SUBSTITUTED CYCLOPROPANECARBOXYLIC ACIDS AND DERIVATIVES

by

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TABLE OF CONTENTS

INTRODUCTION

The naturally occurring local anesthetic, cocaine, is the ester of benzoic acid and the aminoalcohol, ecgonine methyl ester. The naturally occurring antispasmodic, atropine, is the ester of tropic acid and the aminoalcohol, tropine. Since synthetic esters of certain carboxylic acids and aminoalcohols have found wide use as local anesthetics, while those of other carboxylic acids and aminoalcohols have been used as antispasmodics, the aminoalcohol esters of carboxylic acids in general are of interest as regards both types of pharmacologic activity.

The history of one of the oldest and best known examples of the correlation of chemical structure and pharmacodynamic activity as well as the history of local anesthesia begins with the isolation of cocaine from the leaves of Erythroxylon Coca described in 1860 by Niemann (39). In 1884 Koller introduced cocaine as a local anesthetic.

After extensive studies of the effect of modification of the various functional groups of the cocaine molecule upon its local anesthetic activity, the anesthesiophoric group - the minimum essential for local anesthetic activity - is now regarded (27) as the encircled part of the formula:
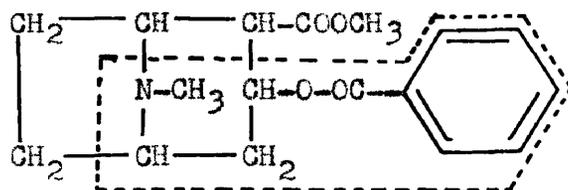
Cocaine showing anesthesiophoric group

and it is possible to write as a general formula necessary for substances to exhibit some degree of local anesthetic activity the

following:

$$Ar-COO-(CH_2)_n-N\begin{smallmatrix}R\\R'\end{smallmatrix} \quad .$$
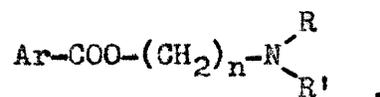
One well-known local anesthetic of this type was introduced clinically in 1905 by Einhorn and Braun who called it novocaine.

$$H_2N-\bigotimes-COO-C_2H_4-N(C_2H_5)_2$$
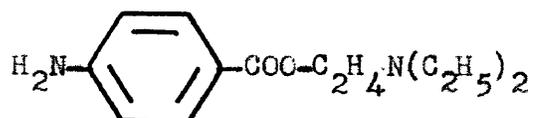
Novocaine

Innumerable analogs have been made since that time according to the principles of homology, vinylogy and isosterism, e.g., stovaine, apothesine and the thiophene analog of stovaine, respectively.

$$\bigotimes-COO-\underset{\underset{C_2H_5}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH_2-N(CH_3)_2$$

Stovaine base

$$\bigotimes-CH=CH-COO-CH_2-CH_2-CH_2-N(C_2H_5)_2$$

Apothesine

$$\begin{matrix} CH-\!\!-\!\!-CH & CH_3 \\ \| \quad\quad \| & | \\ CH \quad\quad C-COO-\underset{\underset{C_2H_5}{|}}{\overset{|}{C}}-CH_2-N(CH_3)_2 \\ \diagdown S \diagup \end{matrix}$$
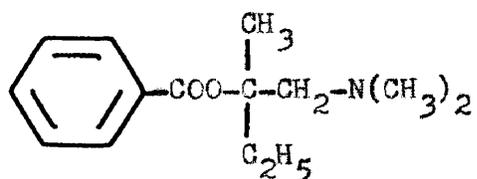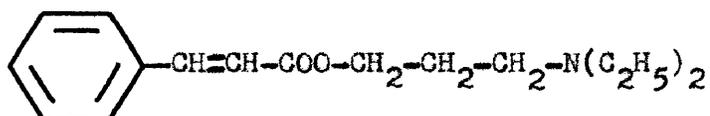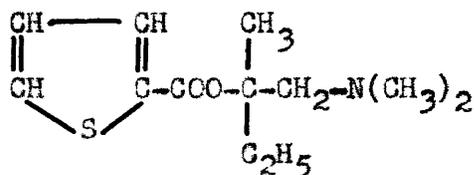
Thiophene analog of stovaine base

More drastic modifications of the acid component of the local anesthetic esters have usually resulted in decrease or loss of activity; however, only a few esters of aliphatic, alicyclic or arylaliphatic

acids have been studied for local anesthetic activity. Diethylamino-
ethyl butyrate hydrochloride possesses traces of local anesthetic ac-
tivity and the potency increases as the length of the stem nucleus of
the acid increases (28). Cano and Ranedo showed that the benzoyl group
of stovaine can be replaced by an aliphatic acyl group, provided this
group is not too small (12). Fourneau (18) reported the basic esters
of α-bromovaleric acid to have a marked action. McElvain and Carney
found the 3-(2-methylpiperidino)-propanol esters of cyclohexane-
carboxylic acid and cyclohexylmethanecarboxylic acid to have a certain
degree of local anesthetic activity (34). In experiments on himself,
Lofgren (31) found 2-diethylaminoethyl cyclohexanecarboxylate to have
slightly less than one-half the duration of local anesthesia given by
the corresponding benzoate. Certainly many more modifications should
be tried before the aliphatic acyl groups can be definitely discarded
as ineffective replacements for the aromatic analogs.

It is of interest at this point to discuss the effect of substitu-
tion of tropic acid, an arylaliphatic acid, for the aromatic acid com-
ponent of the anesthesiophoric group. Such a condition obtains in the
structure of atropine:
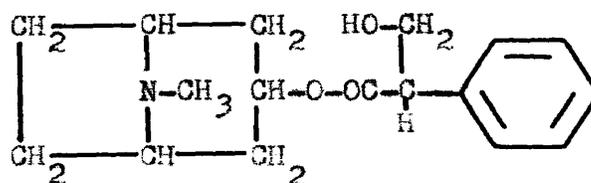
Atropine

Atropine has mydriatic, antisialogogue and antispasmodic properties.
Retention of one or more of these pharmacologic effects is found in
molecules in which the tropine component has been replaced by other
aminoalcohols. Syntropan retains the spasmolytic effect against acetyl-

choline stimulation of isolated intestine but has no appreciable mydriatic or antisialogogue activity (19).

$$\text{C}_6\text{H}_5\text{-CH-COO-CH}_2\text{-}\underset{\underset{\text{CH}_3}{|}}{\overset{\overset{\text{CH}_3}{|}}{\text{C}}}\text{-CH}_2\text{-N(C}_2\text{H}_5)_2$$
with CH$_2$OH on the CH
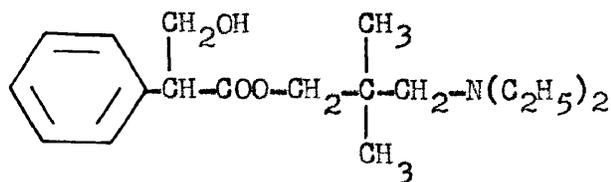
Syntropan

Modifications in the acyl moiety also produce interesting results. The 2-diethylaminoethyl ester of benzilic acid has the same qualitative actions as has atropine; whereas trasentin is quite effective as a spasmolytic but is only feebly mydriatic and is otherwise without parasympatholytic effect (3).

HO-C-COO-CH$_2$-CH$_2$-N(C$_2$H$_5$)$_2$
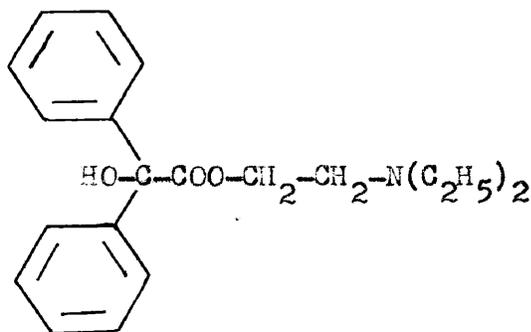
2-Diethylaminoethyl benzilate

H-C-COO-CH$_2$-CH$_2$-N(C$_2$H$_5$)$_2$
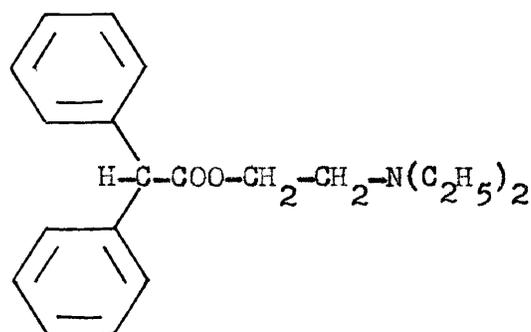
Trasentin (35),(36)

This fruitful discovery was followed by the synthesis of other spasmolytic agents of this general type:

H-C-COO-CH$_2$-CH$_2$-N(C$_2$H$_5$)$_2$

Trasentin 6H (37)

$$\text{CH}_3\text{-CH}_2\text{-CH}_2$$
H-C-COO-CH$_2$CH$_2$-N(C$_2$H$_5$)$_2$

Propavine (46)

$CH-COO-CH_2-CH_2-N(C_2H_5)_2$

Pavatrine (30)

$COO-CH_2-CH_2-N(C_2H_5)_2$
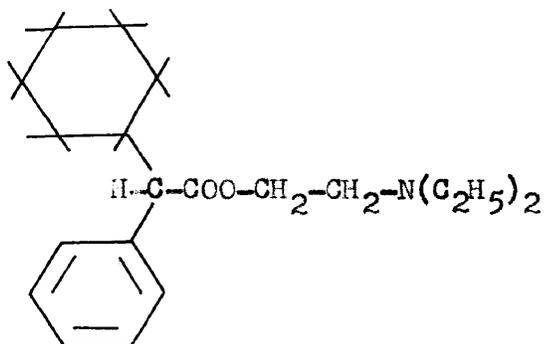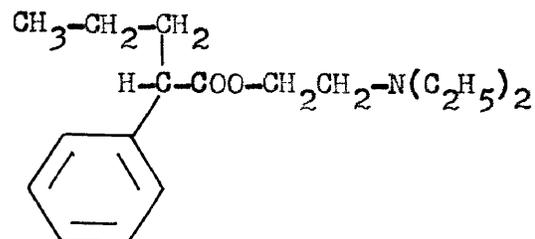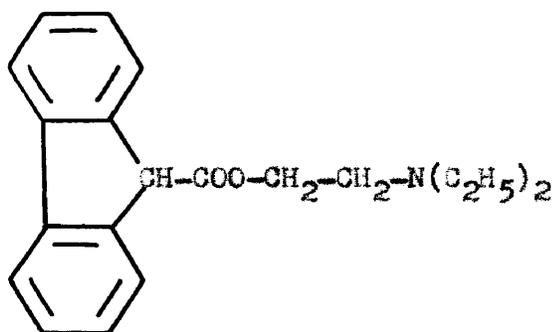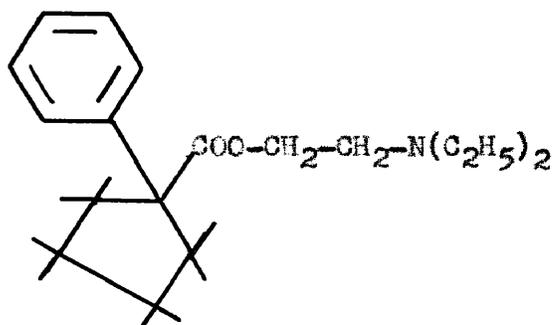
Parpanit (3)

Esters of α-phenylaliphatic acids of the type $C_6H_5-CH(R)-COOH$ have been shown to be quite active spasmolytics and their activity increases with the length of the chain R up to the amyl derivative ($R = C_5H_{11}$) and decreases thereafter (3).

Wagner-Jauregg extended the series with the homolog of trasentin, 2-diethylaminoethyl dibenzylacetate (47). He found it to be three to four times more active as a spasmolytic than papaverine, an antispasmodic having a mode of action different from that of atropine. Unfortunately, clinical tests disclosed the accompanying disturbances of vomiting and vertigo which preclude the use of the compound.

Pavatrine, still more active than trasentin (30), serves as the starting point of a new series. Burtner and Cusic (11) found the 2-diethylaminoethyl ester of 9,10-dihydroanthracene-9-carboxylic acid to be twenty times more active than either trasentin or papaverine against histamine-induced spasms. The 2-diethylaminoethyl ester of xanthene-9-carboxylic acid is said to be the most effective spasmolytic of the series in acetylcholine-induced spasm (11).
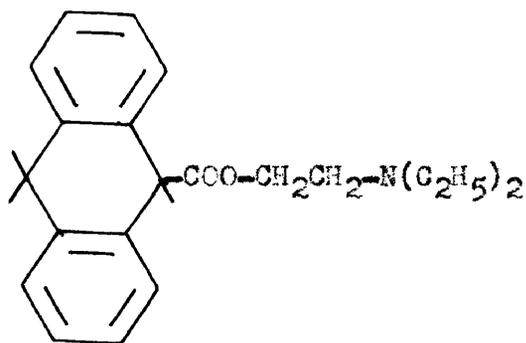
2-Diethylaminoethyl 9,10-dihydro-
anthracene-9-carboxylate
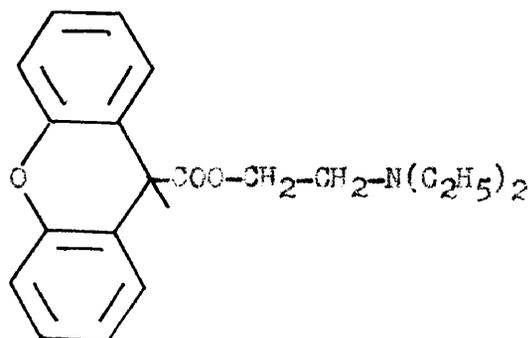
2-Diethylaminoethyl
xanthene-9-carboxylate

Weston (48) studied the basic alkyl esters of 1-phenylcyclopropane-
thiocarboxylic acid and 1-phenylcyclohexanecarboxylic acid and found the
following two compounds to be twice as active as papaverine against
barium chloride-induced spasm and to possess also substantial neuro-
tropic activity:
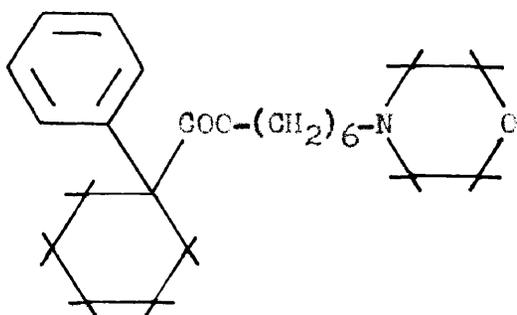
6-(4-morpholino)-hexyl
1-phenylcyclohexanecarboxylate
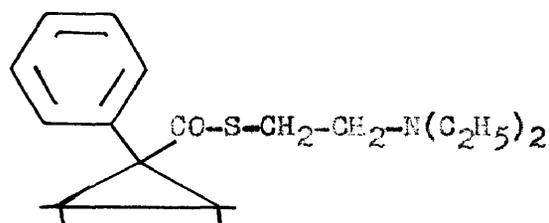
2-Diethylaminoethyl
1-phenylcyclopropane-
thiocarboxylate

The presence of both the neurotropic (atropine-like) and the musculo-
tropic (papaverine-like) activities makes these compounds of consider-
able medicinal interest as spasmolytics.

Subsequently a group of thirty basic esters of substituted ali-
cyclic carboxylic acids was reported by Tilford, Van Campen and
Shelton (45). One of the compounds prepared and tested was the 2-di-
ethylaminoethyl ester hydrochloride of 2-methyl-2-phenylcyclopropane-

carboxylic acid. This compound was found to be about one-tenth as active as trasentin against acetylcholine-induced spasm in isolated smooth muscle and only about one-half as active as trasentin against the effects of barium chloride and histamine.

$$H_3C-\text{(cyclopropane ring, phenyl)}-COO-CH_2-CH_2-N(C_2H_5)_2 \cdot HCl$$
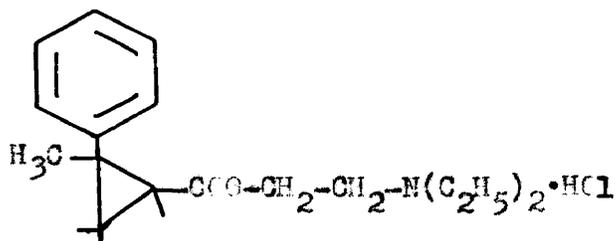
2-Diethylaminoethyl
2-methyl-2-phenylcyclopropane-
carboxylate hydrochloride

Further modifications in this series may bring to light a compound possessing both neurotropic and musculotropic spasmolytic action. This paper reports on the synthesis of compounds which represent new modifications in this series.

REVIEW OF METHODS OF SYNTHESIS OF CYCLOALKANECARBOXYLIC ACIDS

Metalation and Carbonation of Hydrocarbons.—The metalation and carbonation of hydrocarbons was studied by Gilman and Bebb (22). Their procedures were modified by Burtner and Cusic for the synthesis of cycloalkanecarboxylic acids from suitable hydrocarbons (10),(11). Application of this method to the synthesis of fluorene-9-carboxylic acid from fluorene is indicated:

$$\xrightarrow[\substack{\text{or} \\ C_6H_5\text{-Na in benzene}}]{\text{n-Bu-Li in ether}} \xrightarrow[\text{dry ice}]{CO_2} \xrightarrow{H_2O, \ HX}$$
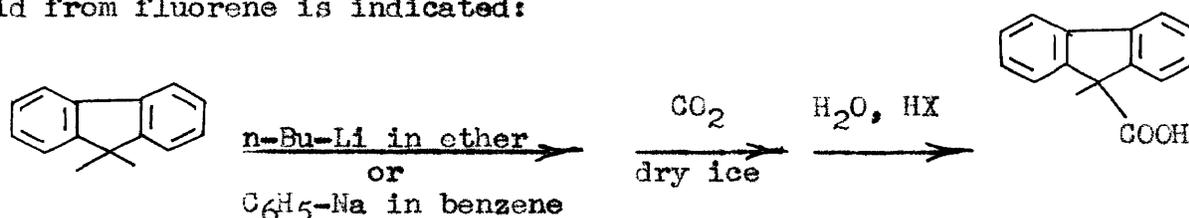
For the synthesis of 9,10-dihydroanthracene-9-carboxylic acid or of xanthene-9-carboxylic acid, fluorene must be replaced by 9,10-di-hydroanthracene or by xanthene, respectively.

Alkylation of the Active Methylene Group in Nitriles and Hydrolysis.-

This method was used by Weston (48) and by Tilford and coworkers (45) who modified the method of Case (13) which was evolved from the directions of Knowles and Cloke (29).

The general method for preparation of a cycloalkanecarboxylic acid is indicated by the following equation:

$$R\text{-}CH_2CN \ + \ \underset{(CH_2)_n}{\overset{Br \qquad Br}{\diagup \diagdown}} \xrightarrow[Na \ + \ NH_3]{NaNH_2} \underset{(CH_2)_n}{R\text{--}C\text{--}CN} \xrightarrow[HX]{H_2O} \underset{(CH_2)_n}{R\text{--}C\text{--}COOH}$$
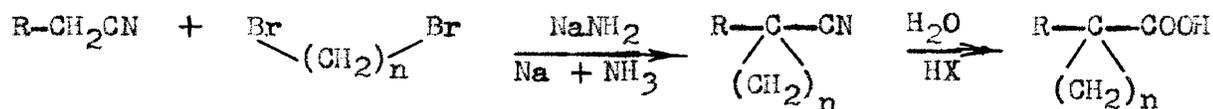
where R represents a phenyl, a benzyl or a naphthyl radical and n varies from 2 to 5 in the compounds studied by these workers.

Recently Tilford and coworkers (44) reported the alkylation of a cycloalkyl cyanide with subsequent hydrolysis as indicated:

$$\xrightarrow{RBr \ + \ NaNH_2} \xrightarrow[HOAc]{HBr}$$
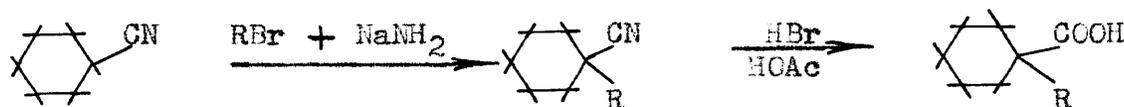
Reaction of Grignard Reagents with Tetrahydrophthalic Anhydride.—
Tilford and coworkers (45) treated phenyl or cyclohexyl magnesium bro-
mide with tetrahydrophthalic anhydride and obtained 2-benzoyl-Δ^4-
cyclohexenecarboxylic acid or 2-hexahydrobenzoyl-Δ^4-cyclohexenecar-
boxylic acid, respectively. The reaction is indicated:
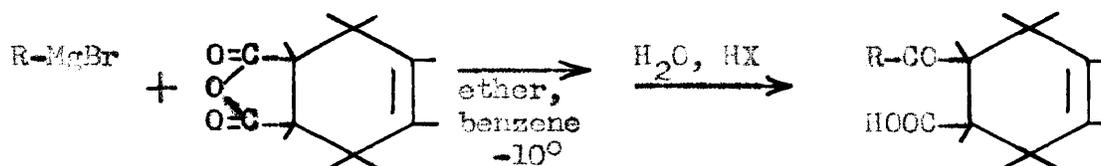
By hydrogenation of 2-benzoyl-Δ^4-cyclohexenecarboxylic acid,
these workers also prepared 2-benzoylcyclohexanecarboxylic acid and
2-benzylcyclohexanecarboxylic acid.

Reaction of Aliphatic Diazo Compounds with Unsaturated Esters.—
Staudinger and coworkers described the synthesis of substituted cyclo-
propanecarboxylic acids by reaction of aliphatic diazo compounds with
unsaturated esters (43). This method may be indicated by the equations
for the preparation of 2,2,3-triphenylcyclopropanecarboxylic acid:
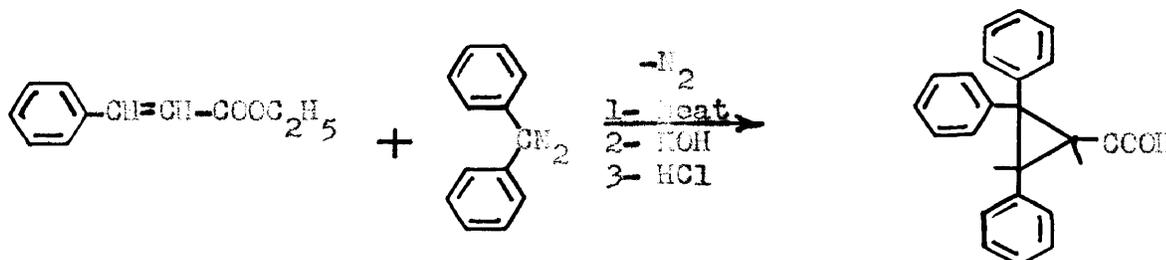
Reaction of Diazoacetic Ester with Unsaturated Hydrocarbons.—
There are innumerable reports, dating from 1893, of the reaction of ethyl
diazoacetate or its homologs with unsaturated compounds. At that date
studies by Buchner (6) indicated that the reaction in the cold resulted
in the formation of a pyrazoline intermediate. When the reaction was
carried out with heating, the pyrazoline intermediate usually could not
be isolated because of the cleavage of nitrogen which resulted in the

formation of derivatives of cyclopropanecarboxylic acid.

Recently D'yakonov has studied the catalytic effect of copper

powder on the reaction of ethyl diazoacetate and vinyl ethers or esters

with heating (16),(17). He obtained esters of cyclopropanecarboxylic

acids and also their unsaturated linear isomers.

$$CH_2=CH-O-R \quad \xrightarrow[\text{Cu, } \triangle]{\overset{-N_2}{N_2CH-COOC_2H_5}} \quad RO \overset{}{\diagdown}\!\!\!\!-COOC_2H_5 \quad + \quad \begin{array}{c} C_2H_5OOC-CH=CH-CH_2-O-R \\ + \\ C_2H_5OOC-CH=C-O-R \\ | \\ H_3C \end{array}$$
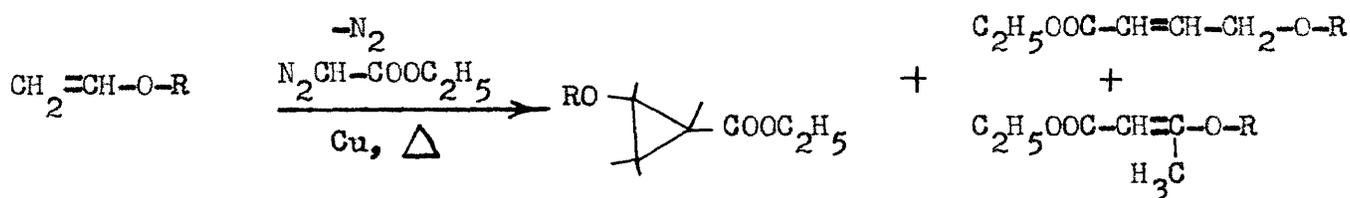
Wieland and Probst (49) studied the reaction of ethyl diazoacetate

and 1,1-diphenylethylene at elevated temperatures and were able to pre-

pare ethyl 2,2-diphenylcyclopropanecarboxylate and the corresponding
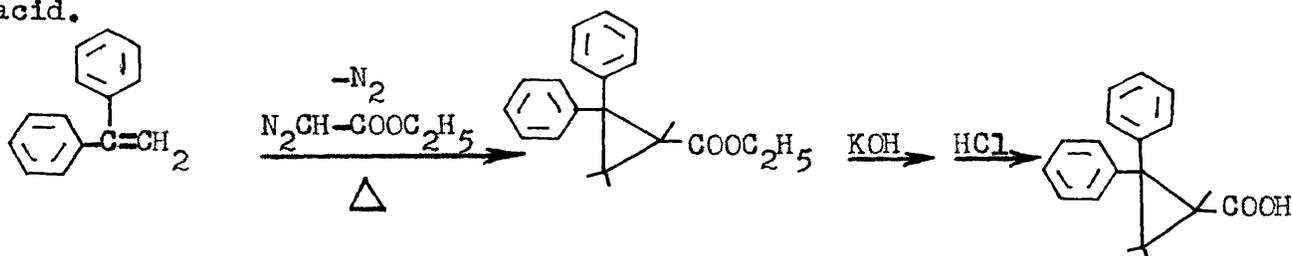
acid.

In 1885 Curtius and Buchner (14) showed that diazoacetic esters

react with benzene and its homologs on prolonged heating to form deriv-

atives of norcaradienecarboxylic acid. Drake and Sweeney studied the

analogous reaction of phenanthrene with ethyl diazoacetate in their

synthesis of dibenzonorcaradienecarboxylic acid (15):
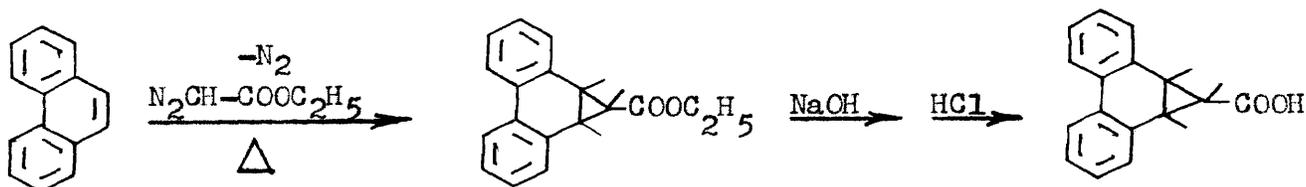
In 1909 Loose (32) reported the catalytic effect of copper on the reaction of pinene and benzene with ethyl diazoacetate in formation of the corresponding cyclopropane derivatives. The effects of copper and inert solvent upon the reaction between phenanthrene and ethyl diazo-acetate have been studied and are reported in this paper.

In 1893 Buchner reported that attempts to produce addition products of styrene and stilbene with diazoacetic ester were unsuccessful (6). Subsequently Buchner and Geronimo (7) were able to obtain 2-phenylcyclo-propanecarboxylic acid from styrene and their method was recently modified by Burger and Yost (8).
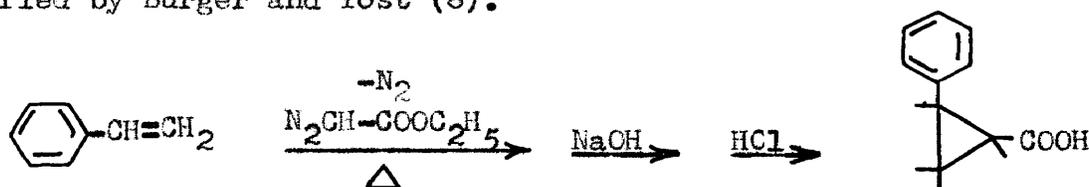
A search of the literature to date failed to reveal any successful reaction of ethyl diazoacetate with stilbene for production of ethyl 2,3-diphenylcyclopropanecarboxylate, and no report of the synthesis of the corresponding acid could be found. The details of the reaction of trans-stilbene with ethyl diazoacetate and its application to the synthesis of 2,3-diphenylcyclopropanecarboxylic acid are described in this paper.
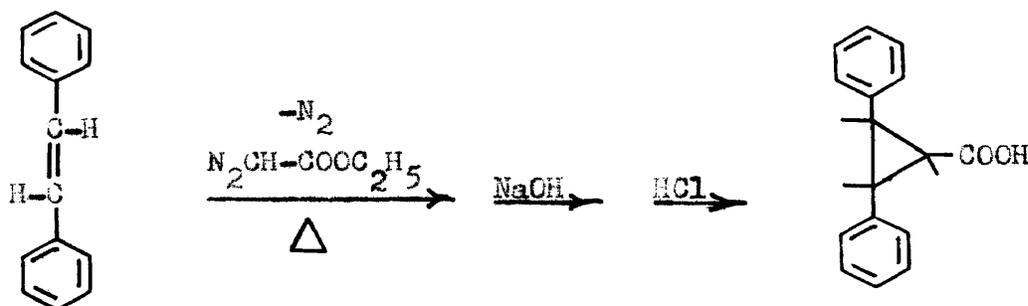
REVIEW OF METHODS OF SYNTHESIS OF DIALKYLAMINOALKYL ESTERS OR

THEIR HYDROHALIDES

Reaction of an Acid Halide with a Dialkylaminoalcohol.—Weston (48) synthesized basic ester hydrohalides by the reaction of an acid halide with a dialkylaminoalcohol, a method described earlier by Mannich (33).

$$R'-CO-X + HO-(CH_2)_n-NR_2 \xrightarrow[\text{benzene}]{\triangle} R'-CO-O-(CH_2)_n-NR_2 \cdot HX$$

The replacement of dialkylaminoalcohol by dialkylaminoalkylmercaptan led to the formation of the thio-analog, $R'-CO-S-(CH_2)_n-NR_2 \cdot HX$. Tilford and coworkers reported the use of pyridine as the solvent in the reaction of an acid chloride and a dialkylaminoalcohol to yield the free basic ester (45).

Reaction of an Acid with a Dialkylaminoalkyl Halide.—Horenstein and Pahlicke (26) originally described the formation of a basic ester hydrohalide by the heating of an acid with a dialkylaminoalkyl halide:

$$R'-CO-OH + X-(CH_2)_n-NR_2 \xrightarrow[\text{i-PrOH}]{\triangle} R'-CO-O-(CH_2)_n-NR_2 \cdot HX.$$
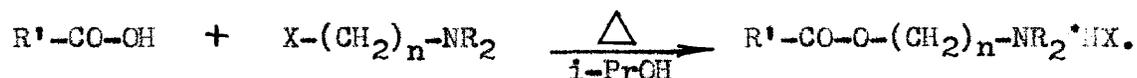
This method was employed by Burtner and Cusic (10) and also by Weston (48).

Amination of an ω-Haloalkyl Ester.—ω-Bromoalkyl esters may be prepared by the reaction of a polymethylene dibromide with the potassium salts of acids:

$$R-CO-OK + Br-(CH_2)_n-Br \longrightarrow R-CO-O-(CH_2)_n-Br + KBr$$
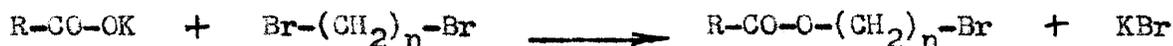
or by the reaction of acyl halides with bromohydrins:

$$R-CO-X + HO-(CH_2)_n-Br \xrightarrow{-HX} R-CO-O-(CH_2)_n-Br.$$
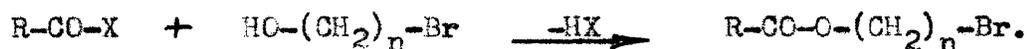
Both methods were described by Weston (48); while the latter was also described in a Swiss patent (21).

Amination of the ω-bromoalkyl ester with a suitable secondary amine produces a dialkylaminoalkyl ester:

$$R-CO-O-(CH_2)_n-Br \quad + \quad H-NR'_2 \quad \xrightarrow{-HBr} \quad R-CO-O-(CH_2)_n-NR'_2$$

<u>Transesterification between an Ester and a Dialkylaminoalcohol.</u>—— Tilford and coworkers (45) described the reaction between an ester and 2-diethylaminoethanol in xylene in the presence of sodium:

$$R-CO-OR' \quad + \quad HOCH_2CH_2N(C_2H_5)_2 \quad \xrightarrow[\underset{\triangle}{Na + xylene}]{-R'OH} \quad R-CO-OCH_2CH_2N(C_2H_5)_2.$$
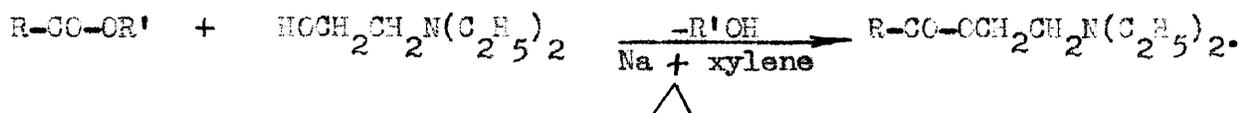
<u>Reaction of a Dialkylaminoalkyl p-Toluenesulfonate with a Salt.</u> —— This method is described in a Swiss patent (20):

$$RCOOH \quad + \quad CH_3-\!\!\!\bigcirc\!\!\!-SO_2-O-CH_2CH_2N(C_2H_5)_2 \quad + \quad KOH \quad \longrightarrow$$

$$R-CO-O-CH_2CH_2N(C_2H_5)_2 \quad + \quad CH_3-\!\!\!\bigcirc\!\!\!-SO_2-OK \quad + \quad H_2O$$
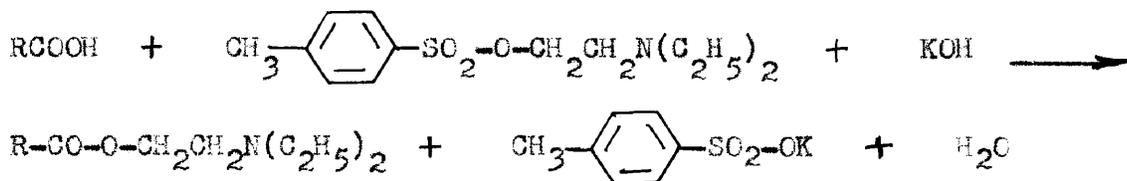
<u>Reaction of a Dialkylaminoalkyl Halide with a Salt.</u>—The heating of the alkali salt of an acid with a dialkylaminoalkyl halide in an inert solvent has found wide application in the synthesis of basic esters (20), (38),(44),(48).

$$RCOONa \quad + \quad X-CH_2CH_2-NR'_2 \quad \xrightarrow[i-PrOH]{\triangle} \quad R-CO-O-CH_2CH_2-NR'_2 \quad + \quad NaX$$

The preparation of the 2-diethylaminoethyl esters of dibenzonor-caradienecarboxylic acid, 2,2,3-triphenylcyclopropanecarboxylic acid, 2,2-diphenylcyclopropanecarboxylic and 2,3-diphenylcyclopropanecarboxylic acid by heating the corresponding sodium salts with N-(2-chloroethyl)-diethylamine in 2-propanol is described in this paper. Extensive

literature search has disclosed no previous synthesis of these partic-
ular esters, or other esters of these acids with aminoalcohols.
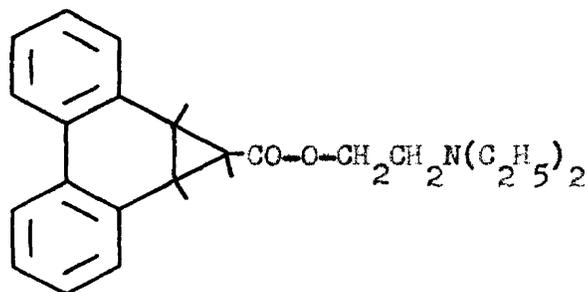
2-Diethylaminoethyl dibenzonorcaradienecarboxylate
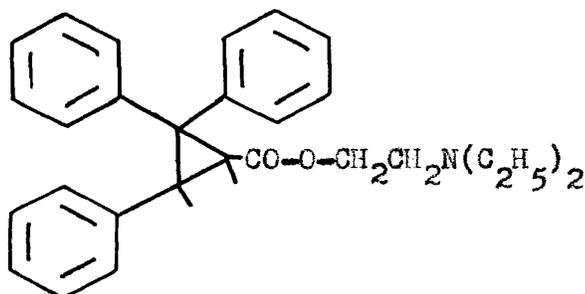
2-Diethylaminoethyl 2,2,3-triphenylcyclopropanecarboxylate
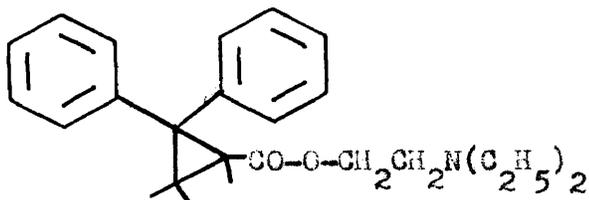
2-Diethylaminoethyl 2,2-diphenylcyclopropanecarboxylate
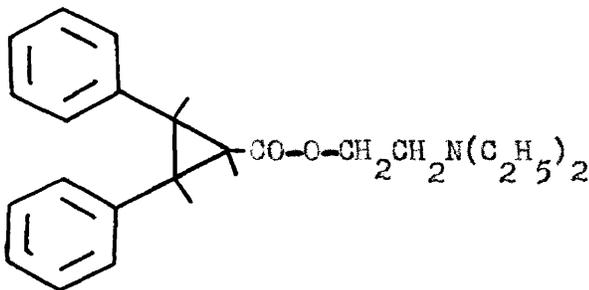
2-Diethylaminoethyl 2,3-diphenylcyclopropanecarboxylate

EXPERIMENTAL

SUBSTITUTED CYCLOPROPANECARBOXYLIC ACIDS

Two methods of synthesis were studied: the reaction of diphenyl-
diazomethane with an α,β-unsaturated ester and the reaction of ethyl
diazoacetate with an unsaturated hydrocarbon.

Benzophenone Hydrazone (9),(24).—Benzophenone (37.5 g., 0.206
mole) was dissolved in a mixture of 2-butanol (195 ml.) and toluene
(51 ml.) in a 500 ml. Erlenmeyer flask fitted with a Dean-Stark trap
and a reflux condenser. To this mixture was added hydrazine hydrate
(39 g. of 85% solution, 0.66 mole). The mixture was heated with re-
fluxing for nine hours, during which time 23.6 ml. of water was col-
lected in the Dean-Stark trap. The anhydrous solution of the hydrazone
was transferred to a 500 ml. distilling flask and the solvents were dis-
tilled (63-70°) under reduced pressure. The hot residual liquid was
poured into a 250 ml. beaker and chilled to induce crystallization.
The crystals were filtered with suction and rubbed dry on paper. Re-
crystallization from absolute alcohol yielded 14 g. of white crystals,
melting at 95-8° and representing a 35% yield.

Ethyl 2,2,3-Triphenylcyclopropanecarboxylate (43).—Diphenyldiazo-
methane (prepared from 14 g. of benzophenone hydrazone in an estimated
yield of 12 g., 0.062 mole) and ethyl cinnamate (11 g., 0.062 mole)
were mixed in a 250 ml. Erlenmeyer flask which was stoppered and allow-
ed to stand at room temperature. The red color of the diazo compound
disappeared within two weeks. The yellow syrup resulting after two

months standing, was heated on a steam bath until no further evolution of nitrogen could be detected. The syrupy residue was cooled and scratched to initiate crystallization. After standing several days, the residue solidified. The oily crystals were rubbed on a porous plate to remove the unchanged ethyl cinnamate, and 9.7 g. of yellow crystals were obtained, representing a 46% yield. The crude product was recrystallized from absolute ethanol (55 ml.) with recovery of 6 g. of white crystalline ester of melting point, 101.2-101.8° (corr.).

The cited reference gives the melting point as 93°; however, the product is probably a mixture of diastereoisomeric esters and the melting point might be expected to vary with the different proportions of each racemate in the product, depending on differences in the conditions or manner of preparation.

2,2,3-Triphenylcyclopropanecarboxylic Acid (43).--Ethyl 2,2,3-triphenylcyclopropanecarboxylate (6 g., 0.018 mole) was heated under reflux with 50% excess of alcoholic potassium hydroxide for one hour. The alcohol was distilled and the residual potassium salt was dissolved in 500 ml. of warm water (the aqueous dispersion of this potassium soap was opalescent and somewhat turbid and had to be kept warm to prevent crystallization which occurred easily on cooling). The acid was precipitated as a cream-colored granular solid by the slow addition of a slight excess of dilute hydrochloric acid with stirring. The precipitated acid was filtered and dried. The 5 g. of acid, corresponding to 91% yield from the ester, had a melting point of 202.5-204° (corr.). Staudinger gave 192° as the melting point of this acid, but a variation in the proportion of diastereoisomeric acids would explain this difference in melting points.

The neutral equivalent of the acid was found to be 320.8, in reasonable agreement with the molecular weight of 314.4 for the monocarboxylic acid.

Ethyl Diazoacetate.—Ethyl diazoacetate was prepared in 65% yield by the method of Womack and Nelson (50),(17) and was used without further purification as soon as possible after preparation.

2,2-Diphenylcyclopropanecarboxylic Acid (49).—Ethyl diazoacetate (16 g., 0.14 mole) was mixed with 1,1-diphenylethylene (24 g., 0.13 mole) in a 500 ml. round-bottomed flask equipped with a reflux condenser and mechanical stirrer. The mixture was heated at 130° for two and one-half hours with efficient stirring, and then allowed to cool overnight. Subsequently this reaction mixture was heated on a steam bath under reduced pressure to remove any unreacted ethyl diazoacetate and then distilled at 7-8 mm. pressure, yielding three fractions: I - boiling up to 141°, principally 1,1-diphenylethylene; II - 2.0 g. boiling at 141-160° and III - 9.7 g. boiling at 160-184°.

Fractions II and III were separately saponified by refluxing with 30 ml. and 125 ml. of N/2 alcoholic potassium hydroxide, respectively. The alcohol was distilled from the saponification mixtures and the residual solids were dissolved in water. The free acid was precipitated by the slow addition of a slight excess of dilute hydrochloric acid with stirring. Fraction II yielded 0.6 g. of pink-brown crystalline mass which on recrystallization from carbon tetrachloride gave 0.5 g. of white crystals melting at 174.7-176.3° (corr.). Fraction III yielded 3.0 g. of light brown crystals which were mechanically separated from 3.0 g. of brown resin. Separate recrystallizations from carbon tetrachloride gave 2.4 g. and 0.9 g. of white crystals having melting points

of 170.3-171.5° (corr.) and 171.0-172.5° (corr.), respectively. The total weight of once-recrystallized material corresponds to 12% based on the weight of 1,1-diphenylethylene used. The three portions of acid were combined and recrystallized once more from carbon tetrachloride yielding white crystals melting at 171.6-171.8° (corr.) in agreement with the melting point reported by Wieland and Probst (49).

The higher melting points may indicate that it is desirable to refine the acid further but a twenty to twenty-five per cent loss of material resulted during each recrystallization. Since the melting point was sharp (0.2° range), the acid was sufficiently pure for use after two recrystallizations.

Dibenzonorcaradienecarboxylic Acid (15).—The apparatus used was essentially that described by Drake and Sweeney. The reaction was carried out in a 500 ml. round-bottomed flask having three parallel necks equipped with a mercury-sealed mechanical stirrer, a reflux condenser and a 50 ml. burette to serve as a dropping funnel. In the top of the condenser was fitted a T-tube, one outlet of which was connected to the top of the burette to equalize the pressures and the other outlet was connected to a Mariotte flask for collecting nitrogen evolved in the reaction. The nitrogen was allowed to displace water which flowed from the Mariotte flask (efflux capacity of seven liters) through a leveling bulb into a large graduated cylinder. The reaction flask was supported in a Glascol electric heating mantle containing an iron-constantan thermocouple which was connected at the cold (ice-water) junction with a millivoltmeter to enable determination of the reaction temperature.

Purified phenanthrene (1) (161 g., 0.905 mole) was placed in the

reaction flask and the outside temperature was brought to 150°. After the phenanthrene had melted, the mechanical stirrer was started and allowed to rotate slowly throughout the entire reaction. Ethyl diazo-acetate (39 g., 0.34 mole) was then added dropwise from the burette over a period of twelve and one-half hours.

Evolution of nitrogen started within a few minutes after the addition of the first drops of the ester, and 150 ml. were collected at the end of twenty minutes. With constant rate of addition, nitrogen was evolved at a constant rate. The rate of nitrogen evolution dropped sharply after the addition of the last portion of the ester. A total of 8160 ml., measured at 27°, was collected.

The reaction mixture was dissolved in 95% alcohol (375 ml.) along with sodium hydroxide (15 g.) dissolved in water (20 ml.). The mixture was refluxed for two hours to saponify the ester, and then the alcohol was removed as completely as possible by distillation at reduced pressure. The residue was extracted with hot water (1 liter) applied in portions. The aqueous extract was shaken in a separatory funnel with several portions of ether to remove the contaminating phenanthrene and then was concentrated to one-half of its volume (approximately 500 ml.) on a steam bath under reduced pressure after the addition of norite (0.5 g.). The norite treatment failed to decolorize the aqueous solution. The acid was precipitated from the warm filtered solution of the sodium salt by the slow addition of a slight excess of dilute hydrochloric acid with stirring. The mother liquor was light yellow after the precipitation. The acid did not appear to be sticky; however, the mixture was cooled overnight and then filtered. The dry, powdered crude acid weighed 32 g. corresponding to 41% yield based on the nitrogen evolved.

The finely powdered crude material was rubbed to a paste with cold dioxane (50 ml.) on a fritted glass funnel and the liquid was removed by suction as quickly as possible. Most of the brown impurity and some of the product dissolved immediately in the dioxane and was filtered off. The remaining solid was dissolved from the funnel with hot dioxane (170 ml.). The hot solution was decolorized by heating with norite (1 g.) for five minutes. The mixture was filtered through fluted paper and cooled. Filtration of the crystalline precipitate followed by washing with cold dioxane and drying over calcium chloride in a vacuum desiccator gave white crystals (2.1 g.) melting at 257-8° (corr.). Drake and Sweeney reported the melting point to be 257.5-258°.

On standing, the saturated dioxane mother liquor deposited an additional 0.5 g. of almost pure acid. The 2.6 g. of pure acid represents a yield of 3.3% based on the nitrogen evolved.

Preparation of Dibenzonorcaradienecarboxylic Acid Using an Inert Solvent.—The reaction was carried out in the Drake-Sweeney type apparatus using ethyl diazoacetate (24 g., 0.21 mole), phenanthrene (90 g., 0.50 mole) and cetane (90 g.) (replacing an equal weight of phenanthrene with the inert hydrocarbon as the solvent). Five and one-half hours of heating at 150° caused a total evolution of 4100 ml. of nitrogen collected at 27°.

The reaction mixture was saponified and the sodium dibenzonorcaradienecarboxylate was extracted with hot water as described previously. Acidification of the solution of the sodium salt produced a sticky brown mass which was removed and purified somewhat by rubbing with cold dioxane which was immediately sucked off with most of the brown material. Recrystallization of the lightly colored residue gave white crystals (1.55 g., corresponding to 4.0% yield based on the nitrogen evolved)

with a melting point of 257-8° (corr.).

Preparation of Dibenzonorcaradienecarboxylic Acid Using a Copper Catalyst.—The same type of apparatus as previously described was used in this experiment. To phenanthrene (110 g., 0.618 mole) stirred with powdered copper (15 g.) between 140° and 150°, was added dropwise ethyl diazoacetate (19.7 g., 0.173 mole) over the course of eight and one-half hours, resulting in the evolution of 3500 ml. of nitrogen, measured at 27°.

The reaction mixture was worked up as previously described, yielding the crude acid (15 g.) from which the dioxane washing and recrystallization produced the pure acid (2.1 g., corresponding to 6.2% yield based on the nitrogen evolved) with a melting point of 257-8° (corr.). Some of the acid (about 0.6 g.) was subsequently recovered from the mother liquor so that the yield was actually considerably higher.

2,3-Diphenylcyclopropanecarboxylic Acid.—The Drake-Sweeney type of apparatus was used in this reaction. Ethyl diazoacetate (25 g., 0.22 mole) was added dropwise to trans-stilbene (41) (90 g., 0.50 mole) with stirring at 150° during three hours. The volume of nitrogen evolved was 4540 ml. (measured at 27°). The reaction mass was allowed to cool and the resulting solid was allowed to stand several days.

The mass was carefully melted again and poured into a two liter Florence flask. The solid adhering to the inside of the reaction flask was dissolved by means of hot absolute alcohol (1 liter) in portions and the solution was added to the contents of the Florence flask. Sodium hydroxide (20 g., 0.50 mole), dissolved in water (30 ml.), was added to the hot alcoholic solution; and the resulting mixture was heated under reflux for five hours to saponify the ester.

Subsequently the alcohol was distilled from the mixture under reduced pressure. The sodium salt-stilbene mixture was extracted with several portions of hot water, and the extracts were passed through a fritted glass funnel to retain most of the stilbene. After the extract had cooled, some crystalline beads separated. Attempts to extract these with ether were unsuccessful, suggesting that they were actually particles of the desired sodium salt. (Later these were shown to be soluble in water, producing a solution which was basic to litmus paper and which yielded a precipitate of acid upon acidification with dilute hydrochloric acid.) These crystalline beads were removed from the aqueous extract by filtration.

Concentrated hydrochloric acid (45 ml., 0.52 mole) was added slowly with stirring to the clear reddish-brown filtrate; whereupon the mixture became light yellow, and reddish-brown resinous masses accumulated on the sides of the container. These masses became stiff enough to be dislodged within an hour and were filtered, using a Buchner funnel, and sucked as dry as possible. The mass became dry after standing three days and was powdered. The amount of crude acid (16 g., not including the small amount derivable from the beads of the sodium salt) corresponded to a 37% yield, based on the volume of nitrogen evolved.

Attempts to recrystallize the crude acid from the usual recrystallization solvents for organic acids were not successful. One-half of the crude acid was dissolved with the aid of heat in an amount of ten percent aqueous solution of sodium hydroxide slightly in excess of the calculated amount, and the mixture was diluted with an equal volume of hot water. The resulting solution of the sodium salt was chilled in the refrigerator; whereupon light yellow crystals of the

sodium salt separated from the aqueous solution. These crystals were filtered on a Buchner funnel and carefully washed with cold water. They were dissolved in water and the solution was decolorized with the aid of norite. The acid was precipitated by the slow addition of a slight excess of dilute hydrochloric acid with stirring. The white crystalline acid (2.0 g.) was filtered with suction and was powdered after drying several days in a desiccator. The acid melted at 157.0-157.8° (corr.); and its neutral equivalent was found to be 241.6 which agrees favorably with the molecular weight of $C_{16}H_{14}O_2$ (2,3-diphenyl-cyclopropanecarboxylic acid), 238.3.

The acid (1.0 g.) was recrystallized from a mixture of petroleum ether (100 ml.) and carbon tetrachloride (20 ml.). The resulting, white microcrystalline material was filtered with suction on a Buchner funnel, air-dried and stored in a vacuum desiccator over calcium chloride. By this means, pure white crystals (400 mg.) with a melting point of 157.0-157.6° (corr.) were obtained.

Analysis: Calculated for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.34, 80.29; H, 5.98, 5.91.

HYDROCHLORIDES OF 2-DIETHYLAMINOETHYL ESTERS

N-(2-Chloroethyl)-diethylamine.—By application of the method described by Gilman and Shirley (23) for the 3-chloropropyl homolog, substituting 2-diethylaminoethanol for the 3-diethylaminopropanol, N-(2-chloroethyl)-diethylamine (42) was prepared. A 42% yield of the product, distilling at 56° at 24 mm. and at 51° at 21 mm., was obtained.

The free base was used as soon as possible; otherwise it was preserved as the hydrochloride. The latter was formed by dissolving the free base in a slight excess of 6 N hydrochloric acid.

2-Diethylaminoethyl 2,2,3-Triphenylcyclopropanecarboxylate Hydro-
chloride.—The dry sodium salt prepared from 2,2,3-triphenylcyclopro-
panecarboxylic acid (3.2 g., 0.010 mole) was heated with N-(2-chloro-
ethyl)-diethylamine in absolute 2-propanol (50 ml.) under reflux for
six hours. The 2-propanol was removed by distillation on a steam bath,
the last traces being distilled under reduced pressure so that any
small amount of unreacted aminoalkylhalide was also removed.

The residue was extracted four times with 25 ml. portions of ab-
solute ether, each extract being passed through a filter. The filtrate
was allowed to stand overnight in a stoppered 250 ml. Erlenmeyer flask.
This filtrate was filtered again to clarify it and then was saturated
with dry hydrogen chloride and allowed to stand overnight. The crys-
talline hydrochloride was separated from the ether by decantation and
recrystallized from a mixture of absolute ethanol (10 ml.) and absolute
isopropyl ether (45 ml.). The white crystalline hydrochloride weighed
3.8 g. (83% yield) and melted at 134.0-134.7° (corr.). Recrystalliza-
tion of this material from a mixture of absolute ethanol (10 ml.) and
absolute isopropyl ether (45 ml.) produced 3.4 g. of white crystals
which melted at 134.5-135.2° (corr.).

Analysis: Calculated for $C_{28}H_{32}ClNO_2$: Cl, 7.88; N, 3.11.
Found: Cl, 7.99, 7.88; N, 2.93, 2.93.

2-Diethylaminoethyl 2,2-Diphenylcyclopropanecarboxylate Hydro-
chloride.—Essentially the same method of preparation as that described
for 2-diethylaminoethyl 2,2,3-triphenylcyclopropanecarboxylate hydro-
chloride was employed. The dry sodium salt prepared from 2,2-diphenyl-
cyclopropanecarboxylic acid (3.3 g., 0.014 mole) was treated with
N-(2-chloroethyl)-diethylamine (2.1 ml., 1.9 g., 0.014 mole) in ab-
solute 2-propanol (50 ml.) as described. The solvent was distilled

and the residue was extracted with absolute ether. The basic ester hydrochloride was precipitated from the ethereal solution and the ether was distilled. The hydrochloride was recrystallized from a mixture of absolute ethanol (10 ml.) and absolute isopropyl ether (38 ml.), yielding white crystals (4.2 g., 81% yield) which melted at 147.0-147.7° (corr.). The subsequent recrystallization of this material (4.0 g.) from a mixture of absolute ethanol (10 ml.) and absolute isopropyl ether (34 ml.) produced white crystals (3.7 g.) which melted at 147.5-148.2° (corr.).

Analysis: Calculated for $C_{22}H_{28}ClNO_2$: Cl, 9.48; N, 3.74. Found: Cl, 9.62, 9.54; N, 3.75, 3.76.

2-Diethylaminoethyl Dibenzonorcaradienecarboxylate Hydrochloride.—The same method of preparation was used. The dry sodium salt prepared from dibenzonorcaradienecarboxylic acid (3.2 g., 0.013 mole) was treated with N-(2-chloroethyl)-diethylamine (2.0 ml., 1.8 g., 0.013 mole) in absolute 2-propanol (100 ml.) as described. The solvent was distilled and the residue was extracted with absolute ether. The basic ester hydrochloride was precipitated from the ethereal solution and the ether was distilled. The hydrochloride was recrystallized from a mixture of absolute ethanol (17 ml.) and absolute isopropyl ether (50 ml.) yielding white crystals (3.5 g., 70% yield) which melted at 191.8-192.8° (corr.). Subsequent recrystallization of this material from a mixture of absolute ethanol (35 ml.) and absolute isopropyl ether (20 ml.) produced white crystals (3.0 g.) which melted at 192.0-193.0° (corr.).

Analysis: Calculated for $C_{22}H_{26}ClNO_2$: Cl, 9.54; N, 3.77. Found: Cl, 9.63, 9.50; N, 3.75, 3.75.

2-Diethylaminoethyl 2,3-Diphenylcyclopropanecarboxylate Hydrochloride.—The same method of preparation was used. Sodium 2,3-diphenylcyclopropanecarboxylate (1.5 g., 0.0053 mole) was treated with

N-(2-chloroethyl)-diethylamine (0.85 ml., 0.77 g., 0.0057 mole) in absolute 2-propanol (50 ml.) as described. The solvent was distilled and the residue was extracted with absolute ether. The basic ester hydrochloride was precipitated from the ethereal solution and the ether was distilled. The hydrochloride was recrystallized from a mixture of absolute ethanol (10 ml.) and absolute isopropyl ether (50 ml.) yielding white crystals (1.1 g., 52% yield) which melted at 190.4-191.9° (corr.). Subsequent recrystallization of this material from a mixture of absolute ethanol (32 ml.) and absolute isopropyl ether (36 ml.) produced white crystals (0.9 g.) which melted at 190.6-191.4° (corr.).

Analysis: Calculated for $C_{22}H_{28}ClNO_2$: Cl, 9.48; N, 3.74. Found: Cl, 9.60, 9.35; N, 3.75, 3.75.

EVIDENCE SUPPORTING THE STRUCTURE ASSIGNED

2,3-DIPHENYLCYCLOPROPANECARBOXYLIC ACID

The neutral equivalent, 241.6, found for the acid prepared from the ester obtained by heating ethyl diazoacetate with **trans**-stilbene indicates that one carboxymethine ($\equiv$CH-COOH) group was added across one of the double bonds of the hydrocarbon to produce an acid, $C_{16}H_{14}O_2$, with a molecular weight of 238.3. This acid must have one of the following structures:
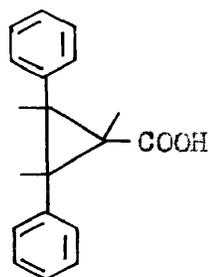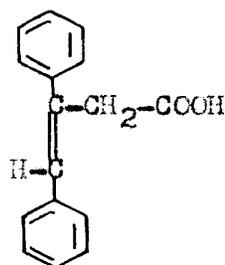
I   II
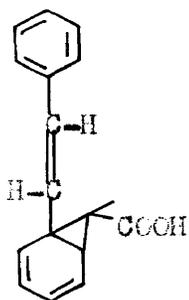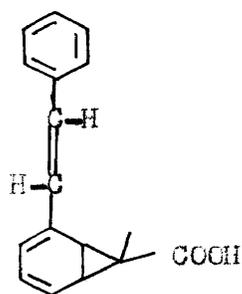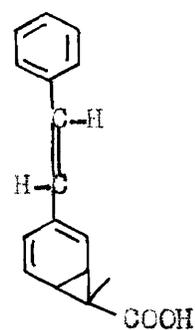
III   IV   V

On oxidation with alkaline potassium permanganate, structure I would be expected to yield only benzoic acid besides carbon dioxide or possibly also oxalic acid; II should yield benzoic acid and carbon dioxide; III, benzoic and phthalic acids; IV, benzoic, phthalic and isophthalic acids; V, benzoic, isophthalic and terephthalic acids.

The sodium salt of the acid did not reduce alkaline potassium permanganate in the cold during seventeen and one-half hours; but, on heating for two hours on a steam bath, an appreciable amount of manganese dioxide was formed. The manganese dioxide and excess permanganate were reduced by sodium sulfite in the presence of dilute sulfuric acid with heating. The precipitated white acid was extracted with chloroform in which phthalic acid and its isomers are only very slightly soluble. The chloroform extract was evaporated leaving a residue which was heated on a hot plate and shown to yield easily sublimable white needles with a melting point of 109-123° (principally benzoic acid) and a non-sublimable residue with a melting point of 158° (the original melting point of the acid).

The aqueous layer was evaporated to dryness and the following observations were made: 1-the fluorescein test for phthalic acid (2) was found to be negative, 2- ignition of the residue did not produce charring, 3- ignition of the residue treated with sodium hydroxide solution did not produce charring and 4- the pyridine-copper sulfate test for terephthalic acid (40) was found to be negative. These tests seem to eliminate structures III, IV and V as possibilities for the acid prepared.

The necessity of heating to cause reduction of permanganate favors structure I because the unsaturated isomer, II, and norcaradienecarboxylic acid derivatives, which are less complex than dibenzonorcaradiene-carboxylic acid, such as III, IV and V should be rather easily oxidized (15). The empirical rule of Buchner, cited by Drake and Sweeney (15), that the condensation of ethyl diazoacetate with an aromatic hydrocarbon to form cyclopropane derivatives always involves addition to a non-substituted carbon atom, is an argument against structure III.

The observation that the pure crystalline acid does not decolorize bromine dissolved in carbon tetrachloride, supports structure I in that it should be the least active toward bromine.

The reaction of dibenzonorcaradienecarboxylic acid with concentrated sulfuric acid to form a green color (15, p. 72) was observed. Loose (32) confirmed Braren and Buchner's report of a similar color reaction (cherry red through violet and blue to green) of "pseudophenylacetic ester" (ethyl norcaradienecarboxylate) (5). The solution of the 2,3-diphenylcyclopropanecarboxylic acid in concentrated sulfuric acid produces only a yellow color with no trace of the green which might be associated with the norcaradiene derivatives.

DISCUSSION OF RESULTS

The application of the specific catalytic effect of copper (32), (17) upon the reaction of ethyl diazoacetate with unsaturated hydrocarbons seems to have almost doubled the yield of dibenzonorcaradienecarboxylic acid from phenanthrene. Unfortunately, an exact comparison of yields of dibenzonorcaradienecarboxylic acid, prepared by the various procedures, is not possible; because the proportion of by-products (15) in the crude acid probably varies with the conditions or manner of preparation, and the dioxane method of purification of the crude acid is very wasteful. The apparently slight solubility of sodium dibenzonorcaradienecarboxylate in cold water may allow simple purification of the acid by recrystallization of the sodium salt from water with decolorization. It is also possible that purification may be effected by recrystallization of the salts formed with suitable amines (25).

The use of the inert solvent, cetane, in the reaction of ethyl diazoacetate with phenanthrene did not alter the yield appreciably. This modification has the advantage that smaller quantities of the expensive purified phenanthrene, or other hydrocarbon, are required.

The use of copper powder in one reaction of ethyl diazoacetate with trans-stilbene led to the formation of what is believed to be the unsaturated isomer (II) of 2,3-diphenylcyclopropanecarboxylic acid (I); because benzoic acid was isolated from the saponified ester instead of the desired 2,3-diphenylcyclopropanecarboxylic acid and the odor of benzaldehyde was prominent in the reaction mixture. The two possible courses of reaction are shown by the following equations, in which an attempt has been made to explain the simultaneous formation of benzaldehyde and benzoic acid.

TWO POSSIBLE COURSES OF REACTION OF
ETHYL DIAZOACETATE WITH TRANS-STILBENE
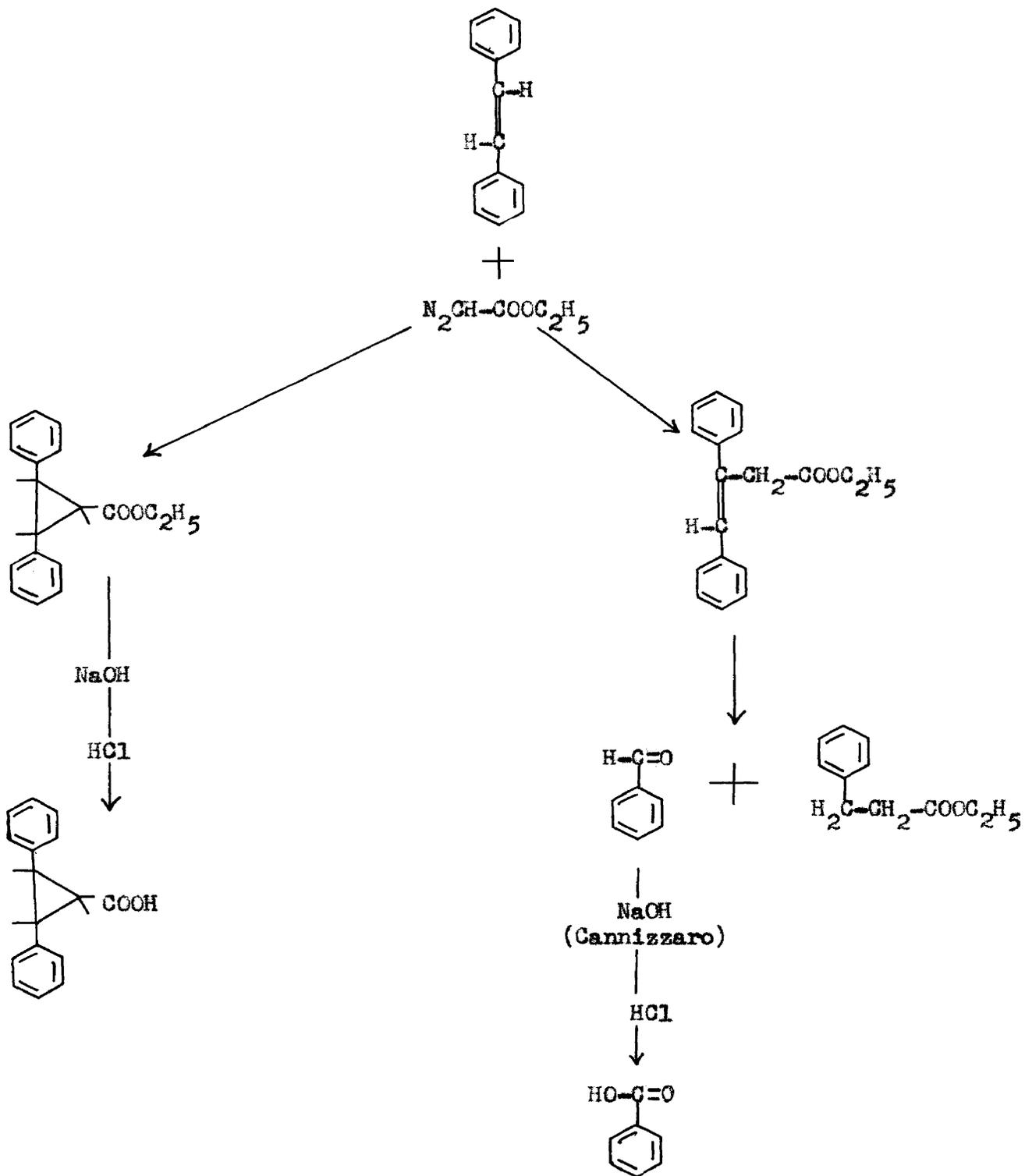
One attempt to confirm the formation of the unsaturated isomer by isolation of hydrocinnamic acid from the pungent acidified filtrate remaining after removal of benzoic acid, was unsuccessful.

The effect of copper in the preparation of 2,3-diphenylcyclopropanecarboxylic acid should be reinvestigated with precautions against the possible deleterious effects of moisture in the ethyl diazoacetate or of excess heating (32) during the reaction. Protection against overheating may be accomplished by adding cetane to the trans-stilbene to form a lower melting mixture, permitting the reaction to be carried out at somewhat lower temperatures (100-125°).

The method employed for preparation of the basic esters is especially applicable for preparation of small quantities of such esters, and the observed yields (52-83%) are satisfactory.

All four of the basic ester hydrochlorides produce a numbing sensation when a few crystals are applied to the tongue. This evidence of possible local anesthetic activity and the structural relationship to known antispasmodics suggest that their pharmacologic properties, especially spasmolytic and local anesthetic activity, should be investigated.

SUMMARY

1. The reaction of ethyl diazoacetate with phenanthrene, 1,1-di-
   phenylethylene and trans-stilbene, and the reaction of diphenyl-
   diazomethane with ethyl cinnamate, were investigated for the prep-
   aration of substituted cyclopropanecarboxylic acids.

2. Cetane, which does not react with ethyl diazoacetate, was sub-
   stituted for part of the excess hydrocarbon generally used as
   solvent in the reaction with ethyl diazoacetate at elevated tem-
   peratures, without decreasing the yield in the case of phenan-
   threne.

3. Powdered copper was observed to exert a catalytic effect upon the
   reaction of ethyl diazoacetate with phenanthrene.

4. An acid not previously described in the literature was prepared
   by the hydrolysis of the product of the reaction of ethyl diazo-
   acetate with trans-stilbene. It was assigned the structure of
   2,3-diphenylcyclopropanecarboxylic acid on the basis of its
   stability toward hot alkali, studies of its oxidative degradation
   products and its color reaction with concentrated sulfuric acid.

5. An undesirable course of reaction was observed in one experiment
   concerned with the effect of powdered copper on the reaction be-
   tween ethyl diazoacetate and trans-stilbene at an elevated tempera-
   ture.

6. The hydrochlorides of the 2-diethylaminoethyl esters of dibenzo-
   norcaradienecarboxylic acid, 2,2,3-triphenylcyclopropanecarboxylic

acid, 2,2-diphenylcyclopropanecarboxylic acid and 2,3-diphenyl-cyclopropanecarboxylic acid, which have not been previously described in the literature, were prepared by reaction of hydrogen chloride with the basic esters obtained by heating N-(2-chloroethyl)-diethylamine with the sodium salts of the corresponding acids.

7. Possible pharmacologic properties of the new basic ester derivatives have been suggested.

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