SPIRO-PYRIMIDINE SYNTHESIS

By

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fulfillment of the requirements for
the degree of Doctor of
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TABLE OF CONTENTS

		Page
I.	INTRODUCTION	1
II.	NOMENCLATURE	12
III.	DISCUSSION OF RESULTS	13
IV.	EXPERIMENTAL	15
V.	SUMMARY	38
VI.	BIBLIOGRAPHY	39

I. INTRODUCTION

The development of synthetic drugs which have no counterpart in nature has been dependent for the most part on the recognition of the relationship between physiological activity and chemical structure. Once a given molecule is known to exert a characteristic physiological action, numerous changes can be made in the parent substance, in order to obtain that compound possessing the optimum of the desired physiological qualities.

There are a number of chemical compounds which, in a given concentration, depress the central nervous system of living animals to the extent that both the automatic activity and the normal responsiveness of the living system are temporarily decreased or even abolished.

The diverse structures of the organic compounds which exhibit either hypnotic or anesthetic properties include hydrocarbons, ethers, alcohols, aldehydes, ketones, acyl ureas, urethanes, hydantoins, barbituric acids, sulfones, orthoformates, glycols, alkyl ureas, esters, oximes, acetals, and amides.

There are various sets of physical-chemical criteria which, in the light of present knowledge seem essential in a substance having hypnotic action, although not all compounds possessing these criteria are, necessarily, hypnotics.

Since the above structures have so little in common, the hypnotic action must depend on some property of the molecule as a whole and, more specifically, on its physical-chemical properties. Thus, changes in chemical structure brought about by the introduction of new groups or elements, or the rearrangement of the spatial relationship of the existing atoms and groups seems to effect the hypnotic

activity by modifying the physical-chemical properties, although specific groups may be responsible for certain side-reactions.

A thread of similarity runs through this apparently diverse group of compounds. In each we find hydrocarbon groups attached to polar groups. The hydrocarbon group gives to the molecule a tendency to lipoid solubility, while the polar groups confer water solubility. Briefly then, one might consider a hypnotic as composed of a fat-soluble hydrocarbon group in which the hypnotic action may be presumed to reside, joined to a water-soluble group which affords the necessary degree of solubility in the body fluids.

The only common chemical characteristic that can be ascribed to this varied group of compounds is a degree of chemical stability which prevents a too rapid destruction in the body (i.e., oxidation, and hydrolysis) before they exert their effect, yet permit a certain necessary degree of degradation, since compounds excreted unchanged exert little or no effect.

Since the preparation of 5,5-diethyl barbituric acid (Veronal or Barbital) by Fischer and von Mering,[1] and Fischer and Dilthey[2], and the subsequent discovery of its hypnotic properties, a large amount of research has been carried out with a view to securing hypnotics superior to this substance. These investigators were aware that certain of the compounds were more active as hypnotics than others and that the effect could be markedly changed by varying the chemical nature of the substituent radical. In general, these attempts have centered on substitution in

position 5, in which the effect of a very large number of organic radicals has been investigated.

Subsequent investigations[3,4] have shown that those barbituric acids in which the sum of the carbon atoms in the two substituent groups in position 5, is six, seven, or eight, are the most effective. When evaluated on rats, cats, rabbits, or mice, by the intravenous or subcutaneous injection of their sodium salts, this group shows, in most instances, a wider margin of safety between the anesthetic dose and the toxic dose than does, for example, diethylbarbituric acid.

From the study of scores of these barbituric acid derivatives, it has been possible to arrive at some reasonable conclusions regarding the pharmacological effects of lengthening the saturated hydrocarbon radicals on the carbon atom in the 5 position,[5] the influence of unsaturation in these radicals,[6] and the effect of substitution on the nitrogen of the barbituric acid nucleus.[7] N-alkyl and N-aryl barbituric acids have been prepared by Hepner and Frankenberg.[8] Also, the results produced by other modifications have been studied, such as substitution of cyclic structures, halogens, ether groups, sulfur, amino radicals, etc. in the barbituric acid molecule.

A correct structural formula was assigned to barbituric acid by Mülder[9] and its synthesis from urea and malonic acid under the action of phosphorus oxychloride was accomplished by Grimaux.[10]

5,5-Dimethylbarbituric acid is obtained by the interaction of the silver salt of barbituric acid and methyl iodide.[11] This method,

however, cannot be applied successfully for the introduction of alkyl groups higher than methyl. Approaches to the higher homologues exist in the condensation of mono- and dialkylmalonyldichlorides, mono- and dialkylmalonic esters, mono- and dialkylcyanoacetic esters, and mono- and dialkylmalononitriles, with urea, thiourea, or guanidine. Thereby, the 5-mono- or dialkyl barbituric acids or the corresponding thio- and imino- derivatives are obtained by condensation in the presence of sodium alcoholates. The latter on hydrolysis give the corresponding barbituric acids.

Some of the varied procedures which have been employed are here briefly outlined.

1. Condensation of the neutral esters of carbonic acid with the diamide of dialkyl malonic acid in the presence of sodium ethylate.[12]

2. Heating of dialkylmalonuric amides with sulfuric acid.[13]

3. Condensation of dialkyl malonic esters with urea in the presence of absolute alcohol and sodium ethoxide.[2]

4. Heating of dialkyl malonic acid esters and urea with the disodium salt of cyanamide.[14]

5. The reaction of dialkylmalonylchlorides with ureo-carbonic esters, COOR splitting off.[15]

6. Melting of dialkylmalonyldiurethanes in ammonia and heating.[16]

7. Treatment of dialkylmalonic acid diamides with oxalyl chloride.[17]

8. Acid hydrolysis of dialkylmalonyl guanidine.[18]

9. Heating of a mixture of guanyl urea and dialkylmalonyl chloride.[19,20]

10. Treatment of the sodium salt[21] or the silver salt[22] of monoalkyl barbituric acids with an alkyl halide.

11. Treatment of the 2-thio-4-imino-5-dialkyl-6-hydroxy-pyrimidines[23] or, 2,4-diimino-5-dialkyl-6-hydroxypyrimidines[24] with acids.

12. Heating of dialkylmalonyl thiourea with aqueous lead acetate.[25]

13. Heating of dialkylmalonyldiurethanes in the presence of carbonic acid derivatives such as urea and diphenyl carbonate.[26]

14. Treatment of 5,5-dialkyl, mono, di, or triiminebarbituric acids with alkyl nitrites.[27]

15. Condensation of dialkyl malonic esters with diurea.[28]

16. Heating of a mixture of guanylurea hydrochloride and dialkyl cyanacetic ester. The product is saponified with sulfuric acid.[29]

Innumerable modifications of these methods have been successfully employed for the synthesis of dialkyl barbituric acids.

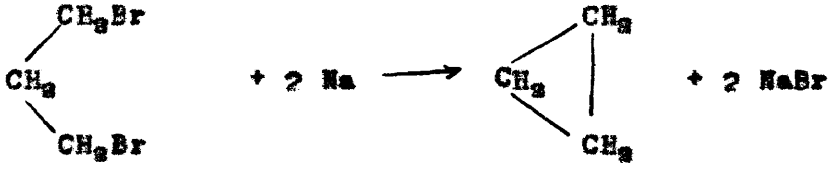
Krantz, Carr, Forman, and Evans,[30] report a cyclopropyl methyl ether (Cyprome) which possesses anesthetic properties more potent than those of diethyl ether. The compound has physiological and physical qualities which render it more desirable for such purposes. Cyclopropane gas, likewise has been shown to possess anesthetic properties. Anesthetization with cyclopropane after the administration of barbiturate produced, in pharmacological studies, no cardiac disturbance. On the assumption that the presence of the cyclopropyl group attributes to a molecule desirable physiological qualities, this research was initiated to synthesize a barbituric

acid containing the cyclopropyl group, and in this way to incorporate within a single molecule, the combined anesthetic qualities of the barbituric acid molecule and of the cyclopropyl group.

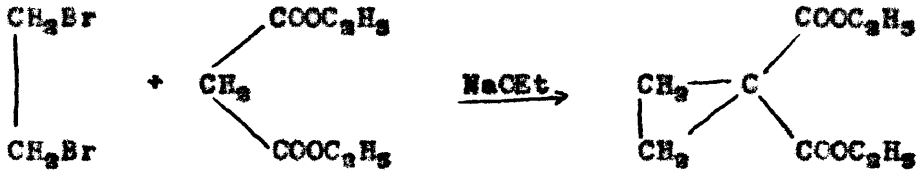
Malonic acid derivatives with a cyclic structure have been extensively studied by Perkin and his co-workers. Perkin obtained the esters of cyclopropane,[31] cyclobutane,[32] cyclopentane,[33] cyclohexane,[34] and cycloheptane-1,1-dicarboxylic acids[35] by condensing the sodium salt of ethyl malonate with the appropriate dibromoparaffins. In this reaction, two products are formed; one in which one molecule of the dibromoparaffin reacts with one molecule of sodium malonic ester with ring-closure to form an ethyl cycloparaffin-1,1-dicarboxylate, and another in which one molecule of dibromoparaffin condenses with two molecules of sodium malonic ester to form a paraffin-α,α,ω,ω-tetracarboxylic ester.

A summary of some of the methods which have been employed to prepare cyclopropane derivatives are as follows:

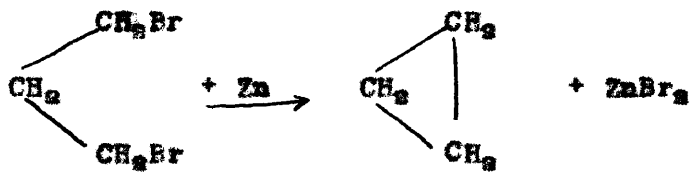
1. The action of sodium on trimethylene bromide.[36]



2. Condensation of ethyl malonate with ethylene bromide.[31]

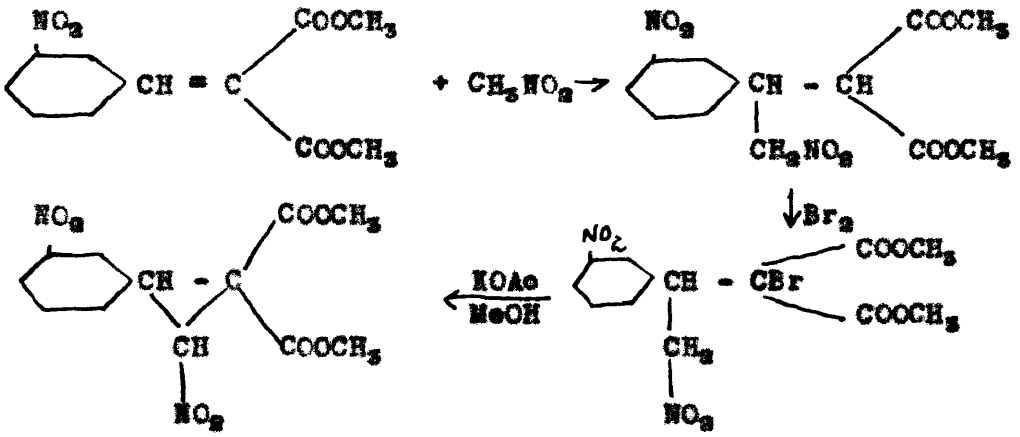


3. Coupling of two alkyl residues by means of zinc.[37,38]

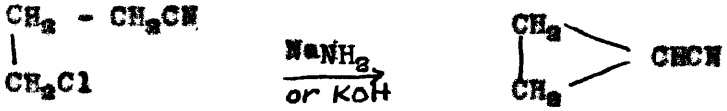


4. Cyclization by the elimination of hydrogen halides.

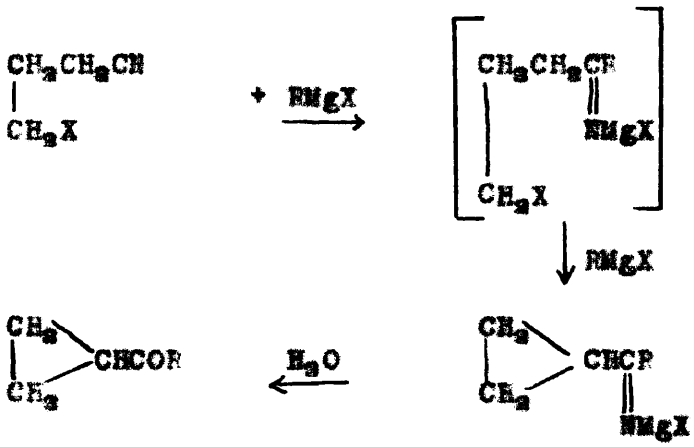
5. The Michael condensation leads to many types of compounds which lend themselves to the synthesis of cyclopropane derivatives. Kohler[39] has developed a method of cyclization which involves the elimination of hydrogen halide by treatment of the bromine derivative with potassium acetate in methyl alcohol. The method may be indicated as follows:



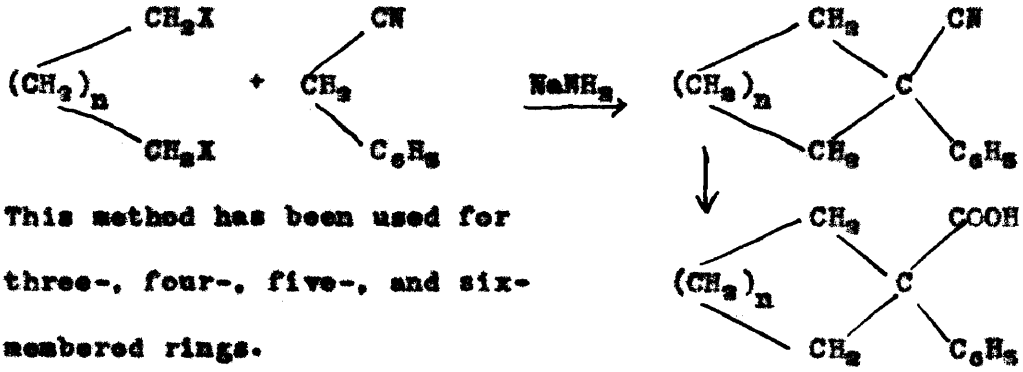
6. Treatment of γ-halonitriles with potassium hydroxide, produces the nitriles of the corresponding cyclopropane-carboxylic acids.[40]



7. Bruylant's modification of the above method involves the addition of a Grignard reagent to a α-halonitrile and leads to the formation of cyclopropyl ketones.

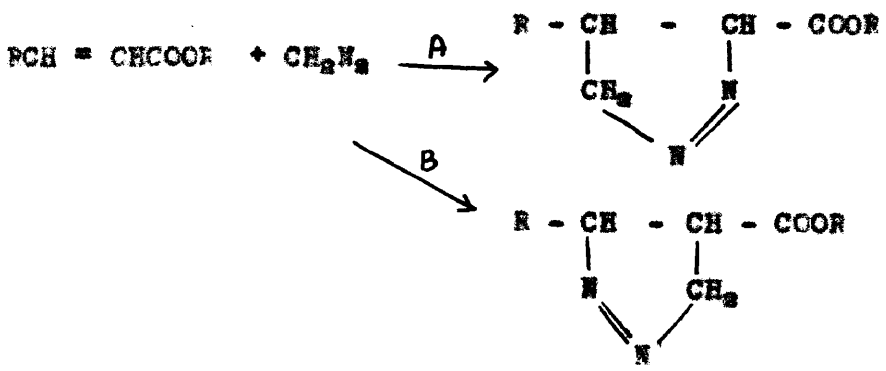


8. The condensation of phenylacetonitrile with polymethylene halides in the presence of sodamide furnishes a method for the preparation of 1-phenyl-1-cycloalkanecarboxylic acids.[41]

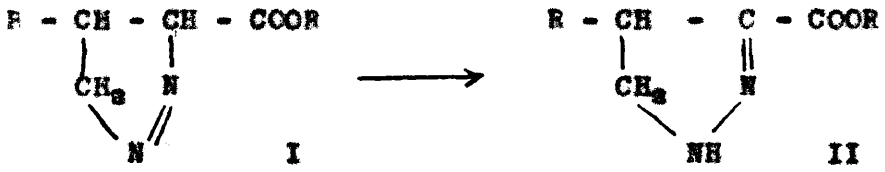


This method has been used for three-, four-, five-, and six-membered rings.

9. It has been shown by von Auwers[42] that the addition of diazomethane to α,β-unsaturated esters proceeds in such a way that the nitrogen atoms become attached to the α-carbon atom, i.e., the reaction follows scheme A rather than B.

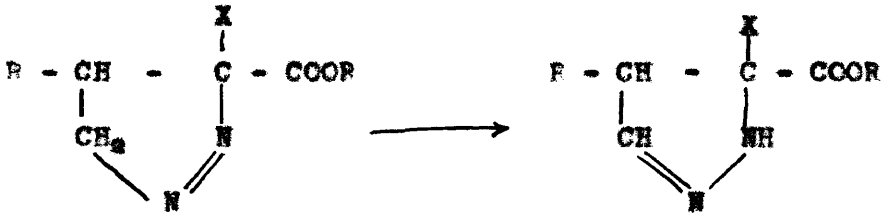


von Auwers (loc. cit.) also showed that under the influence of certain reagents (such as halogen acids), the Δ^1-pyrazolines first formed could be changed to the isomeric Δ^2-pyrazolines and that, wherever possible, this change resulted in the formation of a conjugated system.

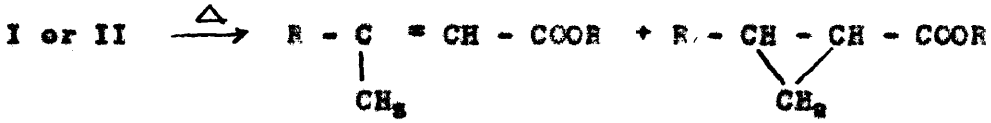


I II

However, in the case of substituted pyrazolines, the alternative reaction was found to take place, i. e.,

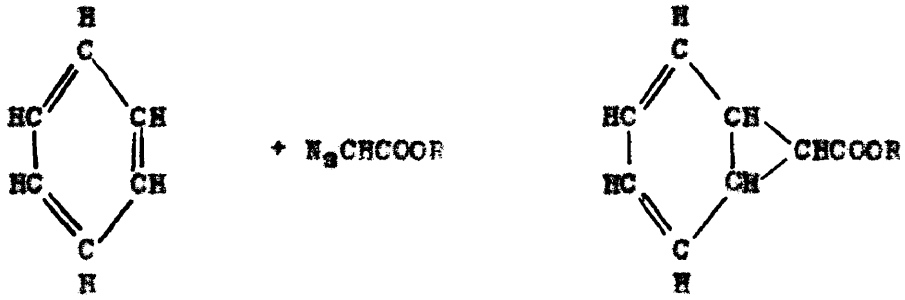


Thermal decomposition of I or II led to olefinic esters and cyclopropane derivatives



and the course of this reaction was determined by the complexity of the pyrazoline; the simpler members in general yielding mostly unsaturated compounds. The more complex esters generally afford a preponderance of alkyl cyclopropanecarboxylates.

10. Diazoacetic ester has been used in a similar fashion. The conversion of ethylenic compounds into cyclopropane derivatives by diazoacetic ester is very general. Buchner has shown that even aromatic rings are attacked.



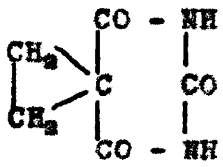
Dox and Yoder have synthesized cyclobutane-1,5-spiro-barbituric acid[49] and cyclohexane-1,5-spiro-barbituric acid by condensing the corresponding cycloparaffin-1,1-dicarboxylic ester with urea in the presence of absolute alcohol and sodium ethoxide.

The corresponding 3-membered ring with one of its carbon atoms identical with the 5-carbon atom of barbituric acid is the simplest derivative of this type. Difficulty was experienced in the first attempts[44] to prepare such a compound. The condensation of ethyl cyclopropane-1,1-dicarboxylate with urea was readily effected but the product was entirely different in its properties from the corresponding cyclobutane and cyclohexane derivatives. The authors conclude that a very stable polymer is formed in this reaction although its constitution has not been definitely established. The insolubility and amorphous character of the product obtained as contrasted with the solubility, crystalline form, and sharp melting point of the corresponding cyclobutane and cyclohexane derivatives justify (according to the authors) the assumption that a polymerization had occurred. Experiments were conducted to determine whether such polymerization could be avoided by altering the conditions of the condensation but in all cases employing sodium ethylate as condensing

agent, the product obtained was invariably amorphous, insoluble in water, acid, organic solvents, and infusible.

The synthesis of cyclopropane-1,5-spiro-2,4,6-triketo-hexahydro-pyrimidine was undertaken by the present writer. The synthesis of derivatives of this compound possessing substituents on the cyclopropane ring was also attempted.

II. NOMENCLATURE

Dicyclic structures such as  , in which

one carbon atom is common to two rings, were first designated by von Baeyer[65] as "spirocyclanes". The term "spirane" was later proposed by Radulescu[45], who worked out a system of nomenclature for such compounds. According to this system, the substance represented by the above formula would be named cyclopropane-2,4,6-triketo-hexahydro-pyrimidine-1,5-spirane. The term "spirane" is objectionable in the case of heterocycles, in that the ending implies a hydrocarbon[43]. Dox and Yoder[43] recommend that the two rings with their substituent groups be named separately in the customary way, and the term "spiro" (in italics) inserted between them, preceded by numbers locating the position of the central carbon with respect to each ring in the order named. Thus, the above compound would be named cyclopropane-1,5-spiro-2,4,6-triketo-hexahydro-pyrimidine.

III. DISCUSSION OF RESULTS

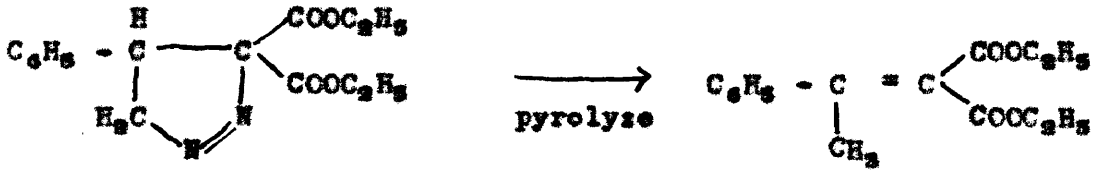
The work of Dox and Yoder[44] on the attempted synthesis of cyclopropane-1,5-spiro-2,4,6-triketo-hexahydro-pyrimidine was repeated. Results identical with theirs were obtained. Likewise, when extreme precautions were taken to insure anhydrous conditions throughout the condensation of the ethyl cyclopropane dicarboxylate and the urea, an amorphous product was obtained. Further attempts to prepare this compound by treatment of the diamide of cyclopropane dicarboxylic acid with ethyl carbonate, employing sodium ethoxide as condensing agent, also produced the amorphous product previously reported. The barbituric acid was prepared by treatment of the diamide of cyclopropane-1,1-dicarboxylic acid with oxalyl chloride. The reaction proceeds as follows

with the loss of hydrogen chloride and carbon monoxide.

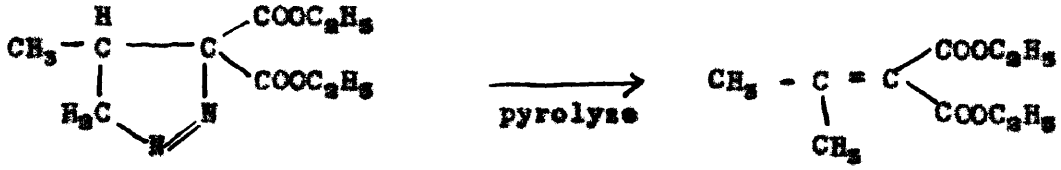
Attempts were made to prepare ethyl cyclopropane dicarboxylates which had aliphatic or aromatic substituents on the cyclopropane ring by the reaction of the appropriate dihalides with malonic ester in the presence of sodium ethoxide as condensing agent. These experiments were not successful due to the difficulty experienced in condensing dihalides possessing a primary and a secondary halogen, or two secondary halogens, with a single molecule of malonic ester. In both cases, the elements of hydrogen bromide were removed from the dihalides to form the corresponding bromo-ethylenic compound.

A further attempt to synthesize an ethyl cyclopropane di-

carboxylate possessing an aromatic substituent on the cyclopropane ring by pyrolysis of the appropriate pyrazoline, yielded the corresponding ethylenic derivative exclusively.



von Auwers[42], reports an analogous reaction in which he obtained a quantitative yield of the ethylenic derivative:



The pyrolysis of the Δ^2-pyrazoline obtained from the Δ^1-pyrazoline shown above likewise produced none of the ethyl cyclopropane dicarboxylate. All of the pyrolysis products were identified.

IV. EXPERIMENTAL

Preparation of Ethyl Cyclopropane-1,1-dicarboxylate according to the method of Dox and Yoder[44]

Three hundred and ten grams of ethylene bromide and 255 gr. of ethyl malonate were placed in a three-liter, three-necked flask provided with a reflux condenser and a mechanical stirrer. A solution of 73 gr. of sodium in 1100 cc. of absolute alcohol was slowly added through a dropping funnel during a period of 2-1/2 hours. The mixture was heated and stirred on an oil bath at 80° C. for 5 hours after which time the milky reaction mixture was neutral to litmus. Most of the alcohol was then distilled off while the solution was stirred continuously. The mixture was now slightly alkaline and hydrochloric acid was added to make the mixture exactly neutral. On the addition of water, the sodium bromide dissolved and a yellow oil separated. The latter was extracted with ether. The ether solution was dried over sodium sulfate after which the ether was removed by distillation. On fractionation of the residue at 759.5 mm. pressure, 231.1 grams of material distilled between 204-217°. Two fractionations finally gave 152 gr. of product boiling at 129-130° at a pressure of 56-58 mm. At 60 mm. pressure the product boiled at 134°. The yield was 51.3 percent of the amount theoretically possible. Dox and Yoder report a yield of 120 gr. or 40 percent for a product boiling at 214-216° (corr.) at 748 mm. pressure.

Condensation of Ethyl Cyclopropane-1,1-dicarboxylate with urea by a modification of the method of Dox and Yoder[44]

To a solution of 3.7 grams of sodium in 65 cc. of absolute alcohol, 10 grams of ethyl cyclopropane-1,1-dicarboxylate and 5 grams

of urea were added and the mixture was refluxed for 4 hours. The alcohol used was first dried over sodium sulfate, refluxed for 5 hours over calcium oxide and finally distilled. The urea was dried in an oven at 80° for 24 hours and kept in an evacuated dessicator over sulfuric acid. Anhydrous conditions were maintained throughout all operations. The white insoluble product was collected on a filter, dissolved in water, and acidified with hydrochloric acid. A voluminous, amorphous precipitate formed which was insoluble in water, acids, and organic solvents but was slowly soluble in caustic alkali. On heating, the product charred without melting. The product resembled that obtained by Dox and Yoder[44] in all respects. Attempts to crystallize the product by slow neutralization of the alkaline solutions or by slow dilution in its solution in concentrated sulfuric acid were unsuccessful. The product was invariably amorphous. Dox and Yoder concluded that a polymerization had occurred.

Attempted Condensation of Ethyl Cyclopropane-1,1-dicarboxylate and Urea by means of an azeotropic distillation.

One hundred grams (0.54 moles) of ethyl cyclopropane-1,1-dicarboxylate, 96 grams of urea (1.62 moles) and 600 cc. dimethylaniline were placed in a three-necked flask provided with a condenser set for downward distillation, a stirrer, thermometer, and a dropping funnel, the contents of which were protected against atmospheric moisture. The mixture was placed in an oil bath maintained at 130° C. and toluene was added slowly by means of the dropping funnel at a rate just equal to the rate of distillation. Vigorous stirring was maintained throughout the distillation. Two liters of toluene were used, the entire distillation taking about three hours. An oily layer separated to the bottom

of the flask. On cooling, the oil solidified to a hard mass which was broken up and filtered. On crystallization from hot water, 29 grams of a white powder was obtained (m. p. 239-240°). One recrystallization from hot water yielded 28.5 grams of white lustrous scales (m. p. 240-241°). The product was shown to be identical with carbonyldiurea.[46]

19.52 mg. sample produced 17.59 mg. CO_2

19.52 mg. sample produced 7.052 mg. H_2O

19.36 mg. sample produced 17.47 mg. CO_2

19.36 mg. sample produced 7.344 mg. H_2O

12.18 mg. sample produced 3.992 cc. N_2

Press. 796 mm., Temp. 26° C.

12.45 mg. sample produced 4.165 cc. N_2

Press. 770 mm., Temp. 24° C.

Calc. for $C_3H_6N_4O_3$: C = 24.65; H = 4.14; N = 38.35

Found: C = 24.58; H = 4.10; N = 38.21

24.61 4.28 38.26

On evaporation of the filtrate from the recrystallization of the carbonyldiurea, 41 grams of a white crystalline material (m. p. 190-191°) was obtained which was shown to be identical with biuret as indicated by a mixed melting point determination. The product gave a positive biuret test.

Preparation of Carbonyldiurea

To further establish the identity of the carbonyldiurea obtained, the compound was prepared according to the method of Walters and Wise.[46]

Six and three-tenths gram of uric acid and 9 grams of sodium hydroxide were dissolved in 1000 cc. of water. The clear filtered solution was treated with 250 cc. of 3 percent hydrogen peroxide and

the mixture allowed to stand at room temperature for 72 hours. The solution was filtered to remove a slight turbidity and the clear filtrate made strongly acid with hydrochloric acid and allowed to stand at room temperature for 24 hours longer. The crystalline material which separated during this period was filtered off, washed with cold water, and purified by repeated crystallization from hot water. The product melted at 233-234°. The product decomposed at its melting point and further investigation revealed that the decomposition temperature was a function of the rate of heating. That the carbonyldiurea obtained by both procedures was one and the same substance was shown by preparing three melting point tubes, two containing each of the separate products and the third containing an equal-weight mixture of the two. On heating the three tubes simultaneously in the same bath, decomposition occurred at the same temperature in each of the three tubes (decomposition temperature 233-234°). Walters and Wise[46] believe that the decomposition point may have been mistaken for the melting point by previous investigators.[47] Schittenhelm and Wiener[47] record the melting point of carbonyldiurea as 233-234°.

Preparation of the diamide of cyclopropane-1,1-dicarboxylic acid according to the method of Ingold, Sako and Thorpe.[48]

Seventy-five grams of ethyl cyclopropane-1,1-dicarboxylate was mixed with 375 grams of concentrated aqueous ammonia and shaken occasionally for three days. On the fourth day the diamide which separated was collected on a filter. The filtrate was evaporated to dryness in vacuo and the combined solids were recrystallized from hot ethyl alcohol (m. p. 192-4°).

Preparation of the diamide of Cyclopropane-1,1-dicarboxylic acid employing liquid ammonia and ammonium chloride catalyst as suggested by Audrieth and Kleinberg[49]

One hundred and five grams of ethyl cyclopropane-1,1-dicarboxylate, 4 grams of ammonium chloride, and 540 cc. of liquid ammonia were placed in a glass container (adapted for use in a bomb) and the mixture placed in a bomb. The reaction was allowed to proceed for 24 hours with continual mechanical shaking at room temperature. The excess liquid ammonia was permitted to evaporate in the hood and the white solid residue was recrystallized from hot ethyl alcohol. 67.3 grams of the diamide (93 percent of the theoretical) was obtained (m. p. 192-194°).

Preparation of cyclopropane-1,5-spiro-2,4,6-triketo-hexahydropyrimidine (5-dimethylene barbituric acid)

Anhydrous oxalic acid was prepared from the hydrate according to the method given in Organic Syntheses.[50] Oxalyl chloride was prepared according to the method of Staudinger[51] by treating oxalic acid (anhydrous) with phosphorus pentachloride.

The method of Einhorn[17] was employed. Six and nine-tenths grams (0.054 moles) of the diamide of cyclopropane-1,1-dicarboxylic acid was placed in a 100 ml. boiling flask provided with an efficient reflux column and protected against atmospheric moisture. To this was added rapidly 9.2 grams (.072 moles) of oxalyl chloride. The reaction mixture began to froth and fumes of hydrogen chloride were liberated. The mixture was then heated for 1-1/2 hours on the steam bath. Twenty cc. of water was added to the frothy mass to destroy the excess oxalyl chloride. The entire mass went into solution and on short standing,

a voluminous, slightly yellowish precipitate formed. On filtration and recrystallization of the solid from hot water, using Norite for decolorization, 3.5 grams of white satiny, lustrous plates were obtained which did not melt below 300°. The material charred at higher temperatures.

19.30 mg. sample produced 33.04 mg. CO_2
19.30 mg. " " 7.290 mg. H_2O

20.50 mg. sample produced 35.16 mg. CO_2
20.50 mg. " " 7.327 mg. H_2O

13.11 mg. sample produced 2.086 cc. N_2
Press. 771 mm.; Temp. 25° C.

12.713 mg. Sample produced 2.022 cc. N_2
Press. 770 mm., Temp. 25° C.

Calc. for $C_6H_6O_3N_2$: C = 46.76%; H = 3.92%; N = 18.18%

Found: C = 46.81, 46.89 H = 3.98; 4.00 N = 18.21, 18.20

Molecular weight determinations were made by the boiling point elevation method using ethyl alcohol as solvent. Relatively large quantities of solvent were required to effect the solution of the solid.

$K_{Ethyl\ alcohol} = 11.5$

Trial I	Wt. of sample = 0.2851 gr.	Trial II	0.2480 gr.
	Wt. of solvent = 30.28 gr.		29.13 gr.
	Boiling point elevation = 0.070°		0.065°

Calc. for $C_6H_6O_3N_2$, M. W. = 154.1

Found: Trial I, 154.7
Trial II, 150.6

Preparation of cyclopropane-1,1-dicarboxylic acid

Five-tenths of a gram of the diamide of cyclopropane-1,1-dicarboxylic acid was hydrolyzed by heating under reflux with a solution

of 0.5 grams potassium hydroxide in 20 cc. of water until no ammonia gas was liberated (2 hours). The mixture was cooled and neutralized with dilute sulfuric acid. A slight excess of acid was added. The acidified solution was filtered to remove a very slight turbidity and extracted with three 10-cc. portions of ether (a fourth portion of ether on evaporation did not leave a solid residue). The ether extract was dried over calcium chloride. The ether solution, on evaporation at room temperature, yielded colorless needles associated with a small amount of oil. The crystals were pressed on a clay plate to remove the oil and redissolved in ether. The ether was evaporated and the process repeated until all oil had been removed. White crystals (0.3 gr.) were obtained (m. p. 140-141°) as reported by Perkin[52] for cyclopropane-1,1-dicarboxylic acid. The acid was likewise prepared by the hydrolysis of ethyl cyclopropane-1,1-dicarboxylate.

Preparation of the bis-(p-bromophenacyl)ester of cyclopropane-1,1-dicarboxylic acid.

Two-tenths of a gram of cyclopropane-1,1-dicarboxylic acid was dissolved in 5 cc. of water and carefully neutralized with a 10 percent sodium hydroxide solution. A drop of dilute hydrochloric acid was added to make the solution slightly acid. Ten cc. of alcohol and 0.4 gr. of p-bromophenacyl bromide were added. The mixture was heated under reflux for 2 hours. A solid separated during the course of the heating. Three cc. of alcohol was added to dissolve the solid and the solution was allowed to cool. The solid which separated was recrystallized from 95 percent ethyl alcohol (m. p. 152°). Allen and Boyer[53] report the melting point as 146°.

10.24 mg. sample produced 18.10 mg. CO_2
10.24 mg. " " 2.916 mg. H_2O

15.61 mg. sample produced 27.63 mg. CO_2
15.61 mg. " " 4.338 mg. H_2O

Calc. for $C_{21}H_{16}O_6Br_2$: C = 48.12%, H = 3.08%

Found: C = 48.25 H = 3.19
48.29 3.11

Preparation of the bis-(p-phenylphenacyl)ester of cyclopropane-1,1-dicarboxylic acid.

The ester was prepared as above. Recrystallization from 95 percent alcohol gave crystals which melted at 178°.

5.941 mg. sample produced 16.67 mg. CO_2
5.941 mg. " " 2.853 mg. H_2O

Calc. for $C_{33}H_{26}O_6$: C = 76.43, H = 5.05

Found: C = 76.54, H = 5.27

Hydrolysis of 5-dimethylene barbituric acid.

Two grams of the barbituric acid was hydrolyzed by heating under reflux with a solution of 1.5 gr. of potassium hydroxide in 25 cc. of water. The mixture was heated until ammonia gas was no longer liberated. The solution was cooled and acidified with dilute sulfuric acid. The acidified solution was extracted with three 10-cc. portions of ether. The ethereal extract was dried over sodium sulfate and evaporated at room temperature. The small amount of oil which was associated with the needles formed was removed, as before, on a clay plate. Colorless needles (m. p. 140-141°) were obtained which when mixed with the cyclopropane-1,1-dicarboxylic acid previously prepared, gave no melting point depression. The bis-(p-bromophenacyl) ester was prepared (m. p. 152°) as before. The hydrolysis product is, therefore, cyclopropane-1,1-dicarboxylic acid.

Attempted synthesis of 5-dimethylene barbituric acid by the condensation of the diamide of cyclopropane-1,1-dicarboxylic acid and ethyl carbonate.

Two grams of the diamide of cyclopropane-1,1-dicarboxylic acid, 5 grams of ethyl carbonate and 2.5 gr. of solid sodium ethoxide were placed in a small test tube provided with a mechanical stirrer and protected against atmospheric moisture. The test tube was placed in an oil bath at 120° for 5 hours, with continuous stirring. Some solid material was formed. The product was removed to a beaker and dissolved in a minimum amount of water. The solid completely dissolved. A layer of unreacted ethyl carbonate formed on top. On acidification with dilute hydrochloric acid, an amorphous gelatinous precipitate formed. Filtrations yielded a mass of white gelatinous solid. The amorphous material when heated with water formed a small amount of an orange oily tar which remained undissolved. Filtration and cooling of the filtrate produced a small quantity of a white solid which dried to a mass of hard, brittle, shiny material and which did not melt below 300° C. The product resembles in all respects the amorphous polymers previously obtained from the sodium ethoxide condensation of urea and ethyl cyclopropane-1,1-dicarboxylate.[44]

Preparation of styrene dibromide - according to the method of Evans and Morgan[54]

To a solution of 48.5 grams of freshly distilled styrene in 400 cc. pure ether were added 126.8 grams of bromine dissolved in 600 cc. ether. The solution of styrene was placed in an open beaker surrounded by ice-water and kept in constant motion by a mechanical stirrer. The rate of flow of the bromine solution was regulated according to the discharge of color. The crude product obtained by distilling off the

ether and subsequently crystallizing the residue from dilute alcohol yielded 120 gr. of styrene dibromide. The yield was 98 percent of the theoretical amount. Some styrene dibromide was obtained from Dr. Haller of the United States Department of Agriculture, Beltsville, Maryland.

Attempted synthesis of ethyl 2-phenylcyclopropane-1,1-dicarboxylate.

One hundred grams of styrene dibromide and 58.5 grams of ethyl malonate were placed in a 3-liter, 3-necked flask provided with a reflux condenser and a mechanical stirrer. A solution of 16.7 grams of sodium in 275 cc. of absolute alcohol was slowly added through a dropping funnel during a period of 2-1/2 hours. The mixture was heated and stirred on an oil-bath at 80° for 5 hours. Most of the alcohol was distilled off and sufficient water was added to dissolve the solid sodium bromide. A deep-red liquid separated. The latter was extracted with ether. The ether solution was dried over sodium sulfate after which the ether was distilled. At a pressure of 6-7 mm., the greater mass of the residual liquid distilled at 72-77°. Above this temperature, a slightly yellowish solid distilled which was identified as styrene dibromide by a mixed melting point determination. Refractionation of the initial liquid fraction was not very efficient and all fractions collected contained bromine as indicated by sodium-fusion elementary analyses. The fractions possessed an irritating odor. Malonic ester was found in each of the fractions by treating each fraction with aqueous ammonia, shaking and permitting the mixture to stand over night. On pouring off the aqueous layer and evaporating the solution, a solid was obtained which was crystallized from ethyl alcohol and by mixed melting-point determination, was shown to be malonamide. In this way, all the malonic ester was removed from the distillate, and refractionation of the dried distillate

gave a liquid which distilled at 71° at a pressure of 6-8 mm. The distillate gave a positive test for halogen and for unsaturation. The material is probably a mixture of α-bromostyrene (b. p. 71° at 8 mm.) and ω-bromostyrene (b. p. 71° at 6 mm.). Malonic ester boils at 73° at a pressure of 6 mm. No condensation between styrene dibromide and malonic ester was, therefore, observed. The alcoholic alkaline treatment merely served to remove the elements of hydrogen bromide from the reaction and produced the corresponding unsaturated derivatives.

Preparation of 2,3-dibrompentane

Pentene-2 was prepared from pentanol-2 according to the method given in Organic Syntheses.[55]

Pentene-2 (73.7 grams) was dissolved in 600 cc. of ether and the solution was cooled in an ice-salt mixture. Bromine (168.5 grams) was added slowly, the rate of addition being regulated according to the discharge of color. Mechanical stirring was maintained throughout. The excess of bromine was removed by shaking the ether solution with an aqueous sodium bisulfite solution. The ether solution was then washed successively with aqueous sodium hydroxide and water and finally dried over anhydrous calcium chloride. The ether was evaporated and the 2,3-dibromopentane distilled. At a pressure of 760.7 mm., the product boiled at 178-181°. The yield was 160 grams. A second distillation produced 116 gr. of material boiling at 178-179° as reported by Wagner and Saizew.[56]

Attempt at the preparation of ethyl 2-methyl-3-ethyl cyclopropane -1,1-dicarboxylate

One hundred and sixteen grams (0.504 moles) of 2,3-dibrompentane and 80 gr. (0.500 moles) of malonic ester were placed in a 3-necked flask

provided with a reflux condenser and a mechanical stirrer. A solution of 23 grams of sodium in 350 cc. of absolute alcohol was slowly added through a dropping funnel during a period of 2 hours. The mixture was heated and stirred on an oil bath at 80° for 5 hours. The mixture turned milky after the first addition of the sodium ethoxide solution. Most of the alcohol was then distilled off and on the addition of water, the sodium bromide dissolved and an oil separated. The mixture was extracted with ether and the ether solution was dried over anhydrous sodium sulfate. On evaporation of the ether and distillation, two fractions were obtained. The first, boiling at 108-110°, is probably 2-bromo pentene-2 as reported by Farrell and Bachman[57]. The second fraction boiling at 198-200° was shown to be malonic ester as evidenced by the preparation of its amide. The dark red-brown residue which remained, solidified to give a crystalline material. The solid was dissolved in ethyl alcohol and on the addition of water, orange-colored needles separated. Recrystallization by repeated solution in cold alcohol and addition of water produced long silky needles. The product melted at 76°.

28.86 mg. sample produced 55.89 mg. CO_2
28.86 mg. " " 18.03 mg. H_2O

30.90 mg. sample produced 59.86 mg. CO_2
30.90 mg. " " 19.19 mg. H_2O

Found: C = 52.85; H = 6.99
52.87 6.95

The above analyses correspond to an empirical formula $C_{14}H_{22}O_8$. The product is ethane tetracarboxylic ester m. p. 76° as reported by Conrad and Guthzeit.[58]

Calc. for $C_{14}H_{22}O_8$: C = 52.83%; H = 6.91%.

The yield of 2-bromo pentene-2 was 77 percent based on the quantity of 2,3-dibromopentane used. The yield of ethane tetracarboxylic ester was 10 percent based on the amount of malonic ester used. Approximately 72 percent of the malonic ester was recovered.

Preparation of benzalmalonic ester according to the method of Knoevenagel[59]

One mole (100 gr.) of malonic ester which was dried over anhydrous sodium sulfate was mixed with slightly more than one mole (70 gr.) of freshly distilled benzaldehyde. Two grams of piperidine was added and the reaction mixtures permitted to stand at room temperature for 2 days and then for 12 hours on the steam bath. The reaction mixture was extracted with ether, washed with dilute hydrochloric acid, and water, and finally dried over anhydrous sodium sulfate. The ether was evaporated on the steam bath and the residue distilled. One hundred and nine grams (70 percent of the theoretical amount) of a colorless liquid boiling at 179-180° at a pressure of 9.5 mm., was obtained. Knoevenagel[59] reports benzalmalonic ester which boils at 185-186° at a pressure of 11 mm.

Preparation of nitrosomethylurea according to the method of Arndt, Loewe and Avan[60]

Methylamine hydrochloride (100 grams) and 300 grams of urea were dissolved in 400 cc. of water and gently refluxed for 2-3/4 hours and then strongly for another 1/4 hour. One hundred and ten grams of sodium nitrite was added and the solution cooled to -10° in an ice-salt mixture. The clear solution was allowed to flow slowly into a cooled mixture of 600 gr. of ice and 110 gr. of concentrated sulfuric acid with efficient stirring. The nitroso derivative was collected on a suction filter, washed with water and dried in a dessicator set in the refrigerator. One hundred and twenty-two grams of product was obtained.

Diazomethane was prepared by the method given in Organic Syntheses[61]. Nitrosomethylurea was added to a cooled mixture of ether and a 50 percent aqueous solution of potassium hydroxide. On warming the mixture to 50°, the diazomethane distilled with the ether. The ether solution of the diazomethane was collected in cooled receivers.

Addition of diazomethane to benzalmalonic ester.

Thirty-one and three-tenths grams of benzalmalonic ester was dissolved in 100 cc. of anhydrous ether and the solution cooled in an ice-salt mixture. Diazomethane in ether solution (from 20.6 gr. of nitrosomethylurea) was added to the above mixture and the combined solutions cooled for 12 hours in an ice-salt mixture. The reaction mixture was then cooled to -70° in an acetone-dry ice mixture. A colorless mass of lustrous crystals formed which were filtered and which melted at 50-51°. One recrystallization gave colorless, lustrous plates which melted at 50.5-51°. Evaporation of the ether filtrate and recrystallization of the solid from ethyl alcohol likewise gave plates which melted at 50.5-51°. Thirty-six grams of material were obtained representing a yield of 98.7 percent.

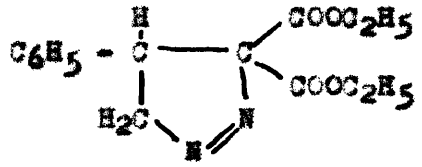
33.74 mg. sample produced 76.54 mg. CO_2
33.74 mg. " " 18.78 mg. H_2O

37.66 mg. sample produced 85.59 mg. CO_2
37.66 mg. " " 19.84 mg. H_2O

Calc. for $C_{15}H_{18}O_4N_2$: C = 62.04%; H = 6.25%

Found: C = 61.95 H = 6.23
62.02 6.17

The product is ethyl 4-phenyl-Δ^1-pyrazoline-3,3-dicarboxylate.



The above structure is assigned by analogy according to the researches of von Auwers[42] in which a Δ'-pyrazoline was prepared by the addition of diazomethane to the analogous malonic ester containing a methyl instead of the phenyl group [i.e., $CH_3CH = C(COOC_2H_5)_2$].

Pyrolysis of ethyl 4-phenyl-Δ'-pyrazoline-3,3-dicarboxylate

Twenty grams of the Δ'-pyrazoline was placed in a large test tube provided with a side-arm, and a thermometer set in a slit cork. The tube was placed in an oil-bath maintained at 125°. The pyrolysis was conducted under a continuous stream of nitrogen gas. Gas evolution began at 98°. The temperature of the molten pyrazoline was not permitted to rise above 120°. After all gas evolution had ceased, the heating was continued for an additional one-half hour. The entire pyrolysis required 3 hours. A yellow, sweet-smelling oil was produced. At a pressure of 5 mm., the material distilled at 141-142° and was a colorless oil. The product gave a positive test for unsaturation with tetranitromethane.

21.35 mg. sample produced 53.82 mg. CO_2
21.35 mg. " " 13.34 mg. H_2O

24.08 mg. sample produced 60.55 mg. CO_2
24.08 mg. " " 14.95 mg. H_2O

Calc. for $C_{15}H_{18}O_4$: C = 68.68; H = 6.92

Found: C = 68.79; H = 6.99
68.62 6.95

The material was produced in 83 percent yield. A tarry dark-brown residue remained from the distillation from which nothing could isolated.

To determine whether the pyrolysis product of ethyl 4-phenyl-Δ'-pyrazoline-3,3-dicarboxylate produced the desired cyclopropane derivative, the molecular refractivity of the product was obtained.

Density $D_4^{20°} = 1.0165$

$n_D^{20°} = 1.5160$

$$M.R = \frac{n^2 - 1}{n^2 + 2} \frac{M}{D} = 77.940$$

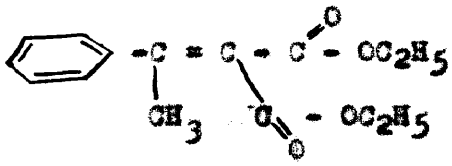
Molecular refractivity - calc. for $C_6H_5 - C(CH_2)(C(COOC_2H_5)_2)$ (A)

$= 69.687.$

calc. for $C_6H_5 - C(CH_3) = C(COOC_2H_5)_2$ (B)

$= 70.710.$

The ethylenic compound, however, possesses a conjugated system as shown below.



The exaltation value for a conjugated system such as is shown above, has not been reported in the literature. The cyclopropane derivative (A) would not possess an exaltation value due to the absence of a conjugated system. It may be assumed, therefore, that the deviation of the experimental molecular refractivity from the calculated value is due to a conjugated system and that the compound under consideration possesses the ethylenic structure (B) as opposed to the cyclopropane structure (A).

Ammonolysis of Ethyl 2-phenyl-1-propene-1,1-dicarboxylate.

One gram of the above ester was placed in a large test tube and 35 cc. of concentrated aqueous ammonia was added. The mixture was stoppered and allowed to stand for 2 days with frequent shaking, The oil partially dissolved. The water insoluble layer was shown to be acetophenone by

the preparation of the 2,4-dinitrophenylhydrazone derivative (m. p. 237°) and by a mixed melting point determination with known acetophenone-2,4-dinitrophenylhydrazone.

The aqueous layer was evaporated on the steam bath and the solid residue recrystallized from ethyl alcohol. The product (m. p. 170-171°) was shown to be malonamide by a mixed melting point determination.

The ammonolysis, therefore, cleaved the ethylenic linkage of the propene ester.

The ammonolysis was also attempted using liquid ammonia. The same results as before were obtained (i.e. acetophenone and malonamide were isolated).

Hydrolysis of Ethyl 2-phenyl-1-propene-1,1-dicarboxylate.

Three grams of the above ester was heated under reflux with a solution of 2 grams of potassium hydroxide in 20 cc. of water for a period of 3 hours. The mixture was cooled and filtered to remove a slight turbidity and was then neutralized with dilute sulfuric acid. The solution became cloudy. It was then extracted with two 10-cc. portions of ether and on evaporation of the ether solution, a slightly yellowish oil was obtained. On standing, a portion of the oil crystallized. To purify the solid acid present and to separate it from any oil the silver salt was prepared. The partially solidified oil was dissolved in aqueous ammonia and slightly more than the calculated quantity of aqueous silver nitrate was added. The precipitated silver salt was washed with water and dissolved in a small amount of concentrated ammonia water. Dilute hydrochloric acid was added and the precipitated silver chloride was filtered. The aqueous filtrate was extracted with

two 10-cc. portions of ether. The ether solution was dried over anhydrous sodium sulfate and the ether evaporated. An oil remained which soon crystallized to yield colorless prisms (m. p. 135-136°). The material was shown to be identical with malonic acid by a mixed melting point determination.

Hydrolysis of the propene-ester apparently served to cleave the ethylenic linkage as in the previous ammonolysis. The literature[62] reports the cleavage of the ethylenic linkage of ethyl 2-phenyl-1-propene-1-cyano-1-carboxylate by treatment of this cyanoester with barium hydroxide.

Attempts to prepare Ethyl 2-phenyl-1-propene-1,1-dicarboxylate.

Equimolar quantities of malonic ester and acetophenone were mixed and piperidine acetate, prepared by mixing equimolar amounts of piperidine and glacial acetic acid, was added. The mixture was permitted to stand for 2 days at room temperature and then heated on the steam bath for 12 hours. On working up the reaction mixture, the starting materials were recovered. If the reaction mixture is heated under reflux for 8 hours, no condensation occurs. Likewise, heating under reflux for 34 hours produced no reaction. In all cases, the malonic ester and acetophenone were recovered.

A further attempt using acetic anhydride and anhydrous zinc chloride as condensing agents and heating the mixture under reflux for 100 hours, was without success.

An attempt was made to prepare the propene diester from the corresponding cyano-ester. Ethyl cyanoacetate was prepared according to the method given in Organic Syntheses[63]. The cyanoacetic ester so prepared was condensed with acetophenone as described by Scheiber and

Meisel.[62]

Acetophenone (180.1 grams) was mixed with 84.8 grams of cyanoacetic ester. Aniline-zinc chloride, prepared by treating 14.0 grams of aniline with 20.5 grams of zinc chloride, was added and the reaction mixture was heated for 12 hours in an electrically-heated oil-bath maintained at 130°. On the addition of ether, solid zinc chloride was thrown out of the solution. The mixture was extracted with ether and the ether solution dried over anhydrous sodium sulfate. The ether was evaporated on the steam bath and the residue fractionally distilled in vacuo. At 6 mm., the material distilled at 157-158°. Fifty-five and four-tenths grams of a colorless liquid was obtained. The yield was 30 percent of the theoretical amount. The product is ethyl 2-phenyl-1-propene-1-cyano-1-carboxylate.

Hydrolysis and esterification of ethyl 2-phenyl-1-cyano-1-propene-1-carboxylate

Twenty-one and five-tenths grams of the cyano-ester was placed in a 250 ml. flask fitted with a reflux condenser. With thorough shaking there was first added 15 cc. of absolute alcohol and then gradually a cooled mixture of 15 cc. absolute alcohol and 25 cc. concentrated sulfuric acid. The mixture was heated for 5 hours on the steam bath with frequent shaking. The flask was cooled well and shaken with 100 cc. of water, and then extracted with two 50-cc. portions of ether. The ethereal extract was washed with aqueous sodium carbonate solution until no longer acid and then dried over anhydrous sodium sulfate. The ether was evaporated and the residue fractionally distilled. The greater portion of the cyanoester was recovered unchanged. Acetophenone and malonic ester were isolated and identified respectively as the 2,4-dinitrophenylhydrazone

and as the diamide. Hydrolytic treatment, therefore, served to cleave the ethyleaic linkage as before.

Isomerization of ethyl 4-phenyl-Δ'-pyrazoline-3,3-dicarboxylate.

Preparation of ethyl 4-phenyl-Δ^2-pyrazoline-5,5-dicarboxylate.

Seven grams of the Δ'-pyrazoline was dissolved in 20 cc. of ether and shaken with 50 cc. of dilute aqueous hydrochloric acid (1:1) for a period of 10 minutes. The aqueous layer was separated and the ether layer was dried over sodium sulfate and evaporated. An oil formed which on short standing crystallized to give thick solid needles. Recrystallization from 95 percent ethyl alcohol gave an almost quantitative yield of material (m. p. 46-47°). A mixed melting point of this product with the Δ'-pyrazoline, produced a considerable melting point depression. The Δ^2-pyrazoline so formed, evolved nitrogen only when heated to approximately 226° whereas the Δ'-pyrazoline evolved nitrogen at 98°.

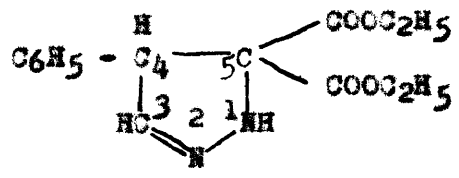
38.57 mg. sample produced 87.94 mg. CO_2
38.57 mg. " " 21.99 mg. H_2O

31.28 mg. sample produced 71.03 mg. CO_2
31.28 mg. " " 17.69 mg. H_2O

Calc. for $C_{15}H_{13}O_4N_2$: C = 62.04%; H = 6.25%

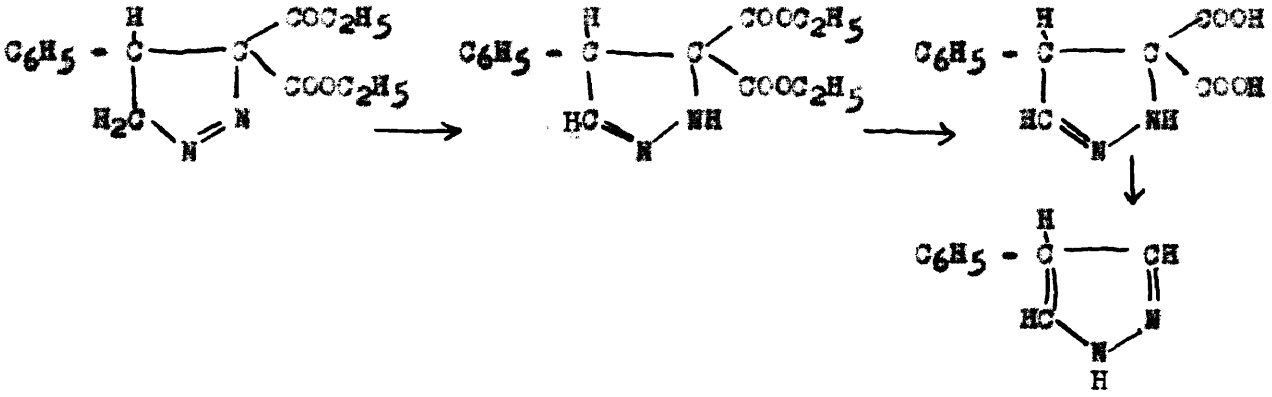
Found: C = 62.22 H = 6.38
62.17 6.35

The isomerization could not have proceeded so as to form a double bond between atoms 1 and 5. By analogy[42], the alternative below remains.



Pyrolysis of ethyl 4-phenyl-Δ^2-pyrazoline-5,5-dicarboxylate.

Twenty grams of the Δ^2-pyrazoline was pyrolyzed under an atmosphere of nitrogen at 230-250°. After all gas evolution has ceased, the material was heated for an additional hour. The entire pyrolysis required three hours, after which the reaction mass had a dark-brown color and an unpleasant odor. A very small portion of a white crystalline solid (needles) sublimed and condensed on the sides of the pyrolysis tube.(m. p. 228-229°). The material was shown to be a 4-phenyl pyrazole and may be accounted for by assuming some hydrolysis of the Δ^2-pyrazoline ester during the hydrochloric acid-isomerization, and subsequent decarboxylation on pyrolysis.



The dark-brown liquid was then fractionated at reduced pressure. At a pressure of 5 mm., a liquid distilled at 142-148° which on refractionation distilled at 141-142° at a pressure of 5 mm. The material was shown to be identical with the sole pyrolysis product of the Δ^1-pyrazoline.

21.01 mg. sample produced 52.85 mg. CO_2
21.01 mg. " " 13.16 mg. H_2O

22.37 mg. sample produced 56.34 mg. CO_2
22.37 mg. " " 13.93 mg. H_2O

Calc. for $C_{15}H_{18}O_4$: C = 68.68%; H = 6.92%

Found: C = 68.65 H = 7.01
68.73 6.97

The material gave a positive test with tetranitromethane and ammonolysis with aqueous ammonia produced malonamide and acetophenone which was characterized as its 2,4-dinitrophenylhydrazone. The refractive index of the colorless liquid (1.5160) was identical with that of the product previously prepared from the Δ^{1}-pyrazoline. The material is, therefore, ethyl 2-phenyl-1-propene-1,1-dicarboxylate. The yield of the material accounted for 34 percent of the starting material.

The remaining portion of the liquid solidified on cooling to produce a yellowish solid associated with a small quantity of oil. After removing most of the oil on a clay plate, the now white solid melted at 150-155°. Recrystallization from benzene using Norite for decolorization produced crystals (m. p. 163-164°). Further recrystallization from ethyl alcohol by allowing the alcohol to stand in the refrigerator for 12 hours, produced plates (m. p. 164-165°).

Carbon-hydrogen analyses were obtained.

23.82 mg. sample produced 58.29 mg. CO_2
23.82 mg. " " 12.02 mg. H_2O

24.50 mg. sample produced 59.87 mg. CO_2
24.50 mg. " " 12.35 mg. H_2O

Found: C = 66.78 H = 5.65
66.68 5.64

The analyses correspond to the empirical formula $C_{12}H_{12}N_2O_2$.

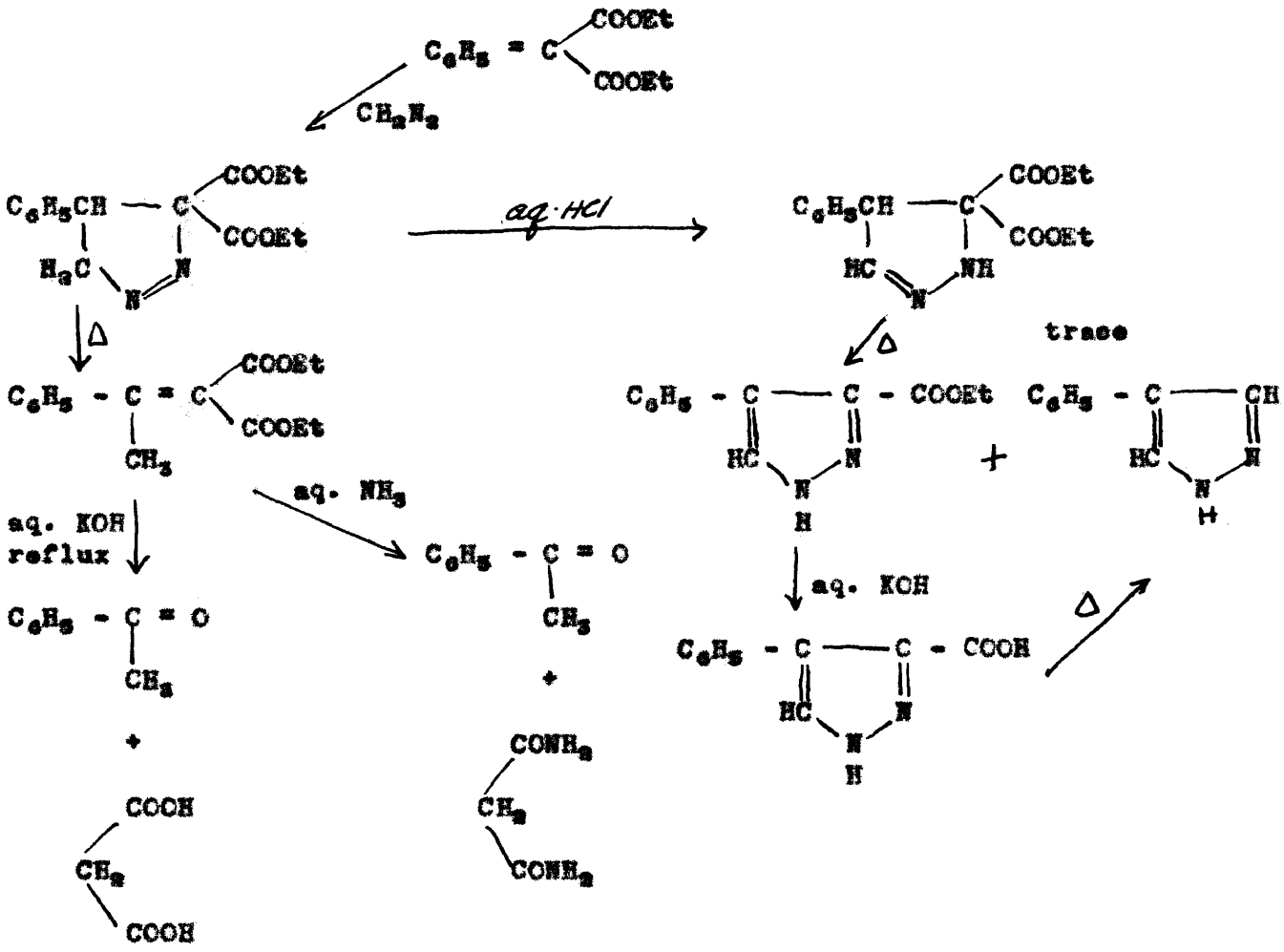
Kohler and Steele[64] report the compound ethyl 4-phenyl pyrazole-3-carboxylate (m. p. 164-165°)

Calc. for $C_{12}H_{12}N_2O_2$: C = 66.67; H = 5.56.

To further establish the identity of this compound, the ester was hydrolyzed with aqueous alkali. 4-Phenyl pyrazole-3-carboxylic acid was produced (m. p. 252-253°) as reported by Kohler

and Steele.[64] On pyrolysis of this product, decarboxylation occurred and 4-phenyl pyrazole (m. p. 228-229°) was obtained. The product was identical with the 4-phenyl pyrazole which sublimed during the pyrolysis of ethyl 4-phenyl-Δ^2-pyrazoline-5,5-dicarboxylate.

The series of reactions, therefore, may be summarized as follows:



V. SUMMARY

1. The work of Dox and Yoder[44] was repeated and results identical with theirs were obtained. Further attempts to effect the condensation of the cyclopropane-1,1-dicarboxylic ester or the diamide to form the barbituric acid by employing alkaline condensing agents were likewise without success.

2. Cyclopropane-1,5-spiro-2,4,6-triketo-hexahydropyrimidine was synthesized by the reaction between the diamide of cyclopropane-1,1-dicarboxylic acid and oxalyl chloride.

3. Attempts to prepare ethyl cyclopropane-1,1-dicarboxylates having aliphatic or aromatic substituents on the cyclopropane ring were unsuccessful.

4. An attempt to prepare ethyl 2-phenyl-cyclopropane-1,1-dicarboxylate by the pyrolysis of ethyl 4-phenyl-Δ^1-pyrazoline-3,3-dicarboxylate resulted in the formation of the corresponding ethylenic derivative, i.e., ethyl 2-phenyl-1-propene-1,1-dicarboxylate.

5. Ethyl 4-phenyl-Δ^1-pyrazoline-3,3-dicarboxylate has been prepared.

6. Ethyl 4-phenyl-Δ^2-pyrazoline-5,5-dicarboxylate has been prepared.

7. The pyrolysis of ethyl 4-phenyl-Δ^2-pyrazoline-5,5-dicarboxylate gave ethyl 2-phenyl-1-propene-1,1-dicarboxylate and ethyl 4-phenyl pyrazole-3-carboxylate.

VI. BIBLIOGRAPHY

1. Fischer and von Mehring, Therap. Gegenw., 44, 97 (1903)
2. Fischer and Dilthey, Ann. 335, 334 (1904)
3. Carnot and Tiffeneau, Compt. rend. 175, 242 (1922)
4. Schenle and Moment, J. Am. Chem. Soc. 45, 243 (1923)
5. Tiffeneau, Bull. soc. chim (4) 33, 183 (1923)
6. Volwiler, J. Am. Chem. Soc. 47, 2236 (1925)
7. Dox and Hjort, J. Pharm. Exptl. Therap. 31, 355 (1927)
8. Hepner and Frankenberg, Ber. 65, 123 (1932)
9. Mulder, Ber. 6, 1235 (1873)
10. Grimaux, Compt. rend. 87, 752 (1878); Bull. soc. chim. (3) 31, 146 (1879)
11. Conrad and Guthzeit, Ber. 14, 1643 (1881)
12. French Patent, 350,428 (1904)
13. French Patent, 354,452 (1905)
14. British Patent, 25,494 (1906)
15. German Patent, 177,694 (1904)
16. United States Patent, 879,156 (1908)
17. German Patent, 227,321 (1909)
    German Patent, 225,457 (1909)
18. United States Patent, 879,499 (1908)
19. United States Patent, 907,664 (1909)
20. German Patent, 351,218 (1905)
21. United States Patent, 1,444,802 (1923)
22. British Patent, 191,008 (1923)
23. French Patent, 343,976 (1905)
24. German Patent, 180,669 (1907)
25. French Patent, 360,334 (1905)

26. British Patent, 15,519 (1906)

27. German Patent, 175,592 (1905)

28. German Patent, 183,857

29. United States Patent, 894,994 (1908)

30. Krantz, Carr, Forman, and Evans, J. Pharmacol. 69, 207 (1940)

31. Perkin, Ber. 17, 54 (1884)

32. Perkin, J. Chem. Soc. 51, 1, 849 (1887)

33. Colman and Perkin, J. Chem. Soc. 53, 185 (1888)

34. Kipping and Perkin, J. Chem. Soc. 57, 304 (1890)

35. Haworth and Perkin, J. Chem. Soc. 65, 591 (1894)

36. Freund, Monatsh. 3, 626 (1882)

37. Lespieau and Wakeman, Bull. soc. chim. 51, 384 (1932)

38. Hass, McBee, Hinds, and Gluesenkamp, Ind. Eng. Chem. 28,1178 (1936)

39. Kohler and Darling, J. Am. Chem. Soc. 52, 424, 1174 (1930)

40. Cloke, Anderson, Laohmann, and Smith, J. Am. Chem. Soc. 53, 2791 (1931)

41. Case, J. Am. Chem. Soc. 55, 2927 (1933); 56, 715 (1934)

42. von Auwers, Ann. 470, 284 (1929); 496, 27, 252 (1932)
Ber. 66, 1198 (1933)

43. Dox and Yoder, J. Am. Chem. Soc. 43, 677 (1921)

44. Dox and Yoder, J. Am. Chem. Soc. 43, 2097 (1921)

45. Radulescu, Ber. 44, 1023 (1911)

46. Walters and Wise, J. Am. Chem. Soc. 39, 2472 (1917)

47. Schittenhelm and Wiener, Z. physiol. chem. 62, 100 (1909)

48. Ingold, Sako, and Thorpe, J. Chem. Soc. 121, 1189 (1922)

49. Audrieth and Kleinberg, J. Org. Chem. 3, 312 (1938-9)

50. Organic Syntheses, Coll. Vol. I, Gilman.

51. Staudinger, Ber. 41, 3563 (1908)

52. Perkin, Ber. 17, 54

53. Allen and Boyer, Can. J. Res. 159 (1933)

54. Evans and Morgan, J. Am. Chem. Soc. 35, 56 (1913)

55. Organic Syntheses, Vol VII, p. 76

56. Wagner and Saizew, Ann. 179 , 307

57. Farrell and Bachmann, J. Am. Chem. Soc. 57, 1281 (1935)

58. Conrad and Guthzeit, Ber. 16, 2632

59. Knoevenagel, Ber. 31, 2591 (1898)

60. Arndt, Loewe, and Avan, Ber. 73B, 606 (1940)

61. Organic Syntheses, Vol XV, p. 3

62. Scheiber and Meisel, Ber. 48, 260

63. Organic Syntheses, Vol VIII, p. 74

64. Kohler and Steele, Am. Chem. Soc. 41, 1104 (1919)

65. von Baeyer, Ber. 33, 3771 (1900)