benzoyl chloride was introduced at the same time. The contents of both flasks, which appeared to develop a solid addition compound of the amine and benzoyl chloride, were heated to boiling whereupon the solid material in each flask redissolved. After 10 minutes boiling, the contents of each flask were cooled to room temperature, the hydrochloride of each ester separating out as white crystals. Each mixture was diluted to 25 ml. with absolute ether and filtered. Three washings of absolute ether from each flask were used to lavage the respective solids on the filter paper. The tropanyl benzoate hydrochloride weighed 0.238 gm. (0.000845 mole) corresponding to a yield of 84.5%, and the pseudo-tropanyl benzoate hydrochloride (tropacocaine hydrochloride) weighed 0.223 gm. (0.000792 mole) corresponding to a yield of 79.2%. The melting point of tropanyl benzoate hydrochloride recrystallized from absolute alcohol was found to be 258° (unc.) or 264° (corr.) which

*The figures in parenthesis are beyond the scope of experimental accuracy.

is in agreement with the reported melting point of $267-8^{\circ}$ (47). The melting point of pseudo-tropanyl benzoate hydrochloride, recrystallized from absolute alcohol, was found to be $266^{\circ}-6.5^{\circ}$ (unc.) or $272-2.5^{\circ}$ (corr.) which is in agreement with the reported melting point of 271° (1).

Relative strength of bases in water. A 0.050 N solution of tropanol and pseudo-tropanol in boiled distilled water was prepared. The tropanol solution had a pH greater than 12.5 measured on a Beckman pH meter. An equivalent strength pseudo-tropanol solution had a pH of 12.18. Since the Beckman pH meter is not very accurate at pH ranges well above 10, it was decided to dilute each solution five times. Tropanol solution, 0.010 N, had a pH of 11.86 and pseudo-tropanol, 0.010 N, had a pH of 11.58.

Potentiometric titration. Twenty ml. of 0.050 N tropanol and pseudo-tropanol diluted with 30 ml. of distilled water were separately titrated with 0.06126 N hydrochloric acid. Readings were made of the pH after each incremental addition of standard acid. The readings are herein tabulated and graphed. For comparison, it is noted that 16.32 ml. of 0.06126 N HCl is equivalent to 20.00 ml. of 0.050 N amine solution.

TABLE I

Titration of 0.050 N Pseudo-Tropanol
with 0.06126 N HCl

ml. Acid Added	pH	ml. Acid Added	pH
0.00	11.63	15.80	3.66
1.00	11.43	15.90	3.14
2.00	11.34	16.00	2.90
4.00	10.97	16.50	2.28
6.00	10.70	17.50	1.86
8.00	10.45	18.50	1.62
10.00	10.17	20.50	1.38
12.00	9.83	22.50	1.20
14.00	9.21	26.00	0.98
15.00	8.26	30.00	0.83
15.50	6.05	40.00	0.62
15.60	5.38	50.00	0.49
15.70	4.42		

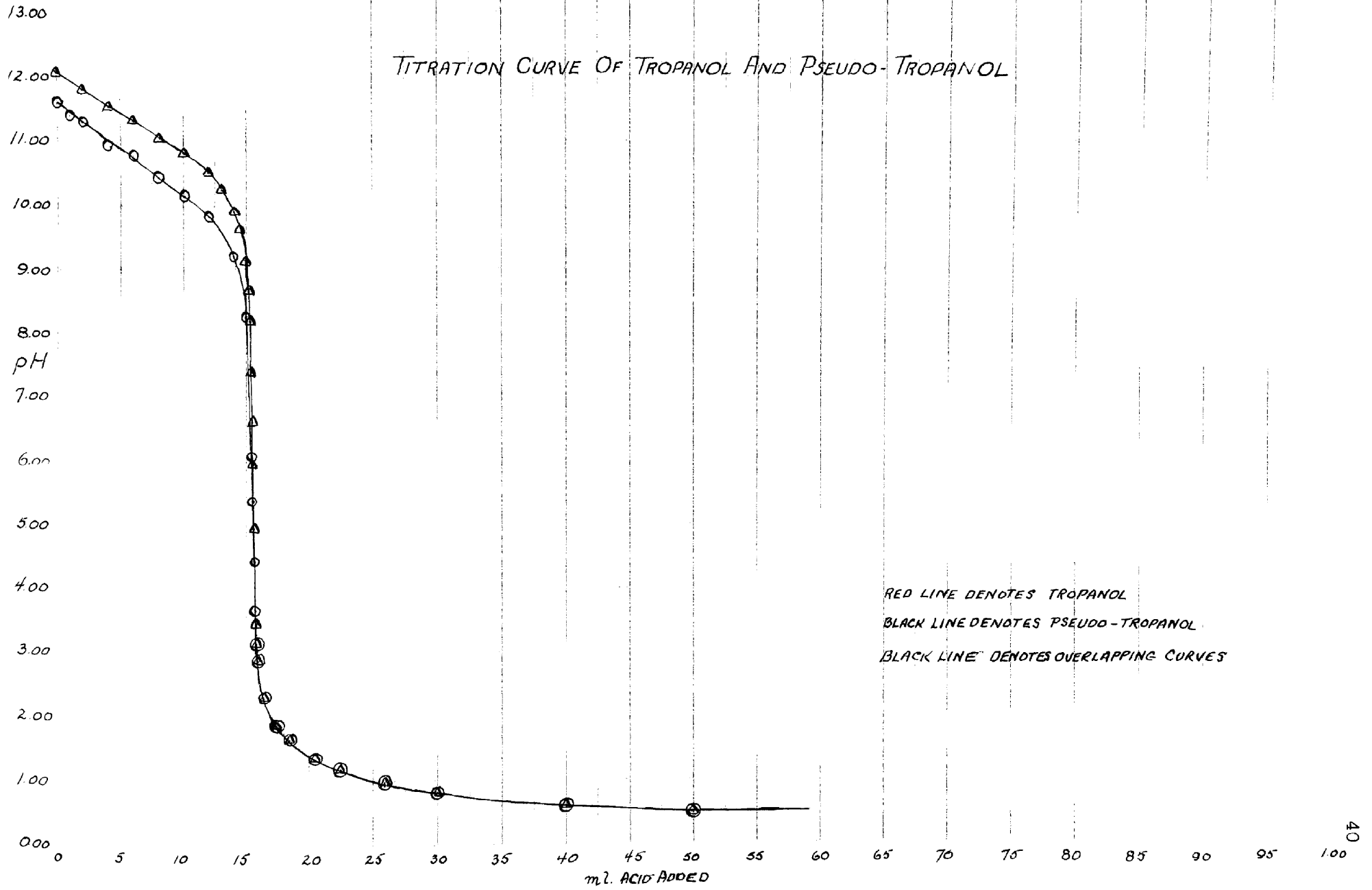
TABLE II

Titration of 0.050 N Tropanol
with 0.06126 N HCl

ml. Acid Added	pH	ml. Acid Added	pH
0.00	12.10	15.60	5.95
2.00	11.83	15.70	4.93
4.00	11.56	15.80	3.46
6.00	11.34	15.90	3.15
8.23	11.07	16.00	2.87
10.00	10.83	16.50	2.30
12.00	10.51	17.50	1.88
13.00	10.26	18.50	1.64
14.00	9.90	20.50	1.38
14.50	9.62	22.50	1.20
15.00	9.12	26.00	1.00
15.20	8.65	30.00	0.85
15.30	8.20	40.00	0.63
15.40	7.40	50.00	0.50
15.50	6.62		

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TITRATION CURVE OF TROPANOL AND PSEUDO-TROPANOL



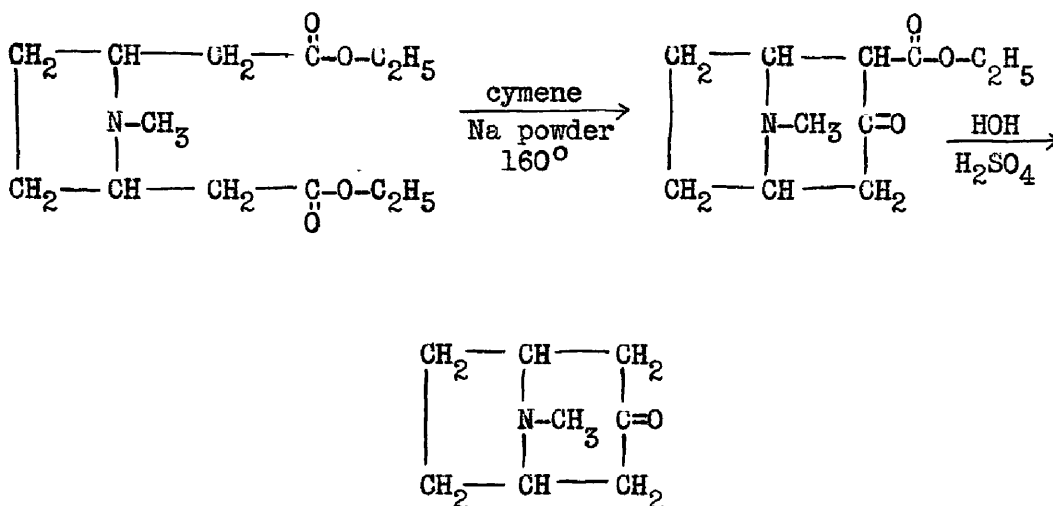
An inspection of the graph as well as of the tables shows that at pH 10, for example, tropanol requires about 3 ml. more of the standard acid than does pseudo-tropanol.

From a consideration of the yields of esters, the pH of aqueous solutions, and the titration curves, it is suggested that tropanol is the trans isomer and that pseudo-tropanol is the cis isomer. In harmony with this is the fact that pseudo-tropanol forms a picrate (heat is required for its formation) with less ease, suggesting a partially hindered amino nitrogen atom. Also, as already mentioned, an inspection of scale models, Figure 3, shows the possibility of hydrogen bonding, possibly formation of an ammonium-like compound in the cis configuration, which may be expected to be less hygroscopic and, perhaps, to have a higher melting point; the hygroscopic properties of tropanol have been noted (vide supra, p. 30). Opposed to the assignation of the trans structure to tropanol are the density data and the melting points. According to the rule of Auwers and Skita the trans isomer usually has the lower density and higher melting point. On the other hand if the tropanol molecule is viewed as a 2,6-ethylenepiperidine derivative, then it is seen that the position of the hydroxyl group in the structure here assigned to tropanol is trans with respect to the ethylene bridge, and thus the Auwers-Skita rule assumes validity. The melting points of the isomeric benzoyl esters are in agreement; tropanyl benzoate melts at 41-42° and pseudo-tropanyl benzoate (the benzoxy group trans to the ethylene bridge) melts at 49°. Also, the rule by Auwers and Skita is not infallible, and, furthermore, the density values must be redetermined before too much reliance is placed in them.

DISCUSSION OF RESULTS

The preparation of tropanol and analogous compounds depends on the preparation of tropanone by methods which try to duplicate the biological conditions of pH, concentration, and temperature. The bulkiness of the aqueous condensation mixture mitigates against a practical isolation of tropanone or homologous ketones, which exhibit marked solubility in water. This drawback, coupled with the sensitivity of the desired ketones to the usual manipulative procedures of concentration and extraction, made difficult the synthesis of sufficient intermediates required for the study of the chemical properties of the ketones and

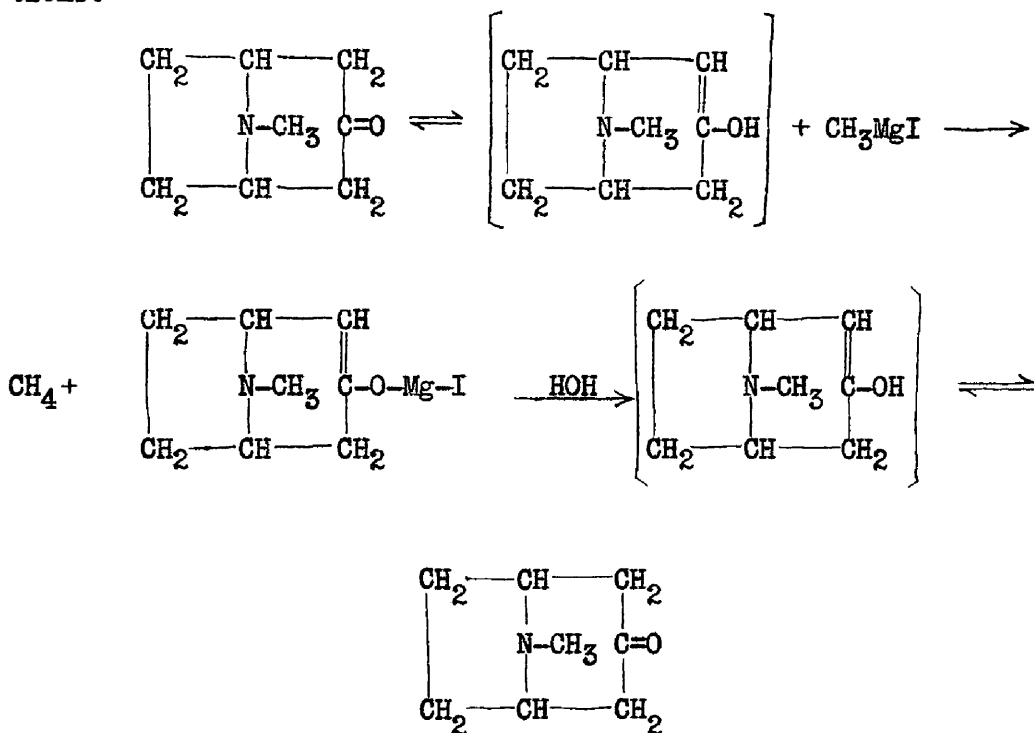
preparation of the related tropanols. Perhaps an approach not entailing the disruption of the pyrrole or pyrrolidine nucleus would be more advisable. One of the early synthesis for tropanone entailing such a method was employed by Willstätter and Bommer (48). N-Methylpyrrolidine-diethyldiacetate was subjected to a Dieckmann type (49) ester condensation as shown in the following equation:



The results of the present investigation, in accordance with Keagle's results (34), show that tropanone is selectively reduced to tropanol in good yields by hydrogenation employing platonic oxide (Adams catalyst) in small amounts. The use of palladium-on-charcoal catalyst is reported to give a mixture of tropanol and pseudo-tropanol (34). Tropanone does form enolates, cf., results of Grignard type reaction; hence, the speculation that enolization precedes reduction of tropanone to pseudo-tropanol by sodium in absolute alcohol, conditions that certainly favor enol formation. It would be well indeed to study the conditions of temperature, concentration, catalyst, and basic agents necessary to effect a selective catalytic reduction of tropanone or its homologs to the pseudo configuration because catalytic hydrogenation is a superior

method which, as herein studied, makes extremely facile the separation of the reduction products in good yields. Then the picture would be complete, i.e., the appropriate reduction of tropanones to the tropanol or pseudo-tropanol homologs, depending on whether atropine-like or tro-pacocaine-like drugs, respectively, are desired.

The reaction of Grignard reagents with tropanone is best explained by assuming enolization of the ketone as shown in the following equations:



The *cis* configuration as suggested for pseudo-tropanol and the *trans* configuration for tropanol are more easily understood when use is made of the Fisher-Hirschfelder atomic radii models. The various observed physical and chemical properties with the doubtful exception of densities do conform to the variations expected from a study of the models. Here again, it must be stated that the Auwers-Skita rule is not an inflexible dogma.

There are several other reactions with tropanone which deserve study, e.g., the nitrosation of tropanone to the 2,4-dioxime of 2,3,4-tropantrione (50) and subsequent reduction or hydrolysis of the dioxime; the addition of hydrogen cyanide to tropanone in the manner of Bucherer's addition of hydrogen cyanide to cyclic ketones (51) and subsequent reduction or hydrolysis. One can readily perceive that a number of potentially useful compounds can be made by a more thorough study of tropanone as a possible foundation moiety out of which new alkaloids can be forged.

SUMMARY

1. Various methods were essayed for the production of succindialdehyde directly from pyrrole.
2. Succindialdoxime was prepared in 40% yields from freshly distilled pyrrole. Numerous efforts to increase the yield or lessen the expense of preparation were unsuccessful. Evidently pure hydroxylammonium chloride and sodium carbonate are specific in the preparation of the dioxime by this route.
3. Succindialdehyde was obtained by the reaction of nitrous acid on succindialdoxime.
4. Small amounts of free tropanone, N-ethyl-nor-tropanone, and N-isopropyl-nor-tropanone were obtained from the condensation of methylamine, ethylamine or isopropylamine, respectively, with succindialdehyde, and acetonedicarboxylic acid in aqueous media at pH 6 at room temperature.
5. The above ketones were successfully reduced to their corresponding alcohols by hydrogenation in the presence of platinic oxide catalyst. Since catalytic reduction of tropanone gives tropanol, it is assumed that the stereoconfigurations of the N-homologs of tropanol are identical.
6. Pseudo-tropanol was formed by the reduction of tropanone in ethanol with excess metallic sodium.
7. On the basis of atomic scale models, a comparison of the various physical and chemical properties of tropanol and pseudo-tropanol suggest that the former is trans-tropanol, and the latter, cis-tropanol. Since the prefix "pseudo" is objectionable, it is proposed to replace it with "cis".
8. The advisability of further study of the reactions of tropanone as an intermediate is discussed.

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"How dull it is to pause, to make an end,
To rust unburnished, not to shine in use,
As tho' to breathe were life!"

-----Alfred, Lord Tennyson