

cocaine $\text{R}_1 = \text{CH}_3$; $\text{R}_2 = \text{C}_6\text{H}_5\text{CO}$ (V)

cinnamoylcocaine $\text{R}_1 = \text{CH}_3$; $\text{R}_2 = \text{C}_6\text{H}_5\text{CH} = \text{CHCO}$ (VI)

Cocaine (V) is the benzoyl derivative of ecgonine methyl ester; cinnamoyl cocaine (VI) is the cinnamoyl derivative of ecgonine methylester.

Many attempts have been made to correlate pharmacological action with chemical constitution by introducing various changes in the cocaine molecule (2). Ecgonine, ecgonine methyl ester or benzoyl ecgonine have no anaesthetic properties.

Therefore it seems to be necessary to block up both free hydroxyl and free carboxyl in ecgonine in order to produce anaesthetic properties. The nature of the alkyl group R_1 plays a minor part only. Benzoyl ecgonine ethyl ester ($\text{R}_1 = \text{C}_2\text{H}_5$) and the analogous propyl and butyl esters are powerful anaesthetics; the benzyl and phenyl-ethyl esters of benzoyl ecgonine are also anaesthetics.

The effect of the acid radical R_2 , which esterifies the alcoholic hydroxyl group in the ecgonine molecule, is more important; in order to produce anaesthetic properties the group must be benzoyl or a substituted aromatic residue.

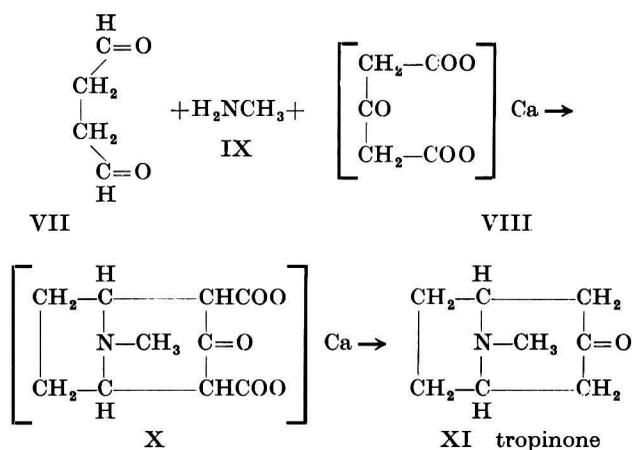
Atropine is a powerful mydriatic. Many other tropeines, i.e. esters of tropine, have been prepared. The esters of tropine with aliphatic acids have no mydriatic effect; the mandelic ester of tropine is a useful mydriatic. Benzoyl- Ψ -tropine (tropacocaine) (III) is a powerful local anaesthetic, but shows no mydriatic activity.

Another possibility of making alterations in the cocaine or in the atropine molecule would be the replacement of the group $> \text{N}-\text{CH}_3$ by the group $> \text{N}-\text{C}_2\text{H}_5$ or $> \text{N}-\text{R}$ ($\text{R} = \text{alkyl}$).

Several investigators have observed that there seems to be a marked difference between the ethyl and the methyl groups as regards pharmacological action. We have therefore started preparing N-homologues of tropine derivatives, wherein an ethyl group or a larger alkyl group is attached to the nitrogen atom.

§ 2. In this paper we describe the preparation of N-ethyl-nor-tropinone (XIV), of N-ethyl-nor- Ψ -tropine (XV) and of its benzoate (XVI).

A simple and elegant synthesis of tropinone (XI) has been discovered by R. ROBINSON (3). It depends on the condensation of succinic dialdehyde (VII) with calcium acetone dicarboxylate (VIII) and methyl amine (IX)



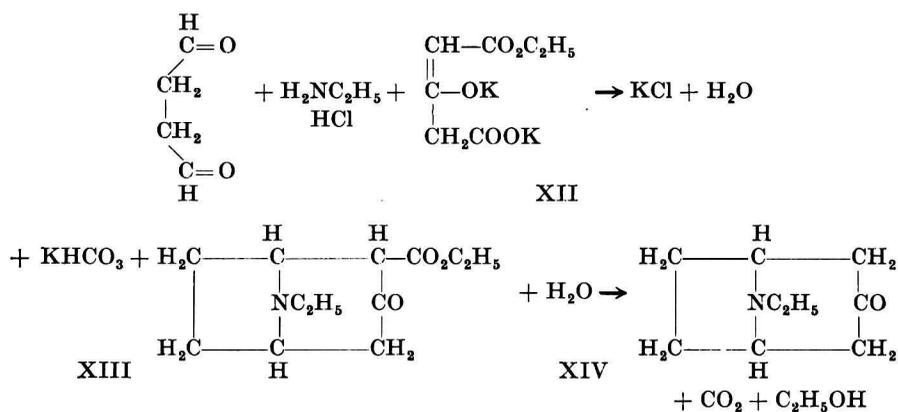
The initial product of this synthesis, calcium tropinone-dicarboxylate (X), has not been isolated. The reaction product was heated with dilute acid, as a result of which the tropinone dicarboxylic acid was decomposed and tropinone was formed.

SCHÖPF and LEHMANN (4) have shown that the conditions under which ROBINSON'S synthesis is carried out affect the yield considerably: in an appropriately buffered solution at P_H 3–11 and at a temperature of 20°–25°, good yields of tropinone can be obtained.

Acetone dicarboxylic acid is an unstable substance, which cannot be kept, but must be used as soon as possible. Therefore the dimethyl or diethyl esters of this acid are more convenient intermediates for synthetic work.

A synthesis of methyl tropinone carboxylate has been carried out by WILLSTÄTTER, WOLFES and MÄDER (5). This synthesis is based on ROBINSON'S synthesis of tropinone and depends on the condensation of succinic dialdehyde, methyl amine and the dipotassium salt of acetone dicarboxylic acid semi ester (XII).

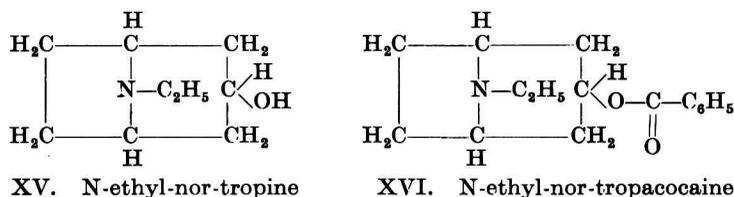
We have extended this synthesis by substituting ethyl amine or other primary amines for methyl amine.



We have not isolated the initial reaction product, i.e. the ester of N-ethyl-nor-tropinone carboxylic acid (XIII); this compound seemed to be decomposed when we attempted to isolate it by distillation at reduced pressure.

Therefore the reaction mixture was acidified by dilute sulphuric acid and heated in order to decompose the carboxylic ester. In this manner N-ethyl-nor-tropinone (XIV) was formed, which was identified in the form of the picrate, the picrolonate and the dipiperonylidene derivative (6). By treating the tropinone homologue (XIV) with sodium amalgam in a weak acid solution we obtained N-ethyl-nor-tropine (XV) in the form of white crystal leaflets (melting point $85^{\circ}.5$).

WILLSTÄTTER (1) has shown that the reduction of tropinone (XI) by this method leads to Ψ -tropine, which is a stereo-isomeride of the tropine obtained by hydrolysis of cocaine or of hyoscyamine. We therefore assume that the N-ethyl-nor-tropine synthesized by us is N-ethyl-nor- Ψ -tropine. By benzylation of this compound we obtained the benzoate XVI. As the natural alkaloid tropacocaine is the benzoate of Ψ -tropine, the compound XVI may be designated as *N-ethyl-nor-tropacocaine*. The hydrochloride of this compound has been obtained in the form of a white microcrystalline powder, melting point $256^{\circ}.5$. This salt has a slightly bitter taste. Its pharmacological action will be investigated.



Independently of and simultaneously with our work KEAGLE and HARTUNG (7) have carried out an investigation on the synthesis of N-homologues of tropinone. These authors have applied SCHÖPF's modification of ROBINSON's synthesis of tropinone. They have carried out the condensation of succinic dialdehyde (prepared *via* the dioxime), acetone dicarboxylic acid and ethylamine. They obtained N-ethyl-nor-tropinone, which has been isolated as the dipiperonylidene derivative. They give for the melting point $184-185^{\circ}$, which is in accordance with our observations*); a complete analysis of this compound has not been published by the American authors, only the nitrogen content is given. These authors prepared also N-benzyl-nor-tropanone and N-hydroxymethyl-

*) Thesis of A. L. HULSENBECK, Amsterdam, appeared in print on June the 26th 1946 (J. B. WOLTERS' Publishing Co. Groningen).

In this thesis the synthesis of N-ethyl-nor-tropinone is described; complete analytical data are given for the picrate, the picrolonate and the dipiperonylidene derivate of this compound. A short preliminary report of these experiments has been published in Chem. Weekblad, 91 (1945).

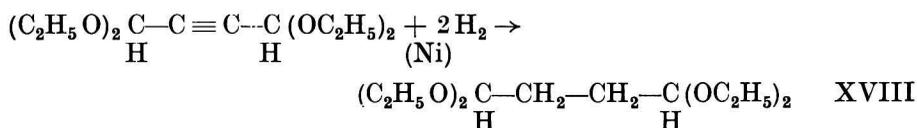
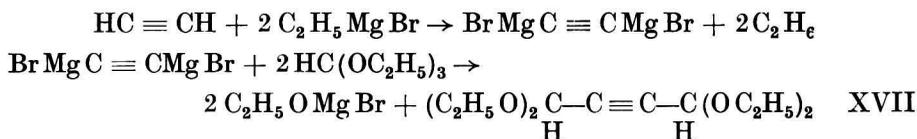
nor-tropanone; these compounds have been isolated as their dipiperonylidene derivatives (analysis: nitrogen content).

§ 3. *Description of the syntheses.*

a. Succinic dialdehyde.

Of the necessary intermediates succinic dialdehyde is the most difficult to obtain. HARRIES (8) prepared this dialdehyde by treating dioxime with nitrous acid. The dioxime of succinic dialdehyde is prepared by the method of CIAMICIAN and DENNSTEDT (9), i.e. the reaction of hydroxyl amine hydrochloride with pyrrole in the presence of alkali.

Although this method has been improved by WILLSTÄTTER and HEUBNER (10) and has been used by several investigators, it is not an attractive method for preparative work. We have studied several other methods for the preparation of succinic dialdehyde and prefer a synthesis represented by the following formulae (6).



By passing acetylene into an ethereal solution of magnesium ethyl bromide a solution of acetylene dimagnesium bromide is obtained. WOHL and MYLO (11) treated this solution with an ethereal solution of ethyl orthoformate $\text{HC}(\text{OC}_2\text{H}_5)_3$ and obtained the tetra ethyl acetal of butynedial (XVII). WEYGAND and HENKEL (12) have improved the experimental conditions under which this synthesis is carried out. Following their prescription we obtained the compound in a yield of 60–70 %, calculated on magnesium.

This butynedial tetra ethyl acetal (XVII) is an unstable compound, which cannot be kept and must be worked up as soon as possible. The catalytic hydrogenation of XVII is carried out at 20° and an initial hydrogen pressure of 100 atm., using Raney nickel as catalyst. Succinic dialdehyde tetra ethyl acetal (XVIII) (boiling point 114–116°/15 mm) is obtained in a yield of 90 %.

The hydrolytic scission of the tetra ethyl acetal is carried out by shaking it with 0.1 N hydrochloric acid (yield 85 % calculated on acetal). In this manner a solution of succinic dialdehyde is obtained, which is used in the following experiments.

b. N-ethyl-nor-tropanone (XIV).

To a buffer solution consisting of 30.5 g of citric acid ($\text{C}_6\text{H}_8\text{O}_7 \cdot \text{H}_2\text{O}$)

and 55 g of disodium phosphate ($\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$) in 1.5 l of water is added a solution of succinic dialdehyde (prepared by shaking 32 g of succinic dialdehyde tetra acetal with 160 ml of 0.1 N hydrochloric acid), 70 g of the dipotassium salt of the monoethyl ester of acetone dicarboxylic acid and 21 g of ethyl amine hydrochloride; the volume of the solution is made up to 3 l. This solution is stored at room temperature in the dark for $4\frac{1}{2}$ days.

The solution is saturated with potassium carbonate and thoroughly extracted with ether. By distilling off the ether a brown-coloured oily liquid is obtained, which is refluxed with 150 ml of dilute sulphuric acid. The acid solution is distilled with steam in order to remove the non-basic constituents; to the distillation residue is added an excess of sodium hydroxide and the liquid is extracted with ether. After working up the ethereal solution an oily liquid is obtained, which consists mainly of *N*-ethyl-nor-tropinone (fraction *a*).

The *N*-ethyl-nor-tropinone has been identified in the form of several derivatives: *the picrate* melts at 189° . (Found: 47.09 % C, 4.68 % H, 14.75 % N; $\text{C}_9\text{H}_{15}\text{ON} \cdot \text{C}_6\text{H}_3\text{O}_7\text{N}_3$ requires: 47.12 % C, 4.71 % H, 14.66 % N.) The picrolonate melts at 209° . (Found: 54.53 % C, 5.75 % H, 16.95 % N; $\text{C}_9\text{H}_{15}\text{ON} \cdot \text{C}_{10}\text{H}_8\text{O}_5\text{N}_4$ requires: 54.67 % C, 5.56 % H, 16.78 % N.) The dipiperonylidene derivative melts at 183.5° . (Found: 71.97 % C, 5.46 % H, 3.65 % N; $\text{C}_{25}\text{H}_{23}\text{O}_5\text{N}$ requires 71.94 % C, 5.56 % H, 3.35 % N.)

c. *N*-ethyl-nor- Ψ -tropine (XV).

The required quantity of sodium amalgam (prepared from 5 g of sodium and 200 g of mercury) is added gradually to a solution of fraction *a*. in dilute hydrochloric acid, in such a manner that a slight excess of acid is present during the reaction.

The liquid is then basified and extracted with ether. By working up the ethereal solution *N*-ethyl-nor- Ψ -tropine is obtained in the form of white leaflets, which are recrystallized from ether: melting point $85^\circ.5$. (Found: 69.40 % C, 11.03 % H, 8.66 % N; $\text{C}_9\text{H}_{17}\text{ON}$ requires: 69.63 % C, 11.04 % H, 9.02 % N.) The yield is about 5–6 % based on the initial quantity of succinic dialdehyde. The hydrochloride of *N*-ethyl-nor- Ψ -tropine melts at 219° .

d. Benzoate of *N*-ethyl-nor- Ψ -tropine (XVI).

A mixture of 0.640 g of benzoyl chloride and 0.490 g of XV is heated at 150° for $1\frac{1}{2}$ hours. The mixture is basified with a solution of sodium carbonate and extracted with ether.

The benzoate of *N*-ethyl-nor- Ψ -tropine has been identified in the form of the picrate or in the form of the hydrochloride. The picrate melts at 162° . (Found: 54.19 % C, 4.96 % H, 11.35 % N; $\text{C}_{16}\text{H}_{21}\text{O}_2\text{N} \cdot \text{C}_6\text{H}_3\text{O}_7\text{N}_3$ requires: 54.09 % C, 4.95 % H, 11.47 % N.)

The hydrochloride of *N*-ethyl-nor-tropa-cocaine melts at $256^\circ.5$. (Found:

64.78 % C, 7.57 % H, 5.08 % N, 12.02 % Cl; $C_{16}H_{21}O_2N \cdot HCl$ requires:
64.96 % C, 7.50 % H, 4.74 % N, 11.99 % Cl.)

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