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STUDIES RELATING TO THE FREE RADICAL CHLORINATION OF CYCLOBUTANECARBOXYLIC ACIDS

by

E. R. Buchman and W. A. Nevill

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Studies Relating to the Free Radical Chlorination of Cyclobutanecarboxylic Acids

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ABSTRACT

The halogenated cyclobutanecarboxylic acids are of importance in connection with projected syntheses of theoretically important cyclobutane derivatives.

To facilitate the direct synthesis of such compounds, the free radical chlorination of two simple models, cyclobutanecarboxylic acid and 1,1-cyclobutanedicarboxylic acid, has been investigated.

Necessary to this study was the synthesis, by means indicative of structure, of 5 isomeric monochlorocyclobutanecarboxylic acids. A chromatographic method has been developed capable of effecting the separation of these isomers from a mixture.

The results obtained in this work are consistent with modern interpretations of organic chemistry theory and extend the scope of its application in the field of free radical chlorination to carboxyl-substituted carbocyclic systems.

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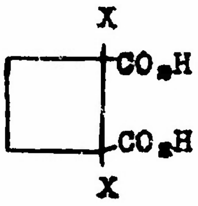
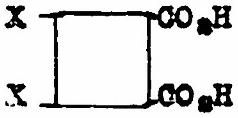
INTRODUCTION

There has been considerable interest in this laboratory in the chemistry of the cyclobutane ring, particularly concerning possible routes to 1,3-cyclobutadiene and its derivatives. Certain halogenated cyclobutanecarboxylic acids might prove useful as starting points in such syntheses.

For instance, one can write single step elimination reactions yielding the cyclobutadiene ring starting from any one of the 4 (disregarding stereoisomers) symmetrical dihalocyclobutanedicarboxylic acids shown below:



I.



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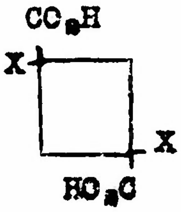
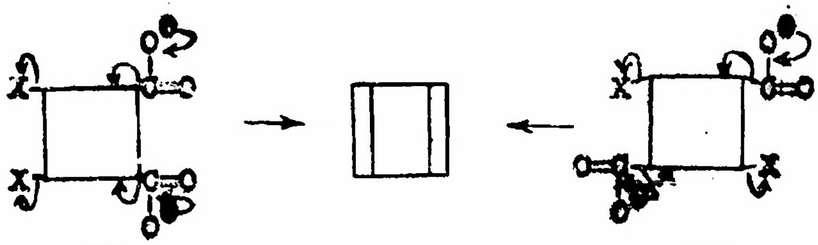


III.

IV.

Theoretically each type can give a cyclobutadienedicarboxylic acid upon loss of 2 HX; however, types II and IV may also possibly undergo a decarboxylative elimination reaction* losing 2 halide and 2 carbon dioxide entities:



II. IV.

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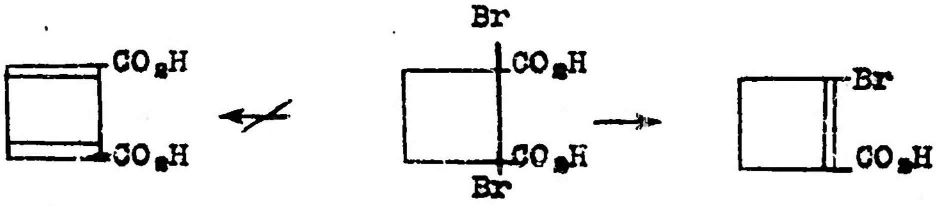
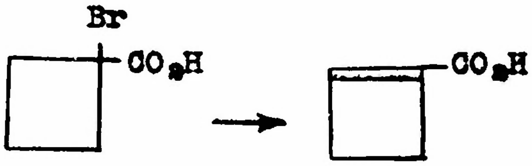
*The spatial arrangement of the cyclobutane substituents may be of great importance in the actual success of this reaction (cf. ref. (1) and (2)).

Perkin, Jr. (3) investigated the only known representative of type I (X = Br, configuration unknown) and found that upon alkali treatment the 2-bromo-1-cyclobutenecarboxylic acid was formed instead of the expected 1,3-cyclobutadiene-1,4-dicarboxylic acid:



This seems to indicate that the decarboxylative elimination proceeds more easily than regular elimination in this series. Domnin and Yakovlev (4) have shown that, in the case where there is no 2-halo group, elimination does readily take place:



Only a single compound is known of type II. 3,4-Dichloro-cis-1,2-cyclobutanedicarboxylic acid was obtained by Cope and Burg (5) from the oxidation of a dichlorinated cyclooctatetraene. This method[+] is laborious for preparing the material in quantity and the starting material is not readily available.

[+] The work was repeated in this laboratory by Nadoff (6); poor yields were obtained following the oxidation procedure given by the above authors (5).

Examples of types III and IV are unknown. In fact, the parent 1,3-cyclobutanedicarboxylic acids only recently became available through work carried out in this laboratory (7).

Perkin prepared his type I acid by a Hell-Volhard-Zelinsky bromination of the corresponding diacid and presumably type III could be obtained in a similar manner. The approach of Cope and Burg to type II suffers from the disadvantages previously stated and its generality has not been investigated. Methods leading to the preparation of compounds of type IV have not previously been studied.

The general purpose of the present investigation is to advance our knowledge of preparative methods leading to the halogenated cyclobutanecarboxylic acids. Specifically, Part I of these studies deals with the synthesis, by methods indicative of structure, of 5 isomeric monochlorocyclobutanecarboxylic acids. Part II is a study of the free radical chlorination of cyclobutanecarboxylic acid.

It is felt that these studies, which necessarily were carried out on the simpler models, will aid future investigators in the preparation of more complex halogenated cyclobutanecarboxylic acids.

PART I. SYNTHESIS OF THE MONOCHLOROCYCLOBUTANECARBOXYLIC ACIDS

In the introduction it was pointed out that only two dihalogenated cyclobutanedicarboxylic acids are known, the 1,2-dibromocyclobutane-1,2-dicarboxylic acid through the efforts of Perkin, Jr. (3) and the 3,4-dichlorocyclobutane-1,2-dicarboxylic acid through the investigations of Cope and Burg (5). Certain other halogenated cyclobutanecarboxylic acids are known, all derivatives of cyclobutanemonocarboxylic acid.

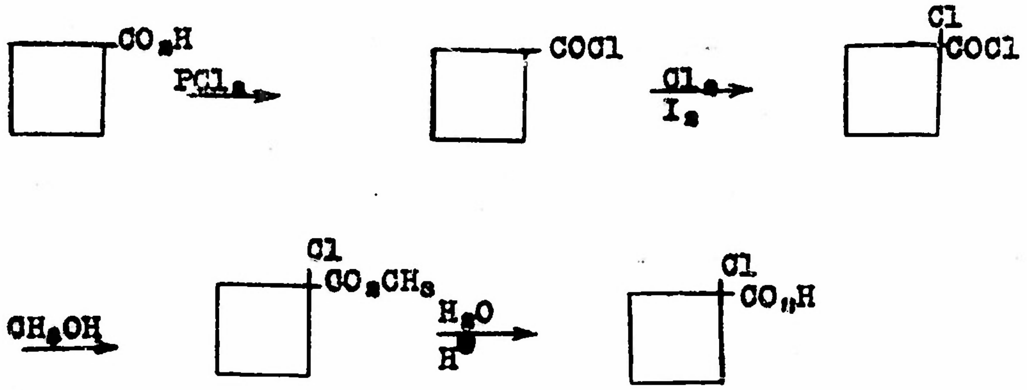
2,2,3,3-Tetrafluorocyclobutanecarboxylic acid has been prepared recently by Coffmann, Barrick, Cramer and Raasch (8) by allowing tetrafluoroethane to condense with vinyl cyanide and subsequent hydrolysis of the product. A trihaloacid was obtained by Perkin, Jr. (3) when bromine was added to 2-bromo-1-cyclobutenecarboxylic acid. Dosmin and Yakovlev (4) reported a 1,2-dibromocyclobutanecarboxylic acid resulting from the treatment of 1-cyclobutenecarboxylic acid with bromine.

Two simple monohaloacids are known. Hell-Volhard-Zelinsky bromination of cyclobutanecarboxylic acid by Perkin, Jr. and Sinclair (9) led to the formation of 1-bromocyclobutanecarboxylic acid. Jones (10), in recent unpublished work, has prepared one 3-chlorocyclobutanecarboxylic acid isomer by a several step procedure.

The last two investigations are pertinent to the present one and they are discussed at length later. The following discussion has been divided into three sections. Section A deals with the preparation of 1-chlorocyclobutanecarboxylic acid. Section B concerns the 2-chloroacids while Section C reports the study of the free radical chlorination of 1,1-cyclobutanedicarboxylic acid and the preparation of the 3-chlorocyclobutanecarboxylic acids.

A. Preparation of 1-Chlorocyclobutanecarboxylic Acid.

The 1-chlorocyclobutanecarboxylic acid may best be prepared from the corresponding monocarboxylic acid through chlorination of the acid chloride, conversion to the methyl ester and hydrolysis, as shown in figure 1:



The scheme for the preparation of the 1-chloroacid.
Figure 1.

Direct conversion of the acid to the 1-chloroacid chloride by the Hell-Volhard-Zelinsky method was not satisfactory. Under conditions similar to those employed by Perkin, Jr. and Sinclair (9) to obtain the 1-bromoacid, a rapid exothermic reaction took place resulting in a complex chlorinated mixture. A smoother reaction was achieved by chlorinating the acid chloride directly. To avoid an excess of chlorine, chlorinations were carried out with the equivalent amount of sulfuryl chloride using iodine as a catalyst and in the absence of light. Only unchlorinated acid chloride was recovered from these experiments. The starting material was also recovered unchanged after treatment of the acid chloride with the theoretical amount of dissolved chlorine in carbon tetrachloride solution and with red phosphorus as the catalyst.

However, by regulating the flow of chlorine (20 % excess) through the acid chloride in the presence of iodine at 100°, chlorination proceeded to give a 15 % yield of the chloroacid chloride. This method (11) probably depends upon ICl as the active chlorinating agent (12). Unsuccessful attempts were made to improve the yield by adding larger amounts of chlorine. Chlorine in excess of 140 % of the theory gave an acid chloride mixture, from which, on treatment with water, a solid was obtained. This solid, m.p. 104.2-105.2° gave analytical results in agreement with a dichlorocyclobutanecarboxylic acid. Little, if any, material was collected in the boiling range of the 1-chloroacid.

The 1-chlorocyclobutanecarboxylic acid was not obtained in pure form by treating the corresponding acid chloride with water. Fractionation and chromatography, employed either separately or consecutively, resulted in a product averaging 1.3 % high in carbon[+]. However, when the crude 1-chlorocyclobutanecarboxylic acid chloride was treated with absolute methanol, pure methyl ester was obtained (15 % yield from cyclobutanecarboxylic

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[+] It is possible that small amounts of anhydrides may be responsible for these high values. After treatment of the crude acid chloride with water there may be present cyclobutanecarboxylic acid and 1-chlorocyclobutanecarboxylic acid as well as the corresponding unreacted acid chlorides. Interaction of these species would be expected to yield the three possible anhydrides, one or more of which could codistill with the desired 1-chloroacid. The argument further supposes that the anhydride contaminant be neither removed nor altered under the chromatographic conditions employed.

acid chloride). This methyl ester was easily converted into the desired 1-chlorocyclobutanecarboxylic acid by an acid hydrolysis, yielding 42 % of acid, b.p. 111-112°/ 12 mm. The overall yield from cyclobutanecarboxylic acid is ca. 5 %. This acid was characterised by its amide and infrared absorption. The infrared data have been collected in tables V and VI (p. 47) and in figure 7, page 48.

EXPERIMENTAL[+]

Diethyl Cyclobutane-1,1-dicarboxylate

A 12-liter, 3-necked, round-bottomed flask, heated by means of a Glas-col mantle, was equipped with a 3-liter separatory funnel calibrated in 500-ml. divisions, a motor-driven half-moon stirrer, a 500-ml. separatory funnel calibrated in 125-ml. divisions, a take-off total-reflux condenser protected from the air by a calcium chloride drying tube, and an entrance for applying air pressure. Attached to the larger funnel at the bottom was a Tygon tube which reached into the flask and did not interfere with the operation of the stirrer. Into the reaction flask was placed 5 liters of absolute ethanol and, with moderate stirring over a period of two hours, 235 g. (10. 2 g. atoms) of sodium metal was slowly added. Toward the end of the addition, the rate was controlled by the rate of reflux of the ethanol. After the solution cooled to room temperature, air pressure was used to force 2 liters of the sodium ethylate solution into the 3-liter funnel. The air pressure was then released and 962 g. (6.0 moles) of diethyl malonate (Eli Lilly grade) was added. The solution was brought to reflux and 1012 g. (5 moles) of trimethylene bromide was added from the 500-ml. separatory funnel in an interval of an hour. At the same time, in a 1:2 ratio (by volume; dibromide:ethylate solution), the sodium ethylate contained in the larger funnel was added. After the addition, the refluxing was continued for 1-1/2 hours, and then the alcohol was distilled off by means of the take-off condenser until the temperature reached

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[+] Microanalyses by A. Elek, Los Angeles. All melting points are uncorrected.

80° (as measured by a thermometer suspended in the condenser). One liter of water and 500 ml. of benzene were added and the stirring was continued for 10 minutes. The clear, two-phase mixture was separated and the water layer was diluted with 500 ml. of water and 500 ml. of benzene. The resulting water layer was extracted twice more with 125 ml. portions of benzene. The benzene washings were added to the original benzene extract and the solvent was stripped off at reduced pressure. The higher boiling red-brown residue was flash distilled from a 2-liter Claisen flask, collecting the fraction boiling at 100-125°/ 15 mm. This material was treated in the dark with bromine until an added 1 ml. of bromine was no longer immediately decolorized. An average of about 30 ml. was required in this step. The amber liquid was fractionated by means of an electrically heated 15 cm. column packed with 3 mm. glass helices. The desired ester was collected over a 5 degree range (the major portion of the ester had b.p. 110-112°/ 15 mm., $n_D^{25} = 1.4343$); the over-all yield after refractionation of neighboring cuts was 55.5 % (555 g.). The reported values are: b.p. 91-96°/ 4 mm., $n_D^{25} = 1.4332$-1.4334 (13) and b.p. 105-112°/ 15 mm. (14).

The above method is essentially that of Cason and Allen (14) as modified by Lemaire (15), who introduced the bromination step to remove any allyl maleic ester (b.p. 93°/ 6 mm.) present.

Cyclobutane-1,1-dicarboxylic Acid

Potassium hydroxide (225 g. = 4 moles) was dissolved in 1 liter of absolute ethanol contained in a 2-liter beaker. The beaker was then cooled in an ice bath and 200 g. (1 mole) of diethyl

1,1-cyclobutanedicarboxylate was slowly added. After the reaction appeared complete, the mixture was placed on a steam bath for 1-1/2 hours and occassionally stirred. The white, pasty product was filtered through a coarse sintered glass funnel. The solid was washed in a beaker with 500 ml. of absolute ethanol and filtered off as above. The washing process was repeated, using 500 ml. of absolute ether and the crude potassium salt was dried to constant weight to free from traces of alcohol. The dry salt was taken up in the minimum amount of water and 300 ml. of concentrated hydrochloric acid was added. The resulting precipitate was filtered off and the filtrate was evaporated nearly to dryness at 44-50° (water bath) under an aspirator vacuum. The mush was shaken thoroughly with 500 ml. of ether and the mixture was filtered. The ethereal filtrate was evaporated (water bath and aspirator as before) until mixing lines in the distillate indicated a second substance distilling. The residue was crystallized from 200 ml. of ethylene dichloride and the solid acid was separated by filtration from the two-phase mother liquor at about 0°. The remaining traces of solvent were removed with a vacuum pump. The yellowish product smelled of hydrochloric acid and was spread out in thin layers in a hood overnight. The resulting white powder weighed 102.8 g. (71.3 %) and melted at 154-5° (dec.). The decomposition point may be raised to 157-158.5° by recrystallization; the reported (16) melting point is 156-158°.

Cyclobutanecarboxylic Acid

Cyclobutane-1,1-dicarboxylic aicd (14.4 g. = 0.1 mole) was placed in a 25 ml. round-bottomed flask and heated at 180° for 20 minutes at the end at which time no further evolution of carbon dioxide was observed (liberated gases were bubbled through a saturated barium hydroxide solution). The crude oil was distilled at 15 mm. collecting the fraction boiling at 96-98°. The yield was 8.49 g. (85 %), n_D^{25} = 1.4411. The reported constants are: b.p. 96°/ 15 mm. (17), 104-106°/ 21 mm. (13) and n_D^{25} = 1.4436 (18).

Cyclobutanecarboxylic acid was also obtained as described by Fischer (19). The acidified solution following saponification of the diethyl 1,1-cyclobutanecarboxylate was subjected to 24 hour continuous ether extraction and then the ether extract was evaporated. The resulting mush was decarboxylated as described above resulting in an average yield of 58.1 % of material, b.p. 98-101°/ 15 mm., n_D^{25} = 1.4415.

Cyclobutanecarboxylic Acid Chloride

A 100 ml., 3-necked, round-bottomed flask was equipped with a dropping funnel, a thermometer whose bulb reached near to the bottom of the flask, and a reflux condenser protected from moisture by a calcium chloride tube. Cyclobutanecarboxylic acid (33.4 g. = 0.334 mole) was added and 30.5 g. (0.222 mole = 19.4 ml. = 100 % excess) of phosphorus trichloride was dropped in over a 20 minute interval. The temperature was raised (oil bath) to 105 ± 5° for an hour. The light yellow liquid was decanted from the viscous yellow-orange residue and the latter was rinsed with a few ml. of phosphorus trichloride. The washing was added to the decanted liquid and the solution was distilled from a Claisen flask whose neck below the side arm was filled with 1-1/2 cm. of 6 x 6 mm. glass rings (bottom layer) and 3-1/2 cm. of

3 mm. glass helices (top layer). The fraction boiling at 65-69°/ 60 mm. was collected and weighed 30.2 g. (77.5 %). The reported value (19) is 65°/ 60 mm.

1-Chlorocyclobutanecarboxylic Acid Chloride

A bubbler filled with chlorine-saturated carbon tetrachloride was calibrated (by counting the number of bubbles corresponding to a known weight of chlorine) and attached through a 3-way joint to a supply of dry air and dry chlorine. A 100-ml., round-bottomed flask, carrying an inlet tube attached to its bottom and plugged by a sintered glass disc at the point of attachment, was equipped with a reflux condenser protected by a calcium chloride drying tube. The inlet tube was attached to the bubbler and a small positive pressure of air was applied. Iodine (0.05 g.) and 20 g. (0.168 mole) of cyclobutanecarboxylic acid chloride were added to the flask. With the aid of an oil bath, the flask was heated to about 105° and the air pressure was replaced by a flow of chlorine (rate 1.6 g./hour). After an equivalent amount of chlorine was added, the reaction mixture was flash distilled, and then finally fractionated at 60 mm. through an electrically heated 15 cm. x 15 mm. column packed with 3 mm. glass helices. A major portion of the acid chloride was recovered unchanged together with 15 % (4.1 g.) of material boiling at 74-78°/ 60 mm. This material presumably contained small amounts of the unchlorinated acid chloride, for its amide, which originally melted at 114-116.5°, upon recrystallization from petroleum ether, yielded fractions which approach the 155-156.5° melting point of cyclobutanecarboxylic acid amide.

An attempt was made to increase the yield by adding an excess of chlorine. When a 125 % excess of chlorine was used, the mixture hydrolysed with water, and the product distilled, a compound boiling at 130-134°/ 9 mm. was obtained in 33 % yield (calculated as dichlorocyclobutanecarboxylic acid). This compound, which spontaneously crystallised, melted at 104.2-105.2° (from petroleum ether).

Anal. Calcd. for $C_5H_6O_2Cl_2$: C, 35.53; H, 3.58 Found: C, 35.58; H, 3.47.
The same compound was recovered in 48 % yield when 41 % excess of chlorine was allowed to react.

A 20 % excess of chlorine gave what may be the optimum amount of monochlorination. When 25 g. (0.21 mole) of cyclobutanecarboxylic acid chloride was treated with 20 % excess of chlorine as described above, the crude yield weighed 30.5 g. indicating that ca. 95 % of the theoretical amount of chlorine had been absorbed by the reacting liquid. However, when this crude mixture was converted to the corresponding ester, as described below, only a 15 % yield of ester was obtained.

Methyl 1-Chlorocyclobutanecarboxylate

The crude mixture (30.5 g.) of acid chlorides, obtained by the method outlined above, was added slowly to 20 ml. (0.5 mole) of ice-cold absolute methanol. The solution was allowed to reach room temperature and then it was refluxed for an hour. The reaction mixture was washed with a saturated sodium bicarbonate solution, a sodium thiosulphate solution, and finally with water. The organic layer was taken up in ether, dried with magnesium sulphate, and flash distilled, collecting the fraction boiling at 80-110°/ 100 mm. Fractionation through an electrically heated 15 cm. × 1 cm. Vigreux column yielded 4.72 g. (15 %, based on cyclobutanecarboxylic acid chloride) of material boiling mainly at 100-

102°/ 100 mm., n_D^{25} = 1.4473. This compound gave analytical figures for methyl 1-chlorocyclobutanecarboxylate:

Anal. Calcd. for $C_6H_9O_2Cl$: C, 48.49; H, 6.10; Cl, 26.54. Found: C, 48.49; H, 6.17; Cl, 26.44.

Amide: A 0.1 g. sample of the above ester was taken up in 2 ml. of concentrated ammonium hydroxide and the mixture was boiled until homogeneous. The reaction product was extracted with ether, the extracts were evaporated and the residue was recrystallized from petroleum ether, m.p. 114-115°.

Anal. Calcd. for C_5H_8ONCl: C, 44.94; H, 6.04. Found: C, 44.96; H, 6.09.

1-Chlorocyclobutanecarboxylic Acid

Methyl 1-chlorocyclobutanecarboxylate (4.6 g. = 0.031 mole) was placed in a 100-ml., round-bottomed flask with 25 ml. of diethyl carbitol and 22.5 ml. of 12 N hydrochloric acid (0.2 mole) and the mixture was heated at 98-105° for 16 hours. After cooling, the two-phase reaction product was extracted with a total of 100 ml. of ether in three portions. The ether extracts were combined and extracted three times with a total of 30 ml. of 5 % sodium hydroxide (ca. 0.064 mole). The alkaline solution was neutralized and brought to a pH of 2-3 and extracted with a total of 50 ml. of ether. The ether extracts were combined and dried with magnesium sulfate and evaporated. The yellow oil remaining was distilled from a 5-ml. Claisen flask. The major fraction, b.p. 111-112°/ 12 mm., was obtained in 42 % yield (1.76 g.). The refractive index was : n_D^{25} = 1.4545. The overall yield from cyclobutanecarboxylic acid is ca. 5 %.

Anal. Calcd. for $C_5H_7O_2Cl$: C, 44.64; H, 5.24. Found: C, 44.58; H, 5.23.

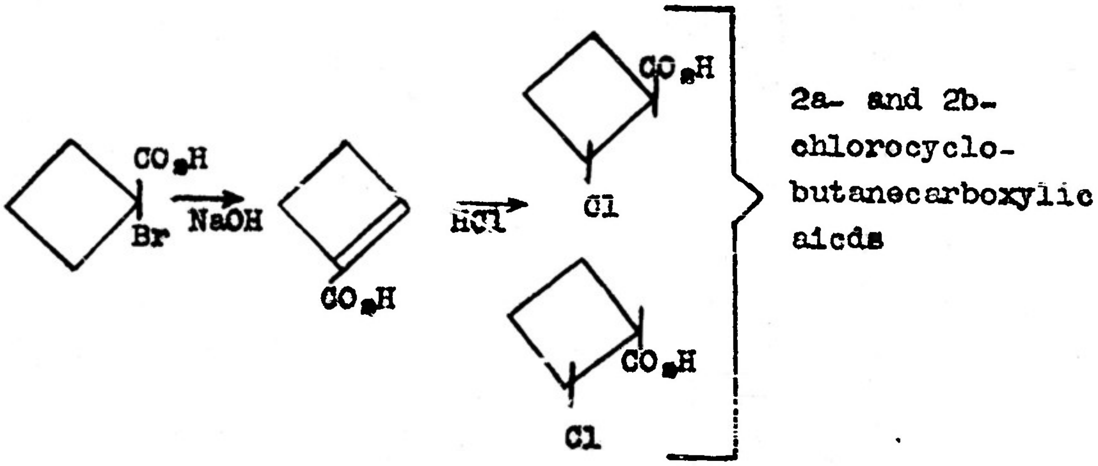
Amide: The 1-chlorocyclobutanecarboxylic acid (0.1 g.) obtained above was placed in a 15 ml. centrifuge tube and was treated with 0.1 g. of cold thionyl chloride in the presence of a drop of dry pyridine. The solution was heated on a steam bath for about 10 minutes and then cooled to about 0°. The crude acid chloride was then dropped slowly into ice-cold concentrated ammonium hydroxide. The precipitate was extracted with a total of 15 ml. of chloroform in two portions and these extracts were evaporated to dryness. Recrystallization of the residue from petroleum ether yielded a solid, m.p. 113-114°. The mixed melting point proved that this amide was identical with the one obtained by ammonia treatment of the corresponding methyl ester.

Infrared Absorption of the 1-Chloroacid

The spectrum was taken in carbon tetrachloride solution (0.050 g./ ml.) using 0.05 mm. sodium chloride cells with a Perkin-Elmer Model 21, Serial 122, double beam spectrophotometer. The acid sample was that for which the microanalysis was given above. Infrared data concerning this acid have been collected in tables V and VI (p. 47) and in figure 7, page 48.

B. Preparation of the 2-Chlorocyclobutanecarboxylic Acids.

Starting from 1-bromocyclobutanecarboxylic acid (9), Domin and Yakovlev (4) prepared 1-cyclobutenecarboxylic acid by treating a dry toluene solution of the former acid with alkali. As shown in figure 2, the addition of anhydrous hydrogen chloride to the cyclobutene acid could lead to a mixture of 2-chlorocyclobutanecarboxylic acids. The stereochemistry of hydrogen halide addition to carbon-carbon double bonds is somewhat uncertain (20); however, it is reasonable to assume that stereospecific addition may proceed in the trans sense (21). Grovenstein and Lee (1) as well as Cristol and Norris (2) have presented evidence that with acrylic acid derivatives hydrogen halide added predominantly in a trans fashion to the double bond. One might expect that 1-cyclobutenecarboxylic acid would yield cis-2-chlorocyclobutanecarboxylic acid (by trans-addition) with lesser amounts of the trans-chloroacid. However, the actual amounts of each isomer formed could depend upon experimental conditions.



The scheme for the preparation of the 2-chloroacids.
Figure 2.

Actually, when anhydrous hydrogen chloride was added to the 1-cyclobutenecarboxylic acid in toluene solution at 0°, the addition gave a 60 % yield of a material with a boiling range of 5 degrees which solidified at room temperature. This material, when recrystallized from petroleum ether, yielded a solid, m.p. 97-99°, and may be termed the 2a-chlorocyclobutanecarboxylic acid.

To more completely investigate the crude product from hydrogen chloride addition, chromatographic separation of the possible acids present was considered. Lester Smith (22) first applied the silicic acid column developed by Martin and Synge (23) to lower fatty acids. Various indicators, including methyl orange (23), anthocyanins (24), and an azo dye (25), have since been employed to enable these colorless acids to be seen on the column. However, bromocresol green (pK = 4.66) seems superior both from the standpoint of sensitivity and leaching properties (26). The method was extended to include the saturated straight chain fatty acids through C_{10}, by Ramsey and Patterson (27). Marvel and Rands (28) subsequently developed a general qualitative and semi-quantitative technique for the determination of many water soluble acids. The method of Ramsey and Patterson seemed preferable in the present study to that of Marvel and Rands due to the slight water solubility of the chlorocyclobutane acids. The former authors also were able to obtain a high degree of selectivity. Using 2,2,4-trimethylpentane as the mobile solvent, a minimum of 10 % of isobutyric acid was detected in samples of butyric acid, although in a single pass through the column the separation was not complete (27c).

In practice, it was found that an isomeric chlorocyclobutanecarboxylic acid mixture was not separated by the Ramsey and Patterson column. However, a modification of their column was developed that easily separated the mixture obtained from the hydrogen chloride addition to cyclobutenecarboxylic acid into two acid fractions. This column, which was operated at atmospheric pressure, employed 17 % aqueous methanol as the non-mobile solvent, n-hexane as the mobile solvent and celite 545 as a flow-rate accelerator. Titration according to the method of Marvel and Rands (28) showed the 2a-chlorocyclobutanecarboxylic acid to be present to the extent of 55 % of the total acid content of the crude product. Another component, which may be termed the 2b-chlorocyclobutanecarboxylic acid, was shown to be present to the extent of 30 %.

These acids were characterized by their infrared absorptions and p-bromophenacyl esters. The 2a-chloroacid at 130° in the presence of concentrated hydrochloric acid was converted within 30 minutes to a mixture of which 80 % of the acid titrated was a compound that moved on the column in a manner similar to the 2b-chloroacid. No 2a-chloroacid was formed when 2b-chloroacid was likewise treated.

EXPERIMENTAL

1-Bromocyclobutanecarboxylic Acid

As described by Perkin and Sinclair (9), 50 g. (0.50 mole) of cyclobutanecarboxylic acid was treated with 5.3 g. of red phosphorus and 150 g. (0.94 mole) of phosphorus pentoxide-dried bromine. The isolated product, m.p. 42-45°, weighed 40 g. (45 %, Perkin and Sinclair report m.p. 48-50°).

1-Cyclobutenecarboxylic Acid

Dry potassium hydroxide (53 g. = 0.945 mole) and 25 ml. of dry toluene were added to a 200-ml., 3-necked, round-bottomed flask equipped with a reflux condenser, dropping funnel and motor-driven Hershberg stirrer. The reaction mixture was placed on a boiling water bath and, with vigorous stirring, 40 g. (0.223 mole) of 1-bromoacid, dissolved in 40 ml. of dry toluene, was slowly dropped in over a period of 30 minutes. During the addition the mixture turned tan and became quite pasty while the toluene was seen to periodically reflux. The mixture was heated an additional 30 minutes during which time the toluene no longer refluxed. The contents were allowed to cool and water was added until the precipitate dissolved (ca. 200 ml.) The water-toluene mixture was acidified with sulfuric acid until the resulting precipitate dissolved (pH = ca. 1). The layers were separated and the toluene layer was washed with about 50 ml. of water, separated, placed in a suction flask equipped with a capillary air leak and then evaporated at 50° and 45 mm. After a solid had separated, the rest of the solvent was removed at room temperature and 12 mm. The yield of red-brown solid was 9.6 g. (44 %). Recrystallization of a sample of the crude product from benzene gave a white solid partly melting at 65-72° but turning, at this temperature, to a clear gum. In a melting block preheated to 78° a sample melted completely but quickly solidified to a milky white gum. (Demnin and Yakovlev report a m.p. of 72°.) No attempt was made to purify the crude product (see next section).

2a-Chlorocyclobutanecarboxylic Acid

Procedure A: The crude unsaturated acid (8.3 g. = 0.085 mole) prepared above was placed in a 100-ml. round-bottomed flask, cooled to 0° and then the flask was placed in a beaker of ice and water which was resting upon a balance. Dry toluene (50 ml.) and 0.1 g. of hydroquinone (to retard polymerization) was added. An inlet tube with a porous glass head was connected to a source of anhydrous hydrogen chloride and suspended into the liquid. After 3.2 g. (0.088 mole) of hydrogen chloride was passed into the solution, the reaction flask was stoppered and stored at room temperature for 20 hours. An additional 3.2 g. (total: 0.176 mole) of hydrogen chloride was added at 0° and this mixture was allowed to react for an additional 20 hours at room temperature. The amber liquid was filtered free from a slight amount of amorphous precipitate, the toluene was stripped off, and the product was distilled at 6 mm., collecting the fraction boiling at 115-120°. The white solid which spontaneously crystallized in the receiver weighed 6.8 g. (59 % yield) and, after recrystallization from petroleum ether, melted at 97-99°. The yield from 1-bromoacid was 25.6 %.

Procedure B: The acid may more conviently be obtained directly without isolation of the unsaturated acid and without loss in overall yield. Potassium hydroxide (106 g.=1.89 mole) and 80 g. (0.446 mole) of 1-bromoacid were allowed to react as given above. The cool reaction mixture was treated with 400 ml. of water and separated. The aqueous phase was washed twice with toluene and the combined toluene solutions were dried with magnesium sulfate for 30 minutes. After separation from the drying agent, the solution was cooled to 0°. In the manner described above, 0.5 g. of hydroquinone and 12.3 g. (0.338 mole) of anhydrous hydrogen chloride were added. After 15 hours at room temperature, the solution was saturated twice more at 24 hour intervals with 8.0 g. and 7.0 g. respectively of hydrogen chloride. The total time of reaction was 62 hours and the total amount of hydrogen chloride added was 27.3 g. (0.745 mole). The product was isolated according to the directions given in Procedure A. A yield of 15.8 g. (28.4 %) of solid m.p. 96.8-98.2° was obtained.

p-Bromophenacyl ester: Using 0.1 g. of the 2a-chloroacid, the procedure recommended by Shriner and Fuson (29) yielded crystals from water-ethanol, m.p. 88-89.5°.

Anal. Calcd. for $C_{13}H_{12}O_3BrCl$: C, 47.08; H, 3.65. Found: C, 46.97; H, 3.66.

Chromatographic Separation of 2a- and 2b-Chloro-cyclobutanecarboxylic Acids

Preparation of the column Mallinckrodt silicic acid (17 g.), specially prepared for chromatographic analysis by the method of Ramsey and Patterson, and 3 g. of celite 545 were placed in a mortar and thoroughly mixed. A solution of exactly 1.7 ml. (± 0.05 ml.) of water, 8 ml. of absolute methanol, 1.5 drops of freshly prepared 1 N (± 0.2 N) ammonium hydroxide and 1 ml. of bromocresol green indicator (0.200 g./25 ml. methanol) solution was added and the paste was mixed until a fine blue-green powder was obtained in the mortar. Enough solvent-grade n-hexane was added so that the combined volume of the adsorbent and the hexane would just fill a 1.8 x 52 cm. glass tube which had a stopcock (2 mm. bore) sealed onto one end. A small cotton plug was placed in the bottom of the ~~tube~~ and, with the stopcock open, the mixture was added in one batch while the slurry was stirred vigorously. The column was tapped gently until the level of the silicic acid showed no settling over a period of 15 minutes.

It had been found that with the original Ramsey and Patterson column (containing no celite), the use of 20-50 cm. of air pressure, as recommended by those authors, resulted in considerable drying out of the lower end of the column and thus mixing of the bands. (Use of vacuum had the same effect.) At lower pressures the rate of flow of eluate was extremely slow. This rate difficulty was somewhat overcome by the use of 15 % celite. Even with celite, however, best separation was achieved at atmospheric pressure. Ease of separation was also found to be directly dependent upon the concentration of water and of ammonia on the column. If each was not present in the amounts specified above, little or no separation took place.

The separation: A 0.0979 g. sample of the crude 2-chloroacid mixture obtained by Procedure B above (cf. p. 21) was taken up in 5 ml. of n-hexane and the solution, plus a small amount of the 2-chloroacid which was yet undissolved, was added slowly along the sides of the tube about 1-2 mm. above the surface of the silicic acid. After this material was adsorbed onto the column, the sides of the tube were washed with 1 ml. of n-hexane. After the sample was completely adsorbed, further tapping of the column was avoided. n-Hexane was added to the prepared column slowly so that the surface of the silicic acid was not disturbed. The column was developed, the level of the solvent being maintained by suspending over the column a stoppered, hexane-filled, 1-liter separatory funnel with its stopcock open and having its exit tip slightly below this level. The development was continued until the effluent contained only traces of acid (8 days). After several days, entrapped air within the column collected into bubbles which were freed by tapping. This allowed a more rapid effluent flow.

Figure 3 is a plot of the titration values of each 10 ml. fraction following the first 80 ml. through the column. The titration method was that of Marvel and Rands (28) using 0.025 N sodium hydroxide, phenol red as an indicator and two drops of 1 % Dreft solution. Fractions 16-41 required 15.58 ml., corresponding to 55 % of the total acid content of the crude mixture; this material was identified as 2a-chlorocyclobutanecarboxylic acid as outlined in the next section. Fractions 1-15 required 8.22 ml., representing 29.5 % of the acid content; this was the 2b-chlorocyclobutanecarboxylic acid. Thus, the 2-chloroacids accounted for 84.5 % of the acid content of the crude mixture.

Identification of the bands: A 5.8 x 56 cm. column was packed in the manner described on page 22 with 166.6 g. of silicic acid, 33.4 g. of celite, 10 ml. of indicator, 17 ml. of water, 80 ml. of absolute methanol, and 15 drops of 1 N ammonium hydroxide. A crude mixture of 2-chloroacids (1.9815 g.) in 100 ml. of hexane solution was introduced onto the column as described above and the column developed with hexane. Two bands clearly seperated and after 1100 ml. of eluate had passed through the column, 100 ml. fractions were collected (during 6 days).

Evaporation of the solvent from middle fractions of the second band yielded a solid which after recrystallization from petroleum ether melted at

Chromatographic Separation of a Mixture of 2-Chlorocyclobutanecarboxylic Acids

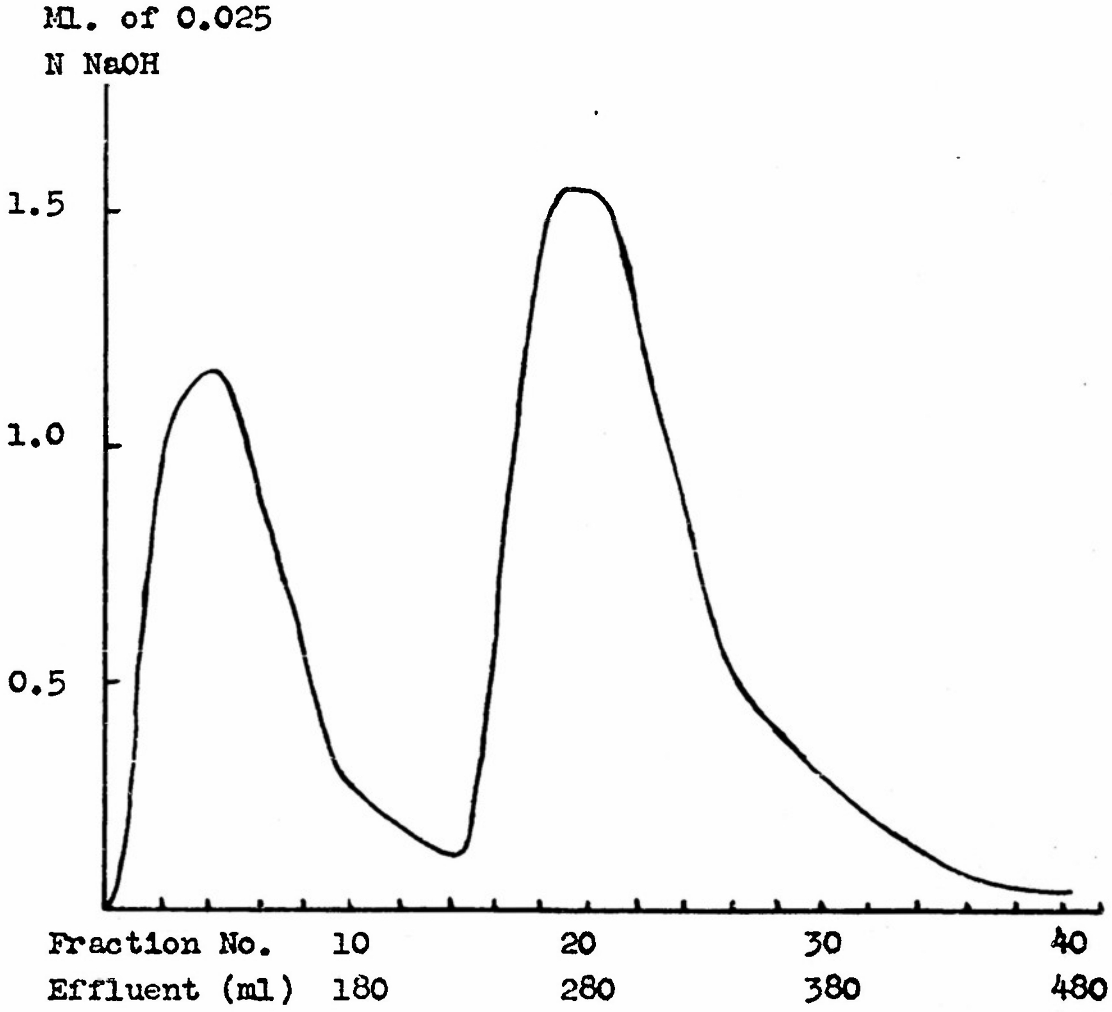


Figure 3.

97.0-98.5°, the 2a-chlorocyclobutanecarboxylic acid.

Anal. Calcd. for $C_5H_7O_2Cl$: C, 44.65; H, 5.25. Found: C, 44.47; H, 5.16

2b-Chlorocyclobutanecarboxylic acid: Isolation of the acid component of the first band by evaporation of the eluate yielded a yellow oil. That this yellow color was not leached bromocresol green was shown by bringing a portion to pH 10 with ammonium hydroxide and noting no color change. Rechromatographing the oil on a 1.8 x 20 cm. column packed with 4.2 g. of silicic acid, 0.8 g. of celite, 2.2 ml. of absolute methanol, and 0.5 ml. of water, resulted in a magenta band which remained at the top of the column but the liquid obtained upon evaporation of the hexane still was a pale yellow. A petroleum ether solution of the yellow oil when cooled to ca. -60° became very viscous but no crystals separated. If, instead of rechromatographing, the original yellow oil was distilled from a 5 ml. Claisen flask, a fraction was obtained boiling at 127-130°/ 15 mm. and consisting of a pale yellow oil, n_D^{25} = 1.4773.

Anal. Calcd. for $C_5H_7O_2Cl$: C, 44.65; H, 5.25. Found: C, 45.47; H, 5.35.

For refractionation of the above distillate, the semimicro distilling apparatus of Gould, Holzman and Niemann (30) was employed using four 6 x 60 mm. tubes as receivers. Fractions were obtained as follows:

No.	b.p./ mm.	weight (g.)	n_D^{25}
1.	96-120°/ 14	0.1184	1.4566
2.	120-122.5°/ 14	0.4780	1.4732
3.	122.5-125°/ 14	0.2320	1.4768
4.	above 125°/ 14	0.0225	- -

All the above fractions were colorless. On the basis of the microanalysis given below, Fraction 2 consisted of 2b-chlorocyclobutanecarboxylic acid with an unknown contaminant. Fraction 3 was analyzed and gave a carbon value 3 % low.

Anal. Calcd. for $C_5H_7O_2Cl$: C, 44.65; H, 5.25. Found (Fraction 2): C, 43.35; H, 5.30.

p-Bromophenacyl ester: Using 0.1 g. of the 2b-chloroacid, the procedure recommended by Shriner and Fuson (29) yielded crystals from water-ethanol, m.p. 73.6-74.1°.

Anal. Calcd. for $C_{13}H_{12}O_3BrCl$: C, 47.08; H, 3.65. Found: C, 47.15; H, 3.76.

Infrared Absorption of the 2-Chloroacids

The spectra were taken in carbon tetrachloride solution (0.050 g./ml. for the 2b-acid and a saturated solution for the 2a-acid) using 0.05 mm. sodium chloride cells with a Perkin-Elmer Model 21, Serial 122, double beam spectrophotometer. The acid samples were those for which the microanalyses were given above. Infrared data concerning these acids have been collected in tables V. and VI. (p. 47) and in figure X, page 48.

Isomerization Studies with the 2-Chlorocyclobutene-carboxylic Acids

Qualitative investigation: Samples of 0.1 g. each of the 2-chloroacids were sealed in separate 6 x 100 mm. tubes containing 0.5 ml. of concentrated hydrochloric acid and placed in an oil bath. The temperature was brought to 140° over a period of an hour and held at 140-155° for 30 minutes. The dark red-brown solutions were extracted with ether and the ether evaporated. The residues were boiled with benzene to remove water and the benzene residues were chromatographed on 20 g. (silicic acid + celite) column prepared as noted on page 22. Besides the usual non-moving material at the top of the column, each column had only one moving band. The effluent peak of the band from the 2a-chloroacid was 80 ml. while that from the 2b-chloroacid was 100 ml. Figure 3 shows that the effluent peak of the 2a-chloroacid on a 20 g. column was 270 ml. while that of the 2b-chloroacid was 120 ml. In each case only 23-24 % of the total theoretical acid content of the column was titrated, suggesting that column held-up and decomposition accounted for the remaining 75 %. It was noted that apparently more material remained at the top than usual for this top band (usually the top 1/5 of the column) extended about half way down each chromatogram when the titrations were completed. Fractionation was continued until 400 ml. of the eluate had been collected.

Quantitative investigation: One tenth-gram samples of 2a-chlorocyclobutanecarboxylic acid were sealed in four 6 x 100 mm. tubes, each with 0.5 ml. of concentrated hydrochloric acid, and placed in a preheated oil bath at 180°. A tube was removed at the end of 1, 5, 15, and 30 minutes. The contents of the tubes varied in appearance from the 1-minute tube which apparently was unreacted through the 5- and 15-minute tubes which were progressively darker to the 30-minute tube which was very well blackened. The method of isolation and analysis was that described in the above paragraph. If the peak obtained by the 1-minute tube's contents is taken as that of the 2a-chloroacid, then the first peak to be titrated occupied a position corresponding to the 2b-chloroacid (i.e., 150 ml. previous, as in figure 3). Table I summarizes the results obtained:

TABLE I.

Time (min.)	Titration values (0.0183 N NaOH) (ml.)		Percent of total		Percent Recovery of Acid[+]
	1st[‡] peak	2nd[++] peak	1st peak	2nd peak	
30	13.46	3.34	80	20	41.4
15	12.86	5.42	70	30	45
5	7.54	8.72	46	54	40
1	---	17.51	0	100	47

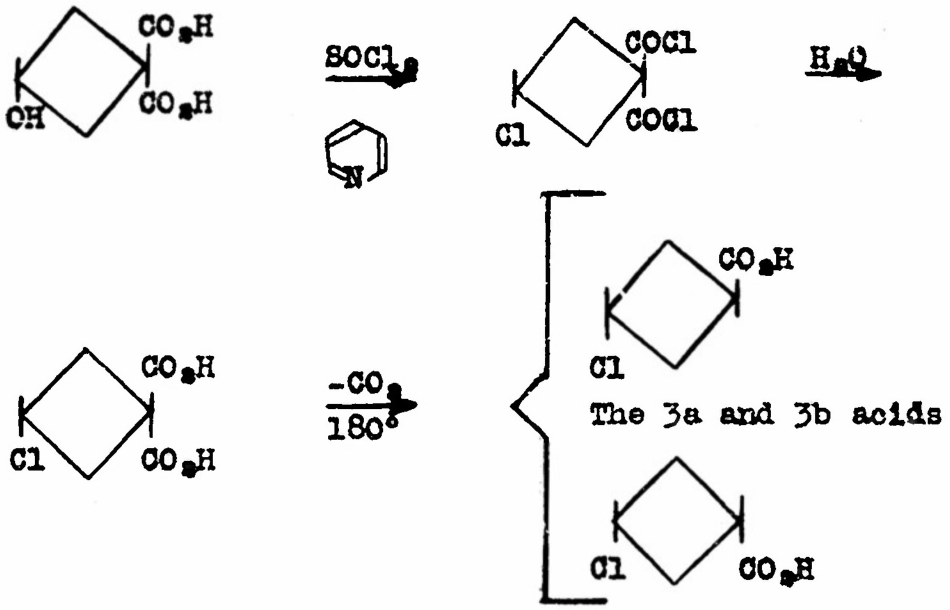
[+] The theoretical recovery was 40.6 ml. Two other time periods were also investigated, 10 and 60 minutes. However, recovery in these two cases was 10-20 % higher than in the cases noted, thus making their inclusion here questionable.

[‡] The position of this band corresponds to the 2b-chloroacid.

[++] The position of this band corresponds to the 2a-chloroacid (see p. 28).

C. Preparation of the 3-Chlorocyclobutanecarboxylic Acids.

Previous to this investigation, R. C. Jones (10) had prepared one isomer of the 3-chlorocyclobutanecarboxylic acid by the copper catalyzed decomposition of the corresponding 3-chloro-1,1-diacid. The latter resulted from the action of thionyl chloride on the 3-hydroxy-1,1-diacid in the presence of pyridine (fig. 4). Upon repeating this work, starting with hydroxyacid prepared previously in this laboratory (31), an oil was obtained from which a solid acid apparently identical with the Jones acid was isolated. This acid, m.p. 51-52.2°, may be termed the 3a-chlorocyclobutanecarboxylic acid. As one may see from figure 4, the Jones preparation would be expected to lead to a mixture of the two forms, the 3a and the 3b:



The scheme for the preparation of the 3-chloroacids.
Figure 4.

The relative inaccessibility of the hydroxyacid as well as the fact that apparently only one isomer was obtained by the Jones method made it desirable to find another pathway to the 3-chloroacids.

Ash and Brown (32) found that certain directive effects were observed in aliphatic chlorination. As a terminal directing group (-COOH, -COCl, etc.) is made more electrophilic, free radical chlorination takes place less readily in the alpha position. Thus, with n-butyric acid they found 45 % each of the beta- and gamma-halogenated products and 10 % of the alpha-haloacid. The corresponding acid chloride gave 48 % gamma-haloacid, 49 % beta-haloacid and only 3 % of the alpha-haloacid.

One would expect[+] that a free radical chlorination of cyclobutane-1,1-dicarboxylic acid or of its equivalent would lead to a mixture of 2-chlorodiacid and 3-chlorodiacid. These acids could then be separated by orthodox methods. It was found, using the cyclobutane-1,1-diacid, that sulfuryl chloride with benzoyl peroxide failed to chlorinate the ring either at 77° for 48 hours in carbon tetrachloride solution or at 100° for 6 hours in sym-tetrachloroethane. If, however, the diacid dichloride was first prepared and isolated, chlorination proceeded without added solvent, the temperature rising as the sulfuryl chloride reacted. The chlorinated material consisted almost entirely of the 3-chlorodiacid, as shown by comparison of the decarboxylation products with authentic materials. This would seem to indicate an enhanced electrophilic character of a 1,1-diacid

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[+] Before the experiment, Professor H. C. Brown predicted, in a private communication, that the 3-chlorodiacid and only negligible amounts of 2-chlorodiacid would result from the chlorination of cyclobutane-1,1-dicarboxylic acid.

dichloride grouping above that attributed to the single COCl group. Ash and Brown have shown a similar enhancement in the series: $-CH_2Cl < -CHCl_2 < -CCl_3$.

Although a pair of isomers might be expected in the decomposition of the 1,1-diacid, it would not seem impossible, as the Jones work and our own repetition seemed to indicate, that the decarboxylation process might favor one isomer practically to the exclusion of the other. In an attempt to circumvent this possibility and to prepare from the 3-chlorodiacid or its equivalent the isomer which apparently had not been obtained by direct decarboxylation, the scheme shown in figure 5 was devised. Separation of the desired isomer was to be effected either at the last step (as indicated in the figure) or at some intermediate step en route.

Staudinger and Ott (33) were successful in converting diethylmalonic acid into the half acid chloride. This latter material was found in this study to react with methanol to give the halfacid ester, m.p. 15-16.5°, described by Dumesnil (34). Upon decarboxylation, 63 % of the expected diethylacetic acid, $n_D^{25} = 1.4030$, was isolated. However, when the method was applied to 3-chlorocyclobutane-1,1-diacid only diacid dichloride and unreacted diacid could be recovered.

A study of the treatment of the diacid dichloride with one equivalent of methanol resulted in yields of unreacted material and, to a minor extent, higher boiling fractions from which, after treatment with water, only diacid was isolated.

At this point it was decided to study more critically, by chromatographic methods, the crude distillate from the decomposition of the 3-chlorocyclobutane-1,1-diacid and a technique was developed

Proposed Syntheses of a Mixture of 3-Chlorocyclobutane Acid

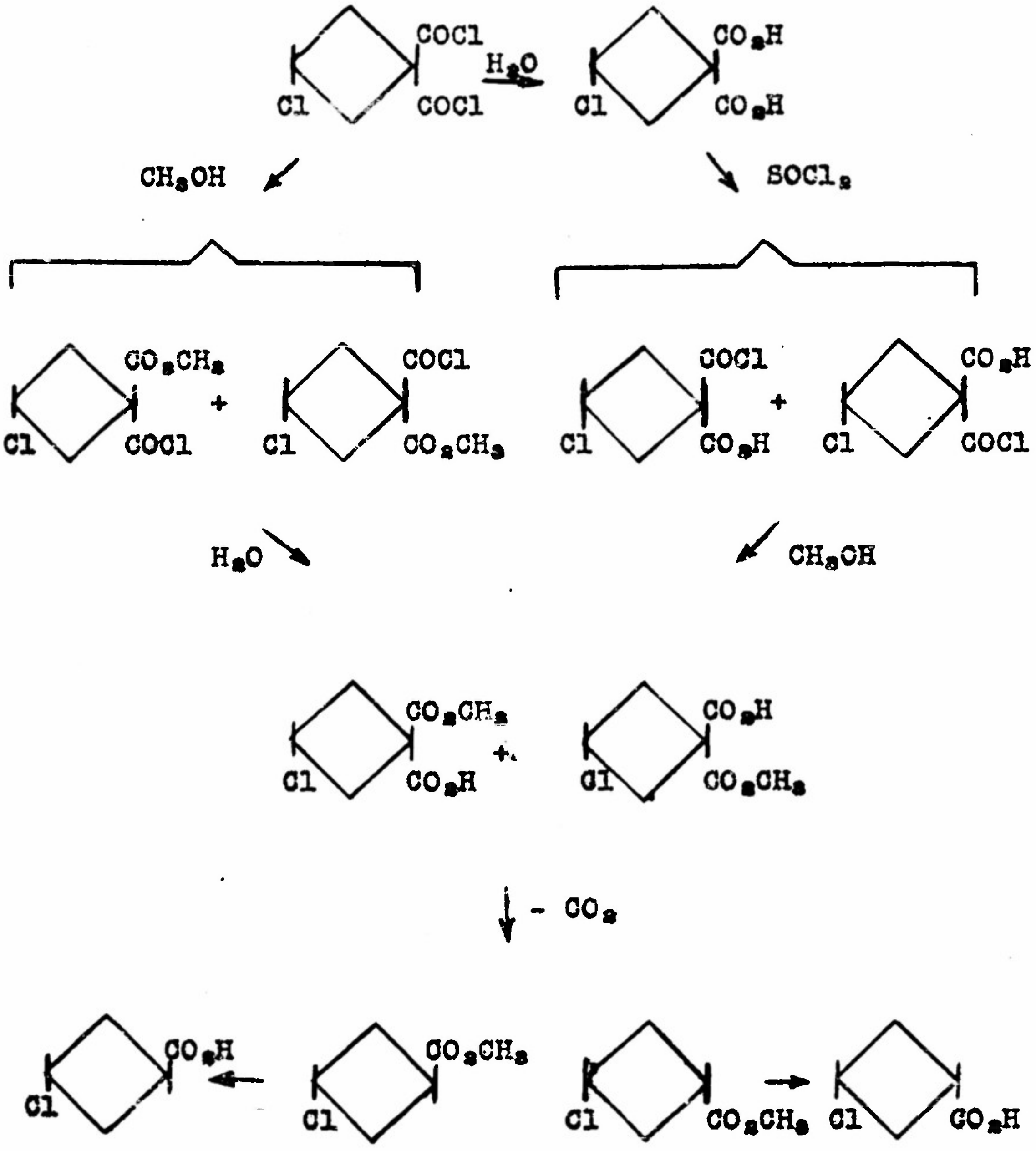

Figure 5.

for this purpose (see pages 18, 22). Application of this method led to the separation of the decarboxylation mixture into two fractions which together accounted for 80 % of the total acid content of the crude oil. One fraction (51 %) consisted of the same acid isolated previously by following the Jones procedure (as shown by mixed melting points of the acids and of the p-bromophenacyl esters), while the other (30 %) was a new isomer, m.p. 43.8-45.5°, which may be termed the 3b-chlorocyclobutanecarboxylic acid.

The two acids have been characterized by their infrared absorptions and p-bromophenacyl esters. The amides prepared from each acid appear to be identical. A preliminary inconclusive attempt was made to isomerise one 3-chloroacid into the other.

EXPERIMENTAL

Cyclobutane-1,1-dicarboxylic Acid Dichloride

A round-bottomed, 500-ml., 3-necked flask was fitted with a reflux condenser, a dropping funnel and a thermometer whose bulb reached nearly to the bottom of the flask. A calcium chloride drying tube on the condenser protected the system from moisture. Cyclobutane-1,1-dicarboxylic acid (104 g. = 0.723 mole) was placed in the flask and 342 g. (215 ml. = 2.892 mole = 100 % excess) of thionyl chloride was added during 20 minutes. The temperature was raised by means of a Glas-col heating mantle until refluxing started (10 minutes). Refluxing was continued for 3 hours, the temperature rising from 45° to 90°, with little or no acid fumes evolved in the last hour. The yellow solution was then fractionated through an electrically heated 15 cm. column packed with 3 mm. glass helices. The yield was 100 g. (77 % of theory) of material boiling at 108-110°/ 60 mm.

To avoid the isolation of the free cyclobutane-1,1-dicarboxylic acid, an attempt was made to convert the dipotassium salt obtained from the saponification of the corresponding ester directly into the 1,1-diacid dichloride by use of thionyl chloride or phosphorus trichloride. When a benzene slurry of the salt was treated with phosphorus trichloride a vigorous exothermic reaction took place. After removal of the benzene, attempts to distill the remaining material resulted in considerable charring and only 10 % of the desired product. Use of thionyl chloride without additional solvent improves the yield to about 25 %. Isolation of the free 1,1-diacid is, therefore, recommended.

Diamide: The above two-degree-range material (0.2 g.) was added slowly to 1 ml. of ice-cold concentrated ammonium hydroxide. The resulting solid was washed three times with 1 ml. of ice-water and recrystallized from hot water giving well defined prisms, m.p. 278-278.5° (dec.).

Anal. Calcd. for $C_6H_{10}O_2N_2$: C, 50.70; H, 7.04. Found: C, 50.65; H, 7.06.

3-Chlorocyclobutane-1,1-dicarboxylic Acid Dichloride

A 200 ml., 3-necked, round-bottomed flask was equipped with a reflux condenser, drying tube, thermometer and dropping funnel as described above for the cyclobutane-1,1-diacid dichloride. Into this flask were placed 100.7 g. (0.556 mole) of the 1,1-diacid dichloride and 2.33 g. of benzoyl peroxide and then 47.2 ml. (78.8 g. = 0.584 mole = 5 % excess) of sulfuryl chloride was slowly added as the solution was brought to refluxing temperature with the aid of a Glas-col mantle. Refluxing was continued until the temperature rose to 110° and few fumes were observed. (This required from 1-1/2 to 2 hours.) The yellow or red-orange solution was fractionated as above with a 4:1 reflux-ratio yielding 62.8 g. (52 %) of b.p. 96-98°/ 14 mm. The yield was raised to 60 % by refractionating neighboring fractions. The starting material was recovered in 25 % yield from lower boiling fractions.

Anal. Calc. for $C_6H_5O_2Cl_3$: C, 33.41; H, 2.32. Found: C, 33.26; H, 2.39.

Diamide: The 3-chlorodiacid dichloride (0.2 g.) was converted to the diamide as outlined for the unchlorinated material above. Recrystallization from hot water gave crystals, m.p. 212.5-213.8°

3-Chlorocyclobutane-1,1-dicarboxylic Acid

From the 3-chloro-1,1-diacid dichloride: The 3-chloro-1,1-diacid dichloride (1.07 g. = 0.005 mole) was placed in a 15 ml. centrifuge tube and 1 ml. of water was added. With vigorous stirring the mixture was heated on a steam bath. After a brief induction period the reaction proceeded without external heating. Ether extraction of the one phase aqueous solution and resultant evaporation yielded 0.89 g. (100 %) of m.p. 135-142° (dec.). By repeated recrystallization from ethylene dichloride the decomposition point may be raised to 158-159.5°. Incomplete melting occurred concurrently with decomposition within this range.

From the 3-hydroxy-1,1-diacid (Modified+ Jones Method): A 300 ml., 3-necked, round-bottomed flask was equipped with a reflux partial-take-off condenser and a dropping funnel. To a mixture of 29.6 g. (0.372 mole) of dry pyridine and 100 ml. of absolute ether contained in the flask was added 20 g. (0.124 mole) of 3-hydroxycyclobutane-1,1-dicarboxylic acid (31). The solution was brought to reflux and 88 g. (55 ml. = 0.740 mole = 100 % excess) of thionyl chloride was

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+In his actual procedure, Jones treated the reaction product with a mixture of ice, water, and ether and quickly extracted three times with ether. The ethereal solution was shaken with saturated sodium chloride solution, filtered through sodium sulfate and allowed to evaporate at room temperature. After the bulk of the ether had evaporated, 50 ml. of water was added and allowed to react at room temperature for 24 hours. The mixture was then warmed on a steam bath and the solution was decanted from the oil, treated with Norit, filtered, and allowed to concentrate at room temperature. This latter step, in this laboratory, required eight days, and the yield of the acid was improved 16 % to give the 56 % reported by Jones. From the standpoint of ease of operation and time consumption, the procedure given in the text above is probably desirable.

dropped in over a three hour period. During the first hour the solution was under total reflux and 50 % of the thionyl chloride was added. The ether was taken off in the second hour and the solution was again under total reflux during the third hour at which time the addition of thionyl chloride was completed. The cooled solution was slowly poured onto 50 g. of ice and then the mixture was heated on a steam bath for an hour with occasional stirring. The original dark oil reacted to give an opaque solution which, after cooling, was extracted with 10-100 ml. portions of ether. The ether was stripped off until the volume was about 100 ml. at which time 100 ml. of ethylene dichloride was added and the solution distilled until the volume was about 40 ml. Upon cooling 8.9 g. (40.5 % of the theory) of solid, m.p. 140° (dec.), was obtained. (Jones reports m.p. 130-160° dec.)

3-Chlorocyclobutanecarboxylic Acid

Decarboxylation A: The 3-chlorocyclobutane-1,1-dicarboxylic acid (3.24 g. = 0.0182 mole), obtained from the corresponding diacid dichloride by hydrolysis (cf. p. 37), was placed in a 10 ml. Claisen flask and heated at 180° for 20 minutes at the end of which time no further evolution of carbon dioxide was observed (the liberated gases were bubbled through a saturated barium hydroxide solution). The crude oil was distilled at 4 mm., collecting the portion boiling at 107-115°. After repeated recrystallization from petroleum ether at dry ice-acetone bath temperature, a solid was isolated, m.p. 49-51.8° (Jones reports m.p. 42.5-45.5°)

Decarboxylation B: This experiment differs from the one above only in that the 3-chlorocyclobutane-1,1-dicarboxylic acid used was obtained by the modified Jones procedure (cf. p. 37) and in that copper powder (0.1 g.) was added as a catalyst. The product, which was collected over the boiling range 110-115°/ 4 mm., weighed 2.82 g. (75 %). The solid, after eight recrystallizations at ca. -60° from petroleum ether, had a melting point of 50.5-52.5°. It showed no melting point depression when mixed with the above 3a-chloroacid (decarboxylation A.)

Amide: Procedure I: The 3a-chloroacid (0.28 g.), obtained by decarboxylation A above, was placed in a 15 ml. centrifuge tube and treated with 0.31 g. of cold thionyl chloride in the presence of a drop of dry pyridine and the solution was allowed to warm to room temperature. After 1/2 hour it was refluxed for 10 minutes and distilled. The crude acid chloride was then dropped slowly into ice-cold concentrated ammonium hydroxide. The precipitate was extracted with a total of 15 ml. of chloroform in three portions and the chloroform solution was evaporated on a steam bath to dryness. The residue was crystallized from dry benzene giving a m.p. 162.8-164°. (Jones reports 166.2-167.4°.)

The 3a-chloroacid obtained by decarboxylation B above was also converted to its amide by the above procedure yielding crystals, m.p. 169.2-170°; this m.p. was not depressed when the amide was mixed with the amide of the above paragraph.

Procedure II: The amide of decarboxylation A 3a-chloroacid was also obtained by refluxing 0.03 g. of phosphorus trichloride with 0.1 g. of the acid for one hour and adding the reaction product slowly to 2 ml. of ice-cold ammonium hydroxide. The resulting mixture was extracted with chloroform, the extracts were evaporated, and the residue was recrystallized from benzene yielding crystals, m.p. 170-171.8°.

Procedure III: A third synthesis of the amide was effected via the methyl ester. 3a-Chloroacid (0.5 g.) (decarboxylation A) was dissolved in 10 ml. of absolute methanol and 2 drops of concentrated sulfuric acid were added; the mixture was refluxed for 5-1/2 hours and the methanol was evaporated. The residue was taken up in ether and the solution was washed with sodium bicarbonate solution, dried with magnesium sulfate and distilled. The distillate was treated with 2 ml. of concentrated ammonium hydroxide and the mixture was boiled to give a homogeneous solution. The reaction product was extracted with ether, the extracts were evaporated and the residue was crystallized from benzene; m.p. 166-174°.

p-Bromophenacyl ester: Using 0.1 g. of the 3a-chloroacid from decarboxylation A, the procedure recommended by Shriner and Fuson (29) yielded fine needles from water-ethanol, m.p. 110-111.2°. The mixed melting point with pure p-bromophenacyl bromide (m.p. 109.8-110.5°) was 86-94°.

Anal. Calcd. for $C_{13}H_{12}O_3BrCl$: C, 47.08; H, 3.65. Found: C, 46.16; H, 3.84.

Using 0.1 g. of the 3a-chloroacid from decarboxylation B, the above procedure was repeated yielding needles, m.p. 111-112°, which showed no depression with the above ester from the 3a-chloroacid of decarboxylation A.

Chromatographic Separation of 3a- and 3b-Chlorocyclobutanecarboxylic Acids

3a- and 3b-Chloroacid mixture: The 3-chlorocyclobutane-1,1-dicarboxylic acid dichloride was converted to the diacid as noted above. However, the diacid was not isolated but the crude mush from the ether evaporation was directly heated to 180° for 20 minutes and the product was distilled at reduced pressure. The yields averaged 66.2 % of 5-6° boiling-range material.

Preparation of the column: A 1.8 x 52 cm. column was prepared from 17 g. of silicic acid, 3 g. of celite, 1 ml. of bromocresol green solution, 1.7 ml. of water, 8 ml. of absolute methanol and 1.5 drops of 1 N ammonium hydroxide according to the scheme as outlined under separation of the 2a- and 2b-chloroacids.

The separation: A 0.1025 g. sample (0.00076 mole) of the mixture was taken up in 2 ml. of n-hexane and the solution was added slowly along the sides of the tube about 1-2 mm. above the silicic acid. After it was adsorbed onto the silicic acid, the sides were washed with an additional 1 ml. of n-hexane. The washing was adsorbed onto the silicic acid and the tube was carefully filled with n-hexane so that the surface of the silicic acid was not disturbed. The column was then developed as described for the separation of the 2a- and the 2b-chloroacids. Figure 6 is a plot of the titration values of the first 40 fractions taken after 90 ml. of n-hexane had passed through the column. The procedure for titration was that of Marvel and Rands (28) using 0.0197 N sodium hydroxide.

A 0.1053 g. sample (0.00078 mole) of a mixture derived from a different sample of 3-chlorocyclobutane-1,1-dicarboxylic acid dichloride was separated under the same conditions and the results of both experiments are summarized in table II.

Identification of the bands: A 5.8 x 56 cm. column was packed in the usual manner with 166.6 g. of silicic acid, 33.4 g. of celite, 10 ml. of indicator, 17 ml. of water, 80 ml. of absolute methanol, and 15 drops of 1 N ammonium hydroxide. The 3-chloroacid mixture (0.9917 g.) dissolved in

Chromatographic Separation of a Mixture of 3-Chlorocyclobutanecarboxylic Acids

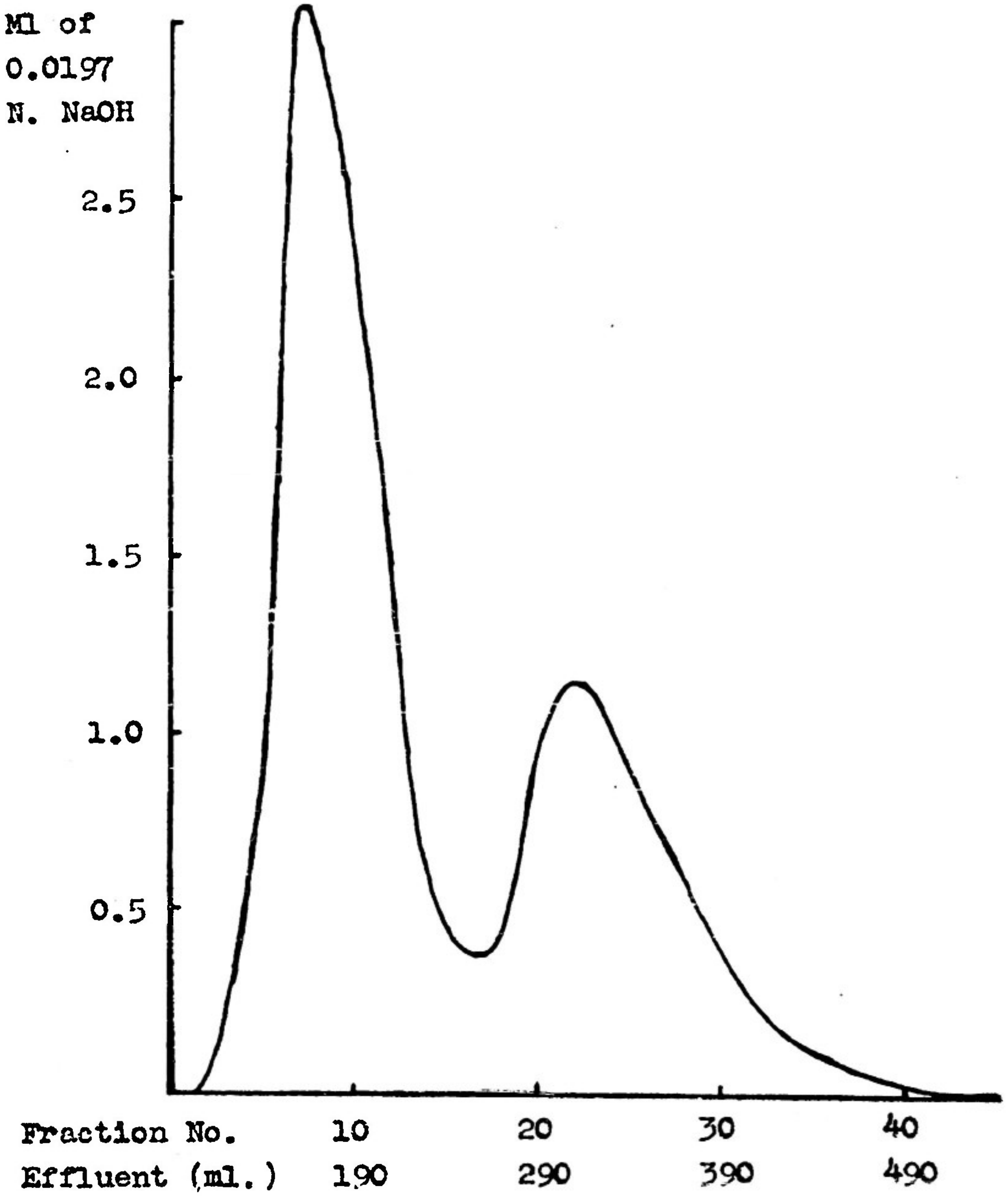


Figure 6.

TABLE II.

Sample	Fractions	Ml. of 0.0197 N NaOH	Percent of total acid	Substance
0.1025	0-15	19.72	55	3a-chloro
	16-36	10.61	30	3b-chloro
0.1053	0-25	14.40	47	3a-chloro
	26-49	9.56	31	3b-chloro
Average:			51	3a-chloro
Total acid content of			30	3b-chloro
mixture accounted for:			81 %	

30 ml. of n-hexane was added and washed onto the column in the usual manner. Development of the column with n-hexane gave two well defined bands[+]. After 1250 ml. of eluate had passed through the column, 50 ml. fractions were collected. Fractions 8 and 11 from the first band were combined, taken up in petroleum ether and recrystallized at ca. -60° yielding a solid, m.p. 51-52.2, the 3a-chloro-acid.

Anal. Calcd. for $C_5H_7O_2Cl$: C, 44.65; H, 5.25. Found: C, 44.69; H, 5.32.

3b-Chlorocyclobutanecarboxylic acid: Fractions 38 and 39 from the second band of the above column were similarly purified at -60° from petroleum ether yielding a solid, m.p. 43.8-45.5°, the 3b-chlorocyclobutanecarboxylic acid. A portion of

---

[+] In one experiment a third band separated from a certain decarboxylation mixture. The acid component of this band was identified as the 2a-chloro-cyclobutanecarboxylic acid by its mixed melting point with authentic material. However, similar separations did not confirm its presence in the same decarboxylation mixture.

this acid when mixed with a sample of the 3a-chloroacid resulted in immediate melting at room temperature.

Anal. Calcd. for $C_5H_7O_2Cl$: C, 44.65; H, 5.25. Found: C, 44.41; H, 5.57.

Amide: This derivative was prepared by the three procedures (cf. p. 39) as outlined under the 3a-chloroacid. Table III summarizes the data concerning the amide of the 3-chloroacids. It would appear that only one amide was formed and that one isomer was possibly converted into the other by an operation in each of the three methods.

TABLE III.

	Method:		
Acid:	1. $SOCl_2$ 2. NH_4OH	1. PCl_5 2. NH_4OH	1. CH_3OH, $H^{\oplus}$ 2. NH_4OH
3a-chloro:	a) 162.8-164	b) 170-171.8	c) 166-174
3b-chloro:	d) 168.5-169.5	e) 171.5-172.8	f) 173-174

Mixed m.p.'s: a/d = 168.9-169.5° b/e = 169-171°

p-Bromophenacyl ester: This derivative, prepared in the usual manner (29) and recrystallized from water-ethanol, gave a solid, m.p. 63.5-64.0°

Anal. Calcd. for $C_{13}H_{12}O_3BrCl$: C, 47.08; H, 3.65. Found: C, 46.65; H, 3.82.

Infrared Absorption of the 3-Chloroacids

The spectra were taken in carbon tetrachloride solution (0.050 g./ml.) using 0.05 mm. sodium chloride cells with the Perkin-Elmer double beam spectrophotometer. The acid samples used were those for which the microanalysis have been reported above. Infrared data concerning these acids have been collected in tables V. and VI. (p. 47) and in figure 7, page 48.

Attempted Isomerization of the 3-Chloroacids

Samples of 0.1 g. each of the pure 3-chloroacids were sealed in separate 6 x 100 mm. tubes containing 0.5 ml. of concentrated hydrochloric acid and heated at 120-130° for 45 minutes. The blackened contents of the tubes were extracted with ether, the ether solutions evaporated, and the residues were boiled with benzene to remove water. The benzene solutions were evaporated and the residues taken up in hexane and chromatographed on 20 g. columns as described in the similar experiment with the 2-chloroacids. Pure samples of the 3-chloroacids were also chromatographed as controls. No evidence was obtained to indicate that appreciable isomerization had taken place.

SUMMARY TO PART I.

It has been the purpose of the present part of the study to prepare 5 isomeric monochlorocyclobutanecarboxylic acids. Five acids have been prepared and a summary of certain data concerning these compounds is given below in table IV.

TABLE IV.

The Monochlorocyclobutanecarboxylic Acids

Acid	M.p.; or b.p./mm.	M.p. of the p-bromophenacyl ester	n_D^{25}
1-Cl	111-112°/ 12	114-115[+]	1.4545
2a-Cl	97-98.5°	88-89.5°	-
2b-Cl	120-122.5°/ 14	73.6-74.1°	1.4732
3a-Cl	51-52.2°	110-111.2	-
3b-Cl	43.8-45.5°	63.5-64°	-

Acid	Microanalyses		Tests:		
	Carbon	Hydrogen	Beilstein	2 % $KMnO_4$	Br_2 in CCl_4
1-Cl	44.58	5.23	(+)	(-)	(-)
2a-Cl	44.47	5.16	(+)	(-)	(-)
2b-Cl	43.35[‡]	5.30	(+)	(-)	(-)
3a-Cl	44.69	5.32	(+)	(-)	(-)
3b-Cl	44.41	5.57	(+)	(-)	(-)
Expect:	44.64	5.24	(+)	(-)	(-)

[+] Melting point of amide; no p-bromophenacyl ester was obtained using the standard procedure (29).

[‡] For a discussion of this value see page 26.

This table shows that the prepared materials are isomers, are not unsaturated, and are each different chemical individuals. Examination of the 7.7-8.4 micron region of the infrared spectra will attest further to the latter conclusion (cf. figure 7 and table V.). While presence of the cyclobutane ring was not definitely proved, its presence is implied from the fact that the infrared absorptions of these isomers and that of the known cyclobutanecarboxylic acid contain four major bands in common (cf. figure 7 and table VI.).

TABLE V.

Distinguishing Region (7.7-8.4 microns) in the Infrared Spectra of the Cyclobutanecarboxylic Acids.

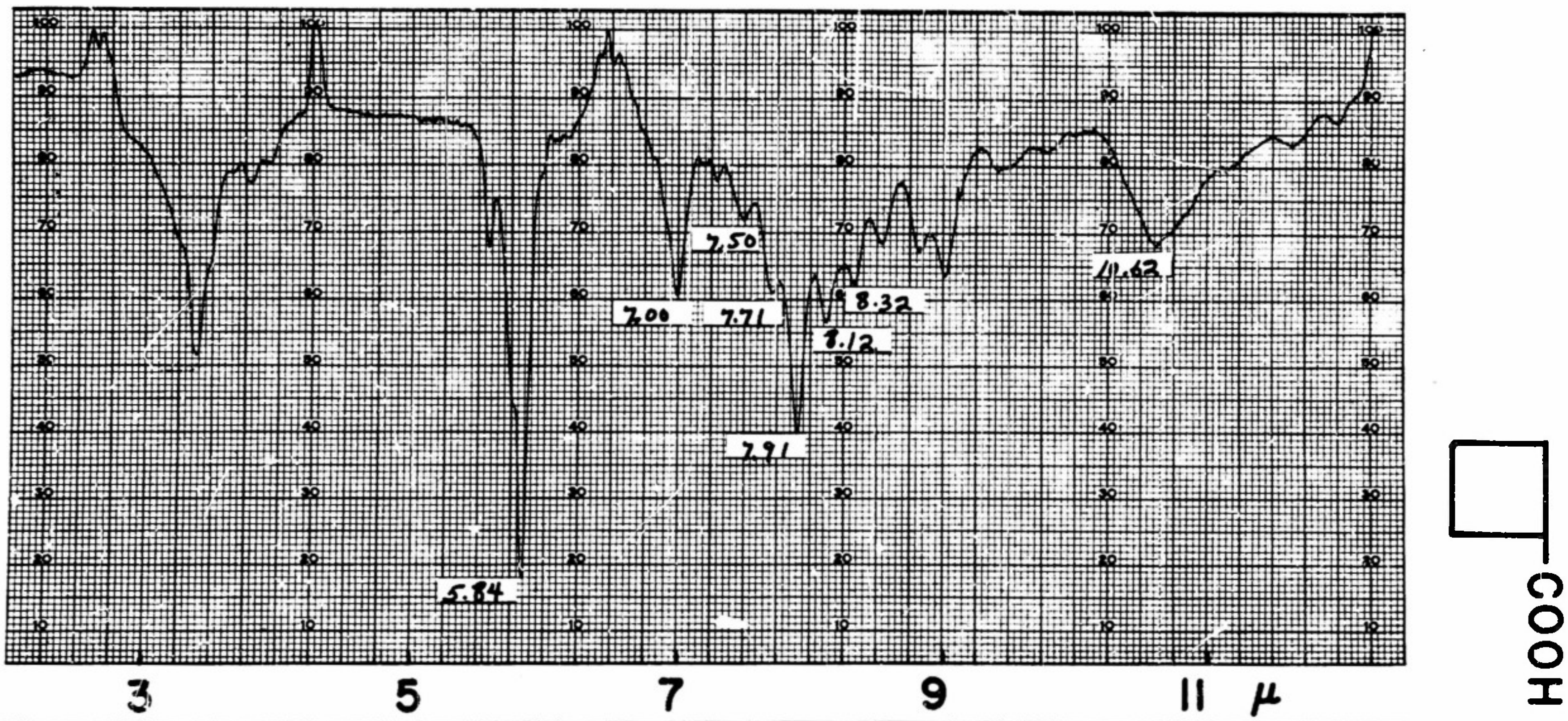
no Cl	7.71	-	7.91	8.12	8.32
1-Cl	7.71	-	7.98	8.25	-
2a-Cl	7.73	7.85	8.02	8.15	-
2b-Cl	-	7.82	7.93	8.18	8.39
3a-Cl	-	7.80	8.00	8.12	-
3b-Cl	-	7.77	7.96	8.12	-

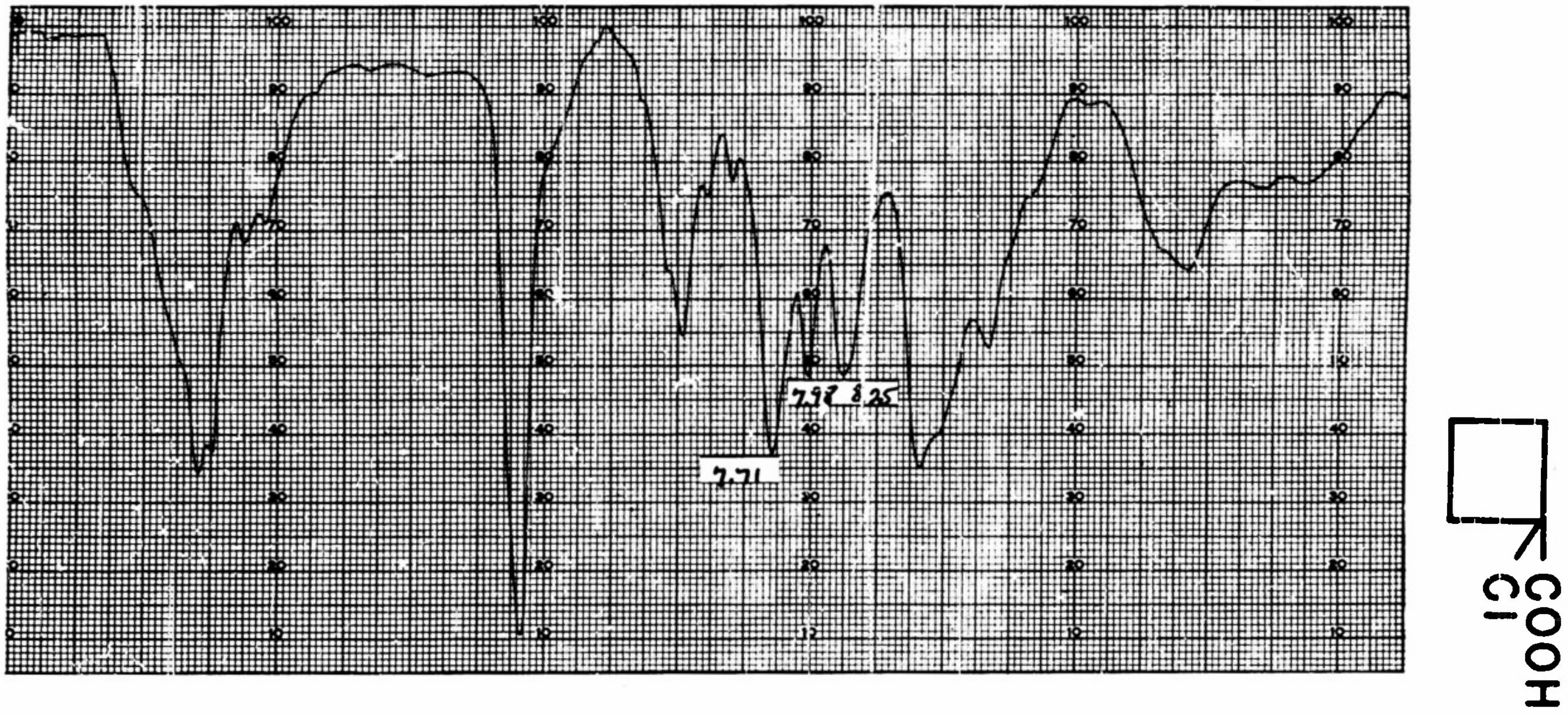
TABLE VI.

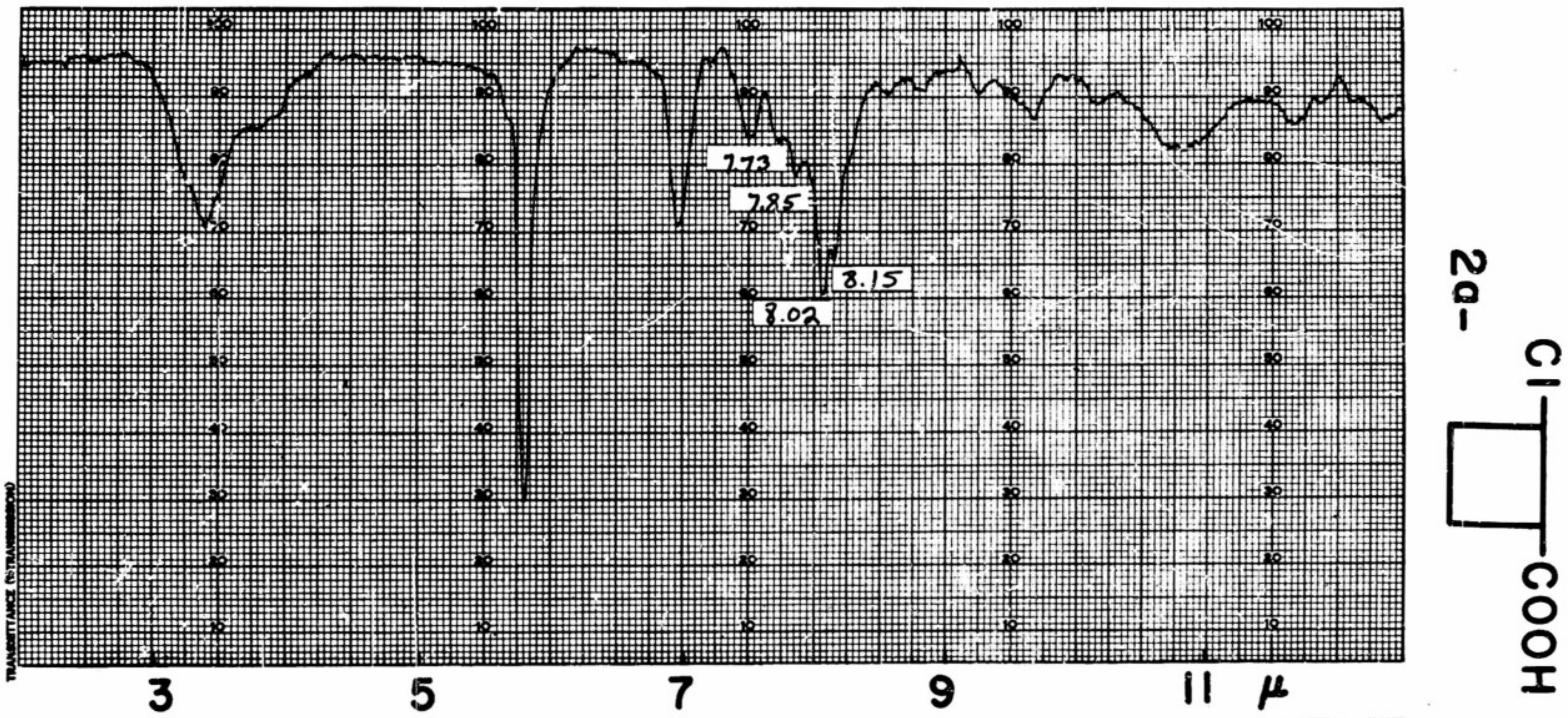
Major Bands in Common in the Infrared Spectra of the Haloacids and that of Cyclobutanecarboxylic Acid (in microns).

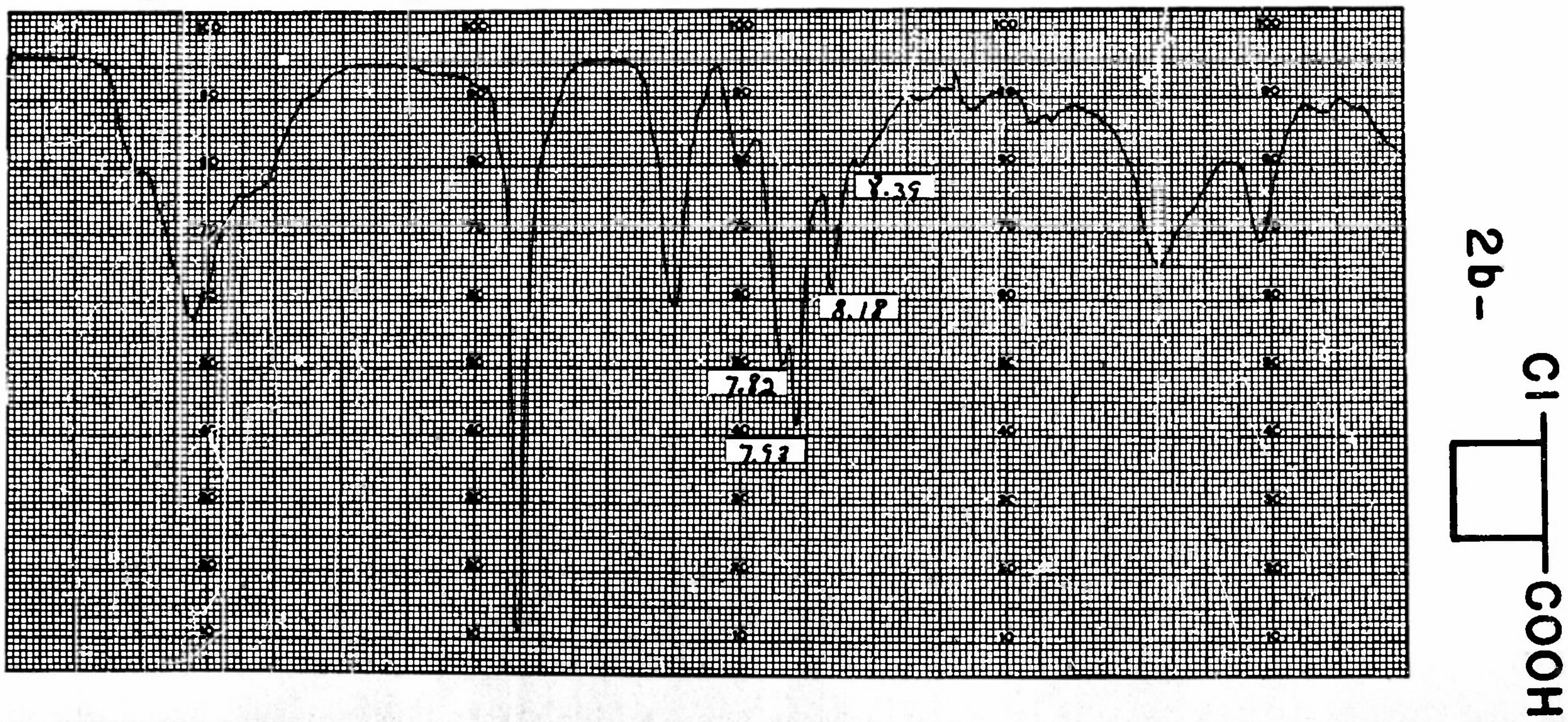
no Cl	1-Cl	2a-Cl	2b-Cl	3a-Cl	3b-Cl
3.38	3.41	3.40	3.39	3.40	3.38
5.84	5.83	5.81	5.84	5.83	5.83
7.00	7.04	6.92	7.00	7.00	6.98
10.62	10.85	10.80	10.65	10.65	10.65

As the result of these data it may be concluded that the five desired isomers have been prepared and characterized.


5.84
7.00
7.50
7.71
7.91
8.12
8.32
10.62
3
5
7
9
11 μ
COOH


7.71
7.98
8.25
Cl
COOH


7.73
7.85
8.02
8.15
3
5
7
9
11 μ
2a-
Cl
COOH


8.39
8.18
7.82
7.98
2b-
Cl
COOH

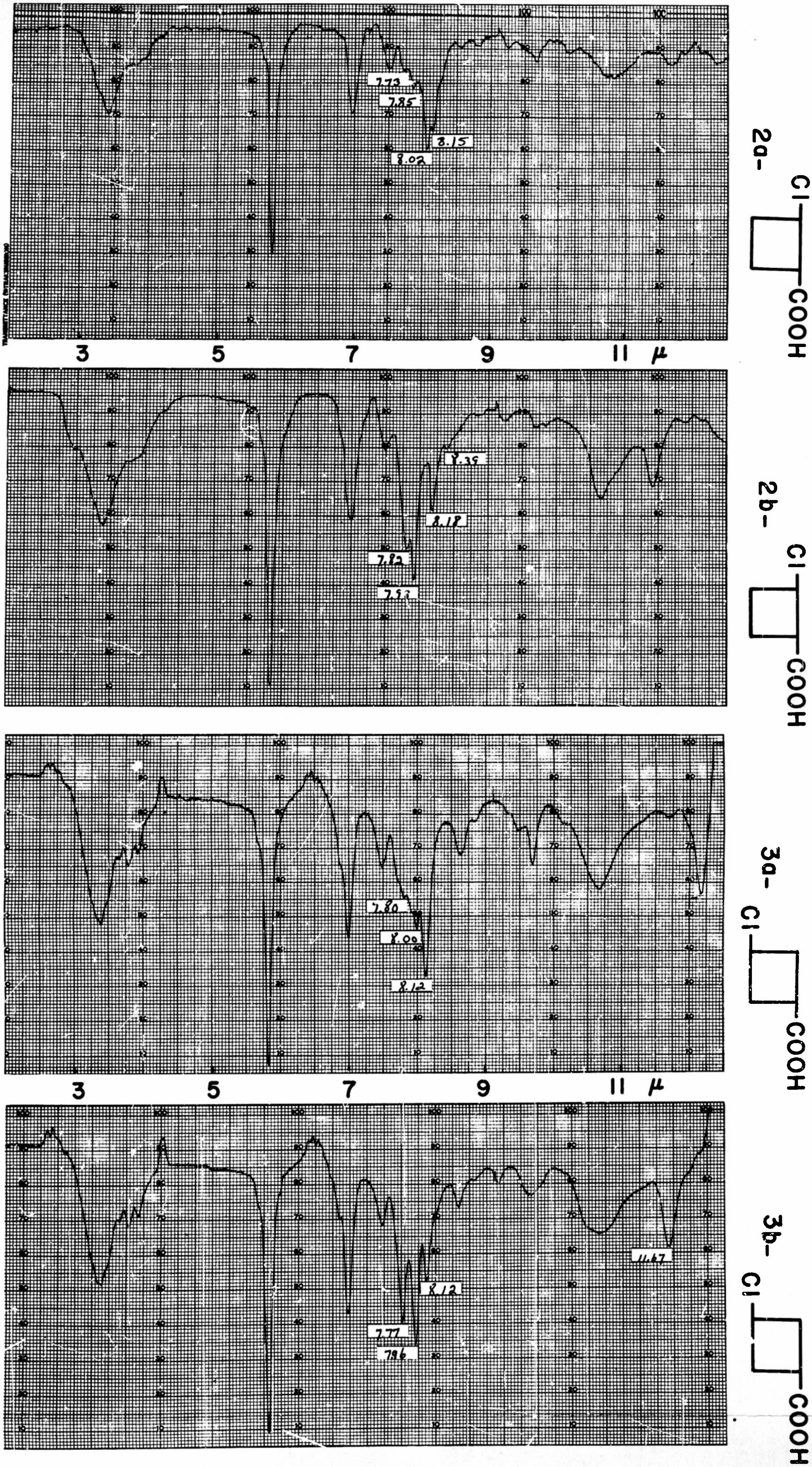

7.73
7.85
8.15
8.02
2a- Cl COOH
3
5
7
9
11 μ
8.39
8.18
7.82
7.93
2b- Cl COOH
7.80
8.00
8.12
3a- Cl COOH
3
5
7
9
11 μ
11.67
8.12
7.77
7.86
3b- Cl COOH

FIGURE 7

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PART II. INVESTIGATION OF THE FREE RADICAL CHLORINATION OF CYCLOBUTANECARBOXYLIC ACID

Part I has dealt with the indirect preparation of 5 isomeric monochlorocyclobutanecarboxylic acids by methods indicative of structure. The advantages of a direct method, i.e. chlorination, are obvious. It is the purpose of this part to investigate the possibilities of this latter method.

Ash and Brown (1) have studied aliphatic chlorination in some detail in the straight chain series. In liquid-phase free radical chlorinations two factors are important: the inductive effect of a substituent and the stability of the organic free radical intermediate.

The carboxyl group as a substituent has a -I effect. This electron attracting group will hinder the removal of a vicinal hydrogen atom, since such a removal necessarily involves the loss of an electron. Moreover, this hindrance would tend to be greatest in the immediate vicinity of the group. One would then predict that free radical chlorination, which is thought to proceed by the initial withdrawal of a hydrogen atom (2), would take place most readily in positions furthest removed from the carboxyl group or its derivatives. That this is the case, was shown by the above authors (cf. p. 31). In the free radical chlorination of 1,1-cyclobutanedicarboxylic acid dichloride, the details of which were discussed in Part I, their theory was upheld (for the first time in a cyclic system) in that chlorination proceeded almost entirely in the 3-position. The results obtained in Part I also can be interpreted as a confirmation of the Ash-Brown observation that the effect of identical substituents is additive.

Organic free radicals seem to react in the order primary > secondary > tertiary (1). It also has been advanced that where two or more products may be possible, the one obtained is the one derived from the most stable free radical intermediate (3). With 1,1-cyclobutanedicarboxylic acid all the possible intermediates are secondary radicals and, therefore, one would expect the inductive effect to control the reaction product, which seems to be the case. However, in the case of cyclobutanecarboxylic acid, in addition to 6 possible secondary radicals, there is a possible and presumably more stable tertiary intermediate involving the 1-position. The results predicted by consideration of the inductive effect are here in opposition to those predicted on the assumption that the most stable free radical intermediate determines the product. An experimental study is thus necessary to determine which effect is more important in the free radical chlorination of this compound.

To investigate the free radical chlorination of cyclobutanecarboxylic acid, one needs a method for the analysis of the chlorinated mixture that would theoretically result. If conditions can be controlled so that only monochlorinated products are obtained, the analytical method need apply only to the separation and identification of the 5 possible position isomers of monochlorocyclobutanecarboxylic acid. The techniques described in Part I should be pertinent to this problem.

Accordingly, the chromatographic method previously developed was studied further as an analytical tool in the isomer separation. A 60 g. (silicic acid + celite) column proved the most convient from the standpoint of accuracy and time consumption. A mixture of 2a-, 2b-, 3a- and 3b-chlorocyclobutanecarboxylic acids was easily separated (ca. 75 % recovery) by such a column. By isolating the bands, the sequence of effluent materials was shown to be 3a-chloro-, 2b-chloro-, 3b-chloro- and 2a-chloroacid. The effluent peaks were also noted. The 1-chloroacid and unchlorinated acid were seperately run and their peaks observed. A value, which may be called the effective R_f, was obtained by averaging R_f values, obtained in the usual manner[+], in the 100-600 ml. effluent range. This approximation was necessary because the silicic acid was packed rather loosely and tended to settle in the 2-1/2 weeks necessary to develop the column. Tighter packing resulted in more constant R_f values but necessitated longer periods of development. The effective R_f values for a given band on columns apparently operating under the same conditions were not always identical. However, on the same column, a shift (from an arbitrary standard) in the R_f value for any band was accompanied by a corresponding shift for the other bands. Consequently, it was possible by applying an appropriate correction to make all columns comparable. The total effluent sequence and column constants for these acids are summarized in table VII.

TABLE VII.

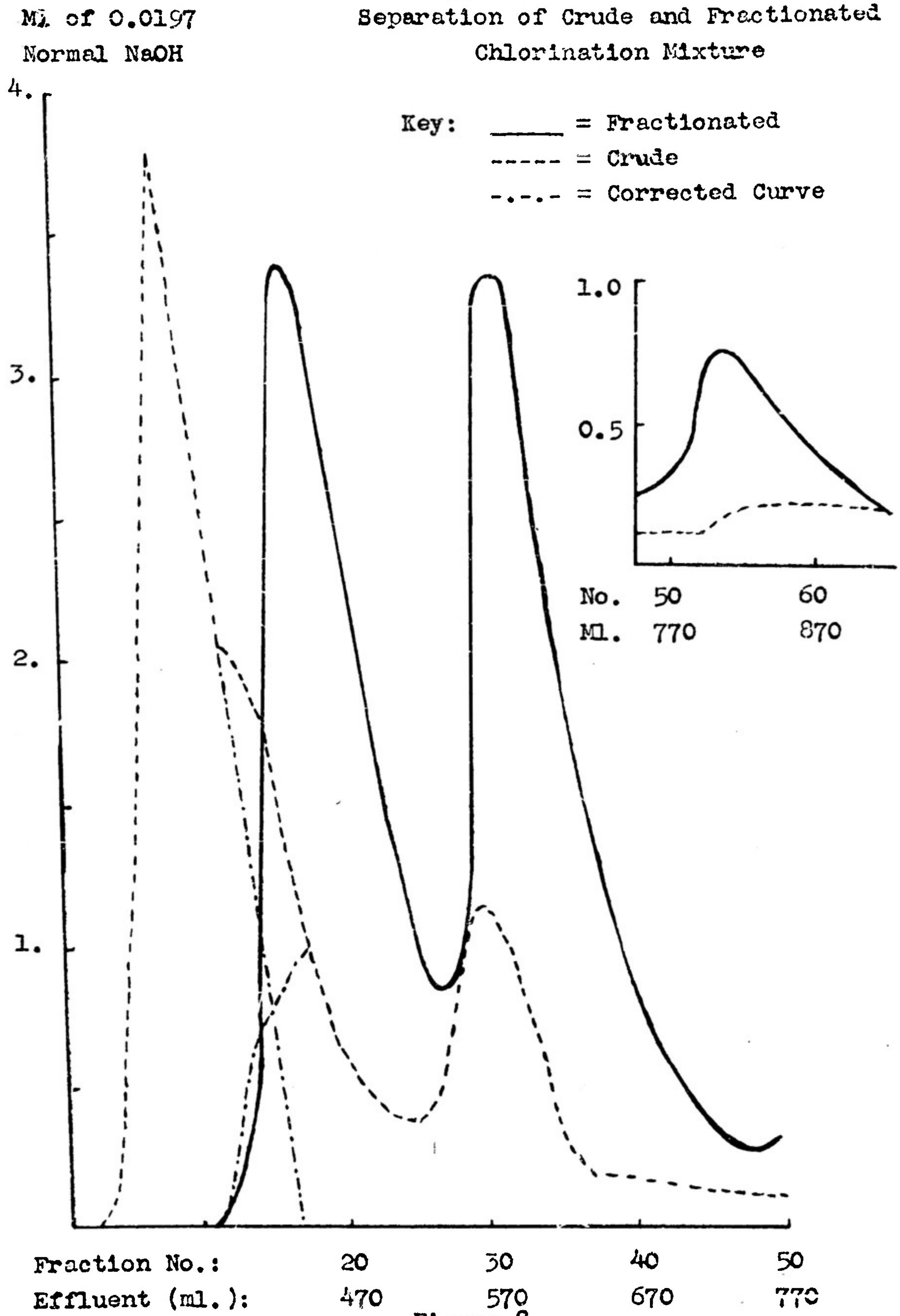
Standard Values for the Effluent Peaks and Effective R_f's for the Cyclobutanecarboxylic Acids (60 g. column).
(Average errors: peaks = ± 30 ml.; R_f = ± 0.007)

Sequence:	no Cl	3a-Cl	1-Cl	2b-Cl	3b-Cl	2a-Cl
Peaks (ml.):	320	380	420	540	720	1060
R_f $\left\{\frac{cm.}{ml.}\right\}$:	0.18_8	0.14_8	0.13_4	0.10_5	0.07_6	0.05_5

[+] R_f is a measure of the rate of flow (cf. p.62).

It will be noted that the range for the 1-chloroacid (390-450 ml.) and that for the 3a-chloroacid (350-410 ml.) overlap and trouble in separation on a 60 g. column might be anticipated. It was found that, when two bands were present together, a titration curve resulted not unlike that of the first band of figure 8. A semiquantitative approximation of the amounts of the two acids was made in such cases by extending the downward slope of the peak and in such a manner resolving the curve into two peaks. The value of this method, as applied to figure 9, will be discussed later (cf. p. 61). When an attempt was made to separate a mixture of 1-chloro-, 2-chloro-, and 3-chlorocyclobutanecarboxylic acids, it was found that complete separation was effected only by using a 120 g. column. Such a column required over a month to develop. Therefore, two 60 g. columns were placed one above the other and, after the first two bands (3a-chloroacid and 1-chloroacid) had transferred themselves onto the second column, each column was separately developed. Values obtained by this method were 5-10 % low and, as a practical analytical tool, it was abandoned.

The actual chlorination of cyclobutanecarboxylic acid was carried out without a solvent and with a 5 % excess of sulfuryl chloride in the presence of benzoyl peroxide, the temperature rising to 115° in a 45-minute reaction interval. Fractionation of the reaction mixture indicated that 49 % of the product was monochlorinated material and that 29 % of the cyclobutanecarboxylic acid was unreacted. Samples of the crude reaction mixture and of the fractionated monochlorinated material were chromatographed on 60 g. columns. Under these conditions equal amounts of the 3a-chloroacid and of the unchlorinated acid may be separated. However, the relatively large



Separation of Crude and Fractionated Chlorination Mixture

Figure 8.

amounts of the unchlorinated acid present in the crude reaction mixture led to the situation shown in figure 8: the curve of the unchlorinated acid overlapping the next (3a-chloroacid) band. Observation of this chromatogram of the crude mixture indicated 5 bands, whose positions up the column agreed with unchlorinated, 3a-chloro-, 2b-chloro-, 3b-chloro- and 2a-chloro-acids, respectively. The analysis of the fractionated monochlorination product indicated that, within experimental error (ca. ± 5 %), 38 % of the total acid content was 2b-chloroacid, 34 % was 3a-chloroacid, 10 % was 3b-chloroacid and 1-chloroacid and 2a-chloroacid were absent. The three acids present in major amounts were isolated and identified. Although a band corresponding to the 2a-chloroacid was seen on the column, this acid could be neither isolated nor titrated and, therefore, must be present in less than ca. 5 %. The 1-chloroacid could also be present to the same extent and not cause a deflection in the titration curve observed for this fractionated mixture (fig. 8). Titration of the acid components of the mixture which do not move down the column indicated they composed 6.5 % of the total acid content of the fractionated mixture. Thus, 88.5 % of the acids present in the monochlorinated fraction were accounted for.

The question may arise as to whether the analyzed fractionation mixture was representative of the original crude mixture. The relative amounts of the chlorinated isomers remains constant if no isomerization, decomposition, or other loss of the acids has taken place during the distillation. Direct evidence on the extent of change during distillation is lacking, but it is believed not to be a source of error greater than that inherent in the analytical method. The failure to observe the 1-chloroacid in the fractionated material is not due to a loss during distillation, since it was shown (in connection with attempts to prepare the 1-chloroacid from its acid chloride) that mixtures of the unchlorinated and 1-chloroacids could effectively be separated by fractionation. A loss of the other acids is excluded since these boil in a still higher range than the 1-chloro isomer.

In view of the ratio of chlorination in the 1-, 2-, and 3-positions of 0:38:44, the chlorination of cyclobutanecarboxylic acid may be said to follow the pattern set in the straight chain series. The results obtained indicate that it is the inductive effect of the carboxyl group which determines the products of the reaction.

EXPERIMENTAL

Separation of a Synthetic Mixture of 2-Chloro- and 3-Chlorocyclobutanecarboxylic Acids

The chromatographic tube was constructed by sealing a standard tapered 45 mm./50-mm. outside joint to the upper end of a 50 x 1.8-cm. glass tube in such a manner that a reservoir of ca. 70 ml. (8 x 3.5 cm.) was left above the narrower tube and below the ground glass portion of the joint. At the lower end of the tube was sealed a stopcock (4 mm. bore) with a 12-cm. blunt-ended take-off stem[+]. Below the stopcock (2 cm.) was sealed a standard tapered 45 mm./ 50-mm. inside joint. Such construction allowed tubes to be used individually or in series (cf. p. 55).

Using the above tube, a 60-g. column was prepared in the usual manner (cf. p. 22) employing 51 g. of silicic acid, 9 g. of celite 545, 24 ml. of absolute methanol, 3 ml. of bromocresol green solution, 5.1 ml. of water and 4.5 drops of fresh 1 N ammonium hydroxide. After the column had settled, 0.0836 g. of crude 2-chloroacid mixture (cf. p. 21, procedure B) and 0.0872 g. of crude 3-chloroacid mixture (cf. p. 40), suspended in 2 ml. of n-hexane, were added. The column was developed in the usual manner until 350 ml. of n-hexane had been collected.

[+] The stem was so designed as to enable convenient stoppering in periods between actual operation of the column. Continuous collection of a complete chromatogram required 6 days. In order to collect 10 ml. fractions for subsequent titration, 2-1/2 weeks were required because the column was operated intermittently (stoppered overnight).

Fractions (10 ml.) were then collected and titrated with 0.017 N sodium hydroxide by the method of Marvel and Rands (4) until 1300 ml. of the effluent had been analyzed. The titration curve is shown in figure 9.

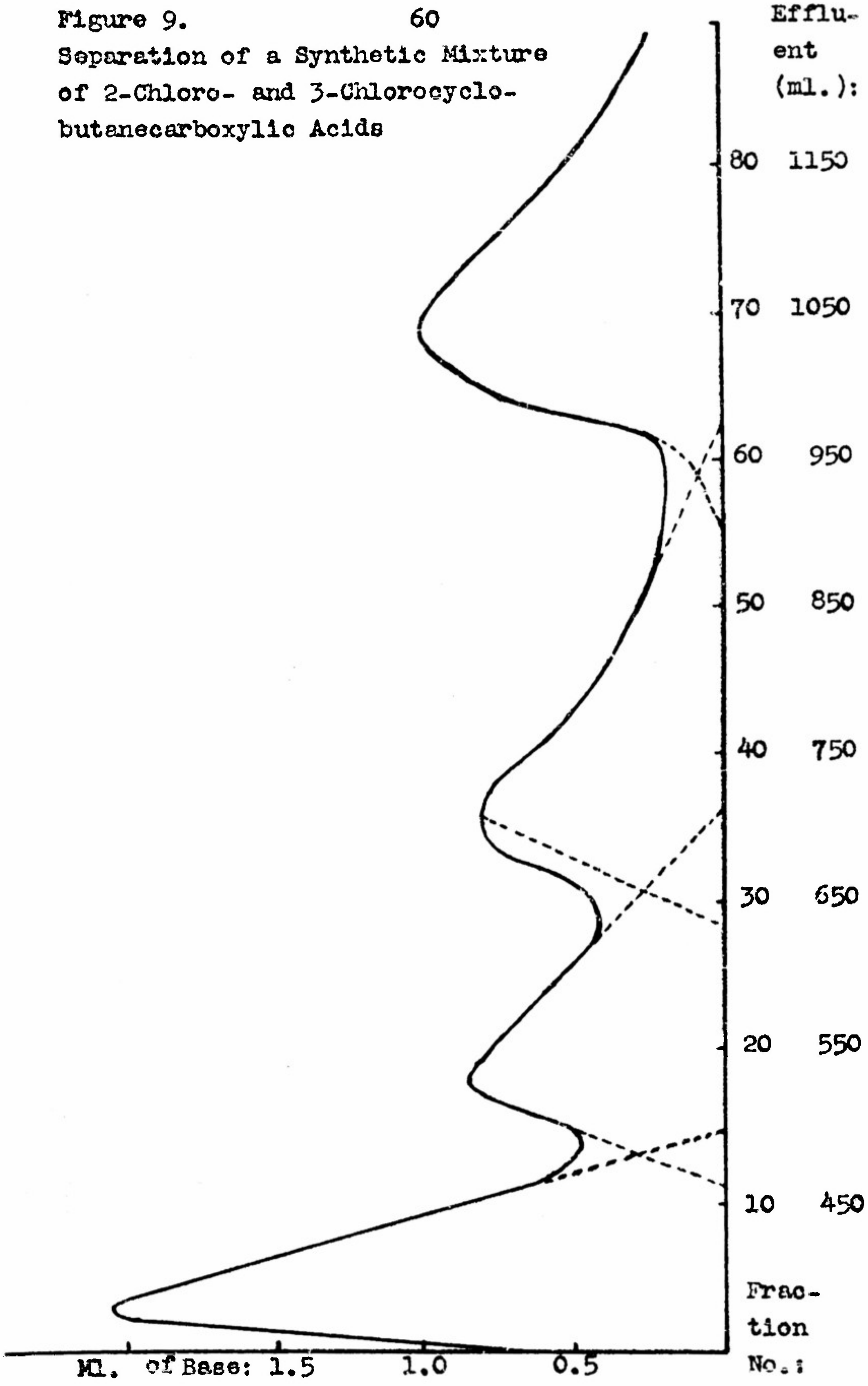
Identification of the bands: The above experiment was repeated using a 40-g. column and 0.0361 g. of 2-chloroacids and 0.0306 g. of 3-chloroacids. When the lower band had reached 19 cm. below the surface of the silicic acid, eluting was stopped. The column was extruded and the bands cut free. Each section was treated with ether, the ethereal solutions were evaporated, the residues were boiled to dryness with benzene and solids obtained were recrystallized from petroleum ether at -60°. The results are summarized below:

Bottom band:	m.p. 46-50°	yellow solid
2nd. band:	- -	yellow oil
3rd. band:	m.p. 37-52°	yellow solid
top band:	m.p. 92-95°	yellow solid

The second and top bands correspond to the 2-chloroacids (2b- liquid; 2a- m.p. 97-98.5°) the chromatographic separation of which has previously been investigated (page 24; the 2b-chloroacid precedes the 2a- isomer). The bottom and third bands must then correspond to the 3-chloroacids (3a- m.p. 51-52.2°; 3b- m.p. 43.8-45.5°), the relative positions of which are known on a column (page 41; the 3a-chloroacid band lies below that for the 3b-acid). The above bands are thus identified and the order is shown to be: 3a-, 2b-, 3b-, and 2a-chloroacid.

The separation method as an analytical tool: The order of the bands having been established, it was possible to check the accuracy of the analysis using the data on which figure 9 is based and comparing the results against those obtained (pages 22ff. and 40ff.)

Figure 9.
Separation of a Synthetic Mixture of 2-Chloro- and 3-Chlorocyclobutanecarboxylic Acids



with simpler columns. The findings, summarized in table VIII, indicate that this column can function effectively as an analytical tool when applied to the four-component system.

TABLE VIII.

Summary of Analytical Data

Acid	Fractions Collected	Ml. of 0.017 N NaOH	Corr. ml.	%[+]	Calcd.[++] %[+]
3a-Cl	0-14	18.06	18.66	25.5	26
2b-Cl	15-30	9.36	9.90	13.5	14.5
3b-Cl	31-62	12.88	11.95	16.5	15.5
2a-Cl	63-102	17.42	16.74	23.5	26.5

[+] Percent of total acid content.

[++] Based on results obtained with two-component columns (2a and 2b; 3a and 3b).

Standard Values for the Effluent Peaks and Effective R_f's for the Cyclobutanecarboxylic Acids

Under the conditions used for separation of 2-chloro- and 3-chloroacids (60 g. column), 0.0606 g. of cyclobutanecarboxylic and (seperately) 0.0638 g. of 1-chlorocyclobutanecarboxylic acid were chromatographed. The effluent values observed[+] for these columns, as well as those which were read from figure 9, have been recorded in table VII. The values of the effective R_f given in table VII were derived as partially shown in table IX (p. 62).

[+] The effluent values were observed from five similar columns and the average error was calculated to be ± 30 ml.

TABLE IX.

Observed R_f values[†] for the Several Cyclobutane Acids.

Acid	Total Milliters of Effluent								
	100	125	175	225	275	300	350	450	Average[‡]
no Cl	-	.195	.190	.165	.158	.157	-	-	0.18_4
1-Cl	.140	.138	.139	.137	.132	.130	.126	-	0.13_4
2a-Cl	.060	.051	.057	.057	.053	.052	.051	.051	0.05_3
2b-Cl	-	.110	.110	.110	.105	.103	.103	.101	0.10_5
3a-Cl	-	.160	.150	.150	.140	.140	-	-	0.14_8
3b-Cl	.095	.082	.083	.080	.076	.077	.076	.075	0.07_6

[†] The R_f (rate of flow) value is numerically equal to the distance traveled (in cm.) by a particular band in a given time divided by the volum (in ml.) of effluent collected during this period.

[‡] The averages represented in this table are the result of numerous columns and do not necessary represent the average of the figures given. Generally, in order to compare columns, a quantity (constant for that column) was added to all values obtained. Before this correction, the average error in the values was calculated to be ± 0.007.

Free Radical Chlorination of Cyclobutanecarboxylic Acid

Cyclobutanecarboxylic acid (20 g. = 0.2 mole) and 0.5 g. of benzoyl peroxide were placed in a 100-ml., 3-necked round-bottomed flask equipped with a dropping funnel, thermometer (bulb in liquid), and a reflux condenser (topped with a calcium chloride tube). Sulfuryl chloride (17 ml. = 28.4 g. = 0.210 mole = 5 % excess) was added slowly during 15 minutes. The solution was brought to reflux in 15 minutes and refluxed for 45 minutes. At the end of this period the solution was pale yellow, the temperature was 115° and little or no evolution of fumes was observed. The crude mixture (25.2 g.) was fractionated by means of an electrically heated 15 cm. column packed with 3 mm. glass helices. The fraction boiling at 98-106°/ 14 mm. (4.04 g.), n_D^{25} = 1.4450, accounted for 20 % of the starting material (unreacted cyclobutanecarboxylic acid). The fractions boiling at 110-124°/ 14 mm. and 117-130°/ 9 mm. were combined (13.36 g., n_D^{25} = 1.4721) and represent a 50 % yield of monochlorocyclobutanecarboxylic acids.

The experiment was repeated with 13 g. of unchlorinated acid according to the directions given above and, of the crude chlorination mixture, a sample (1 g.) was retained for subsequent chromatographic analysis. To insure complete separation of the chlorinated and unchlorinated acids, a 14:1 reflux-take-off ratio was used in the fractionation. Unchlorinated acid (29 %) was recovered boiling at 91.5-100°/ 11 mm., n_D^{25} = 1.4438. At 100°/ 11 mm. there was a sudden rise to 114° and the fraction boiling at 114-130°/ 11 mm. was collected. This fraction, n_D^{25} = 1.4727, weighed 8.18 g. (49.5 % yield, after correcting for sample removed).

Analysis of the chlorinated mixtures: In the usual manner, 0.2085 g. of the material boiling at 114-130°/ 11 mm. (see paragraph above) and 0.1986 g. of the crude mixture from which it was derived were separately chromatographed on 60-g. columns, titrating 10 ml. fractions with 0.0197 N sodium hydroxide. The titration curve for each is shown in figure 8. A band moving as 2a-chloroacid could not be titrated. Data obtained from these columns have been summarized in table X (page 64).

Certain aspects of table X need further comment. Slow moving acid impurities traveled down half the length of the column when the crude mixture was analyzed (1/5 the way down is normal). It is possible that interference was responsible for the marked deviation of the R_f values. The fourth peak of the crude mixture's titration curve was very flat making peak determination unreliable. The effective R_f values and effluent peak values for the components of the fractionated mixture are within experimental error (cf. table VII) except the effluent peak of 3b-chlorocyclobutanecarboxylic acid. However, the rate of movement of this band, its position on the column, and the isolation (see below) of a low melting solid from the band serve to identify this substance. The acid impurity was extruded and cut from the column. The sample was weighed and titrated in the usual manner with 0.0197 N sodium hydroxide, using an equal weight of properly prepared column material as a blank.

TABLE X.

Analysis of the Crude and Fractionated Chlorination Mixtures

Acid	Effective R_f^{+}	Fraction No.	Effluent Peak (ml.)	Ml. of 0.0197 N NaOH	Corr. Ml.	% of total acid content.
CRUDE:						
no Cl	0.17	1-10	320	16.74	22.34	25
3a-Cl	0.13	11-23	420	13.43	7.93	9
2b-Cl	0.11	24-36	540	8.38	8.38	9.5
3b-Cl	0.08	52-72	880(?)	3.69	3.69	4.2
FRACTIONATED:						
3a-Cl	0.14_4	10-26	410	27.13	26.53	34
2b-Cl	0.10_2	27-47	550	28.73	29.13	38
3b-Cl	0.07_5	48-64	790	7.66	7.86	10
Acid impurity:				5.00	-	6.5
						88.5

[+] A positive correction of 0.01 unit was applied to the observed R_f values of the fractionated mixture.

A 0.2191 g. sample of the material, $n_D^{25} = 1.4721$, obtained in the initial chlorination experiment (cf. p. 63) was chromatographed and analyzed in the usual manner. Although the titration curve showed signs of impurity, the results were in general agreement with those obtained for the later experiment. The values found were: 3a-chloroacid = 41 %, and 2b-chloroacid = 32 %. The development of the column was discontinued before the last two bands could be analyzed.

Isolation of column components: The separation shown in figure 8 was repeated with 0.2054 g. of the fractionated mixture and the components of each major band was isolated as on page 59 (except that the bands were eluted rather than cut from the column). The lower band yielded a solid, m.p. 50.1-51.9°, showing no lowering of melting point with authenic 3a-chloroacid. The second band yielded an oil, $n_D^{20} = 1.4728$, (for 2b-chloroacid this constant is 1.4732). A low melting solid was isolated from the third band; however, due to the small amount, recrystallization was not feasible. It was impossible to isolate either a solid or an oil from the faint band moving as 2a-chlorocyclobutanecarboxylic acid. However, it was possible to isolate in poor yield, by recrystallization at 0° from petroleum ether, this acid (2a-chloro) from a synthetic mixture of chloroacids (2a, 3a, 3b) and unchlorinated acid in which it was present to the extent of 8 %.

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