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THE DECARBOXYLATION OF SUBSTITUTED SALICYLIC ACIDS IN QUINOLINE SOLUTION

by

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ABSTRACT

The decarboxylation of salicylic acid in quinoline has been found to be first order with respect to the acid. The influence of substituents on the rate of decarboxylation of salicylic acid has been studied and the Hammett equation applied to the data. In general, electron-donating substituents have been found to favour and electron-withdrawing substituents to hinder decarboxylation in quinoline.

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INTRODUCTION

The study of the effect of changing substituents on the reactivity of a compound has formed the basis for a large part of physical organic chemistry. Hammett, who first defined and organized this field of chemistry, related substituent effects in aromatic compounds to acidities and reaction rates. This relationship is known as the Hammett equation. Hammett's substituent constants are valid for reaction sites on benzene side chains. For reactions with the reaction site on the benzene nucleus, H. C. Brown has recently provided new substituent constants.

Rate data were obtained in this laboratory by Prysiazniuk on the decarboxylation of anthranilic acid in boiling nitrobenzene. Since the reaction obeyed second order kinetics and electron-donating substituents favoured decarboxylation, an electrophilic replacement of the carboxyl by a proton from another acid molecule was postulated. An application of the Hammett equation to the rates of decarboxylation showed a reasonably good fit when either Hammett's or Brown's substituent constants were used.

To further investigate the mechanism of decarboxylation of aromatic acids and to test the application of the Hammett equation to decarboxylation rates for other aromatic acids, the study of the rates of decarboxylation of substituted salicylic

acid was begun and is the subject of this thesis. It was desirable to use the same solvent for the study as that used for anthranilic acid, namely nitrobenzene, but the rate of decarboxylation of salicylic acid in nitrobenzene was found to be too slow to be suitable. Quinoline was then chosen as solvent where decarboxylation was found to be about fifty times faster for salicylic acid.

HISTORICAL

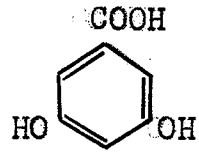
Chemists have observed the decarboxylation of carboxylic acids and have made use of this mode of decomposition in syntheses since the early days of chemistry. The first decarboxylation reaction was reported by Gay Lussac who observed that carbon dioxide was evolved when anhydrous oxalic acid was heated (11). The decomposition of malonic acid into carbon dioxide and acetic acid, which as a type reaction has become one of the most widely used reactions in organic chemistry, was discovered by Heintzel in 1866 (16).

Early reports showed that electron-withdrawing groups attached to the α carbon of aliphatic acids decreased their stability. Nitro-, cyano-, sulfo-, monochloro-, dichloro-, and trichloro- acetic acids were reported to decompose with evolution of carbon dioxide, whereas acetic acid was found to remain undecomposed "below a dull red heat" (20). Moreover numerous early authors stated that soda lime and organic bases facilitated decarboxylation (1,20,30). This evidence indicated that the anion of an aliphatic acid decarboxylated more readily than the free acid and that the role of the electron-withdrawing group or the organic base was to aid ionization of the acid to its anion.

However the ease of decarboxylation of aromatic acids showed opposing tendencies. Although benzoic acid was found to

be stable at 390° C. in a sealed tube, 2,4,6-trinitrobenzoic acid (20) and 2,4,6-trihydroxybenzoic acid (17) could both be decarboxylated in hot water. Hemmelmayr (17) reported the results of a study on the ease of decarboxylation of over forty hydroxy-, bromo-, nitro-, and amino- benzoic acids in water and aniline. He found that in a series of mono- or dihydroxy-benzoic acids at least one hydroxy group was needed in an ortho or para position to induce decarboxylation under the given conditions. However electron-withdrawing groups such as bromo and nitro substituents attached to an acid with ortho and/or para groups facilitated decomposition. The following examples are cited:

In boiling aniline for 1 hour



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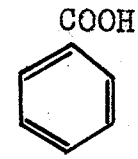

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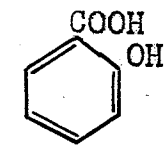

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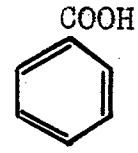

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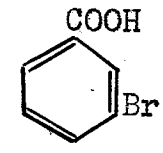

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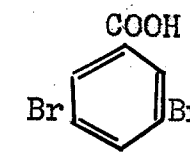

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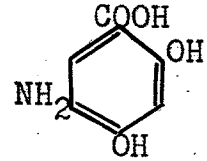
In boiling water for 1 hour



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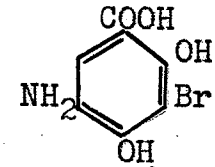

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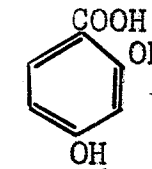

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Relative Amount of Decarboxylation

Early reports have also stated that common hydroxy aromatic acids decarboxylated in the melt, for example, salicylic, 2-hydroxy-1-naphthoic, protocatechuic, gallic (20) and numerous substituted salicylic acids (1). Anthranilic acid and meta and para aminobenzoic acids (20) were observed to decompose above their melting points to yield carbon dioxide and aniline.

More recent investigations attempted to determine the kinetic rate law followed by an acid undergoing decarboxylation in order to establish a mechanism for decarboxylation. B.R. Brown in a review article titled, "The Mechanism of Thermal Decarboxylation", (4) classified decarboxylations into uni- and bi- molecular electrophilic replacement reactions.

The uni-molecular reactions, which he called S_E1, were distinguished by the following rate-determining steps:

$$R\text{-}C(=O)\text{-}O^- \longrightarrow R^- + CO_2 \xrightarrow{H^+(\text{solvent})} R\text{-}H + CO_2 \qquad \text{(a)}$$

$$H^+\text{-}R\text{-}C(=O)\text{-}O^- \longrightarrow H^+\text{-}R^- + CO_2 \xrightarrow{(\text{solvent})} R\text{-}H + CO_2 \qquad \text{(b)}$$

Reaction scheme (a) shows decarboxylation occurring from the anion of an acid and proceeding through a carbanion intermediate which obtains a proton from the solvent to form the product RH. Reaction scheme (b) shows a zwitterionic form of an acid undergoing decarboxylation again through a carbanion intermediate

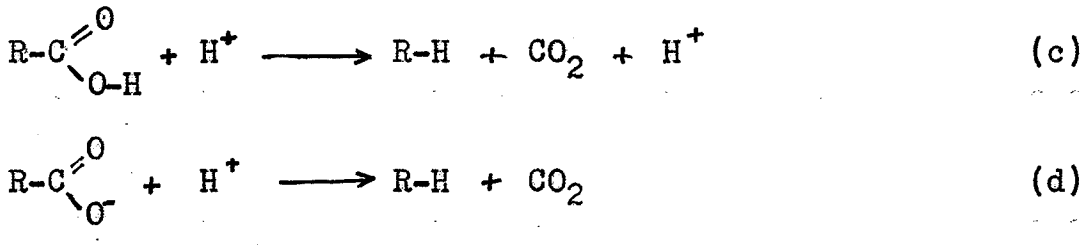
which exchanges its proton with the solvent to form the product RH.

First order kinetics were found for the decarboxylation of aliphatic acids that contained electron-withdrawing groups attached to the α carbon. Examples of these were the decarboxylation of trihalogen acetic acids (4), dibromomalonic acid mono-anion (25), and α-nitroisobutyric acid (27) in water. Since for the trihalogen acetic acids the activation energy for the decarboxylation of the sodium salt was found to be identical to that of the acid it was concluded that decomposition occurred from the anion. Also in the latter two cases it could be shown by varying the hydrogen ion concentration in buffered acid solutions that decarboxylation proceeded from the anion of the acid. For these acids a carbanion intermediate was detected by adding bromine to the acid undergoing decomposition.

Acids which decarboxylated from the free acid were those where zwitterion formation or internal hydrogen bonding could occur. Picolinic and quinaldic acids (4) were examples where decarboxylation was believed to occur through the zwitterion of the acid. β-Keto acids such as α,α-dimethylacetoacetic and malonic acids (4) were thought to decarboxylate from an internally hydrogen-bonded form. The net effect of the formation of a zwitterion or hydrogen-bonded form of the acid was to make the carboxylmore or completely anionic. This evidence has allowed Brown and Hammick (4) to derive the following

empirical rule from experimental results, namely that the carboxyl group is usually in the anionic form before S_E1 decarboxylation.

For the bi-molecular replacement reactions, S_E2, the following rate-determining steps were given:



$$R\text{-}C(=O)\text{-}O\text{-}H + H^+ \longrightarrow R\text{-}H + CO_2 + H^+ \qquad (c)$$

$$R\text{-}C(=O)\text{-}O^- + H^+ \longrightarrow R\text{-}H + CO_2 \qquad (d)$$

These reaction steps depend on the attack of a proton on the α carbon of the free acid or anion.

The bi-molecular replacement reaction was first suggested by Schenkel (31) in 1948 who found that anthracene-9-carboxylic acid was decarboxylated more readily in acidic than in basic solvents. However examples of decarboxylation in acidic medium had been reported much earlier, e.g. in 1879 aniline and carbon dioxide were found as products when p-aminobenzoic acid was heated in concentrated hydrochloric acid (34), and in 1899 mesitoic acid ($2,4,6\text{-}(CH_3)_3C_6H_2COOH$) was reported to decarboxylate in boiling phosphoric or hydroiodic acids (22). Numerous investigations have since shown that rates of decarboxylation of various aromatic acids, which have a high electron density on the carbon α to the carboxyl, are in fact proportional to the hydrogen ion

concentration of the solvent.

The first quantitative evidence for the bimolecular mechanism was produced by Schubert (32) who found that the decarboxylation of mesitoic acid in strong sulfuric acid was a pseudo first order process with the rate varying with changing acid concentration. Willi (36) and Liquori (24) both found the rate of decarboxylation of p-aminobenzoic acid in hydrochloric acid solutions to be approximately proportional to the concentration of the free organic acid. However Stevens (33) suggested a mechanism for the decarboxylation of anthranilic acid in acqueous sulfuric acid which postulated an attack of a proton on the zwitterion of anthranilic acid. Brown and Hammick (5) used liquid resorcinol as solvent in a study of the rate of decarboxylation of 2-, 2,4-, and 2,4,6- hydroxy-benzoic acids and their data was consistent with the bimolecular reaction mechanism, the solvent acting as a proton donor.

It is interesting to refer back to Hemmelmayr's work (page 4) and note that a bimolecular mechanism can explain the peculiar results he obtained, namely that strongly electron-donating groups were necessary to induce decarboxylation and that electron-withdrawing groups then facilitated decarboxylation. He did not measure rates as such, but determined amounts of carbon dioxide evolved, when a series of acids was heated in boiling water or aniline for one hour. Catalysis by phenolic products whose acid strengths increase with electron-withdrawing

groups would yield a result as observed by Hemmelmayr (refer to examples cited on page 4). This observation is further borne out by reports that the anisic acids can be distilled under vacuum without decomposition (20) whereas salicylic acid will decompose almost completely into carbon dioxide and phenol at a similar temperature (1). Although the methoxy group is only slightly less electron-donating than the hydroxy group (21), the anisic acids apparently do not decarboxylate readily in the melt, probably due to lack of catalysis by product.

More recent studies on the effect of substituents on the rate of decarboxylation were made by Beringer (3) who found that the rate of decarboxylation of mesitoic acid in aqueous sulfuric or phosphoric acids were relatively insensitive to changing electron-releasing substituents in the position meta to the carboxyl.

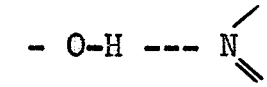
An investigation into the effect of para substituents on the rate of decarboxylation of arylidenemalonic acid derivatives in boiling pyridine was made by Corey (8). The Hammett equation was applied to rates of four substituents and a smooth curve was obtained instead of a straight line as predicted by the Hammett equation when Hammett's substituent constants were used. However these points show a linear relationship if plotted against Brown's substituent constants which appeared in the literature much later.

Willi (35) found the rates of decarboxylation of p-methyl-, p-methoxy-, p-hydroxy- and p-amino- salicylic acids increased in that order in aqueous hydrochloric acid solution. These rates showed a good linear relationship when the logarithm of the rate constants were plotted against Brown's substituent constants. It was evident that a proton attack on the α carbon of salicylic acid was the rate-determining step.

Prysiazniuk (29) found that electron-releasing substituents favoured decarboxylation of anthranilic acid in boiling nitrobenzene and since the rate showed second order kinetics with respect to the acid, a proton attack on carbon α by another acid molecule was postulated. The decarboxylation of p-aminobenzoic acid was also found to be second order and autocatalysis was observed for the decarboxylation of p-hydroxybenzoic acid in nitrobenzene.

The problem of determining the role played by a participating solvent molecule in a decarboxylation reaction has been attacked by Yankwich (10) and Clark (7). Yankwich found the decarboxylation of malonic acid (and to a much lesser extent the mono-anion) was catalysed by quinoline. The reaction showed first order kinetics with respect to the acid and the rate was proportional to the concentration of quinoline in an inert solvent. A spectroscopic study of the free malonic acid in quinoline-dioxane solutions showed carboxyl solvation which was not shown by the anion. It was thought that the direct influence

of the quinoline was probably on the hydrogen atom of the carboxyl group resulting in a hydrogen-bonded structure of the following type (38,37):



A series of rates of decarboxylation found for malonic acid in dioxane containing progressively larger amounts of quinoline, were extrapolated to pure quinoline and this value was found to be higher than that observed experimentally in pure quinoline. Yankwich concluded that carboxyl solvation in the free acid though apparently a necessary prerequisite to the specific catalytic action of quinoline was "intrinsically" inhibitive to the course of decarboxylation.

Clark (7) made a systematic study of the kinetics of decomposition of malonic acid in non-aqueous basic type solvents. The data showed that an increase in the effective negative charge on the nucleophilic atom of the solvent lowers the enthalpy of activation of the reaction, and Clark stated that this substantiated a postulate first made by Fraenkel and Yankwich (10), namely that in the decomposition of malonic acid in quinoline a transition complex was formed between the carboxyl carbon atom of the acid and the unshared pair of electrons on the nitrogen atom of the amine. As mentioned (page 10) Yankwich maintained in later publications that malonic acid solvation in quinoline occurred through the carboxyl hydrogen. Clark also

showed from his kinetic data that the entropy of activation became progressively more negative as the steric requirements of the catalytic solvent increased.

EXPERIMENTAL

Materials

Quinoline, synthetic grade, was dried over potassium hydroxide pellets and fractionated under vacuum. The fraction at 101 - 103° C. (8 - 9 mm.) was collected and stored over potassium hydroxide pellets. The index of refraction was 1.6246 at 25° C. (literature value, $n_D^{24.9}$ 1.6245).

Most of the substituted salicylic acids were available commercially and are listed in Table I with relating data. Except where a solvent of recrystallization is given, the acids were found to have a sharp melting point (about .5° C.) and were used without purification. A sharp melting point for the acid was used as criterion of purity. The remaining acids studied were synthesized as described in the following paragraphs. Since only small quantities of an acid were required, yield was sacrificed for purity in recrystallization steps.

All melting points below 235° C. were determined in a Hershberg melting point apparatus (18) using conventional short Anschütz enclosed-scale thermometers for which the calibrations had been checked against a platinum resistance thermometer. The silicone fluid in the apparatus was heated externally by resistance wire wound around the base arm and controlled by means of an Autotransformer. Temperature reproducibility of ±.1° C. was achieved with some care.

Table I

SUBSTITUTED SALICYLIC ACIDS

Substituent	Source	Melting Points, ° C Observed	Literature Values
4-amino	Matheson, Coleman & Bell	140d	146-7
5-amino	Matheson, Coleman & Bell[1]	286-7(water)[3]	280,283
4-hydroxy	Eastman Organic Chemical[1]	223.6-.8(toluene)[3]	213,226d
5-hydroxy	Eastman Organic Chemical[2]	206,2-.8d	200,202-3
4-ethoxy	Eastman Organic Chemical[2]	155.2-.7	154
5-chloro	Matheson, Coleman & Bell	174.0-.6(aq.alc.)[3]	172,176
5-bromo	Matheson, Coleman & Bell	167.8-168.4	164,166
3,5-dibromo	Aldrich Chemical	228.2-.7	227.5,228
5-nitro	Eastman Organic Chemical[2]	231.7-232.2	228-9
salicylic acid	Merck, U.S.P. (Bulk)	159.8-.9	159

1. Practical grade
2. White label grade
3. Solvent used in recrystallization

- 14 -

5-Methoxysalicylic acid was prepared by methylating 5-hydroxysalicylic acid (14). A solution of 7.1 gm. (.052 moles) 5-hydroxysalicylic acid (Eastman Organic Chemical) in 40 ml. 10% sodium hydroxide solution (.1 mole) was refluxed with 9 ml. dimethylsulfate (12.1 gm., .1 mole). The latter and another 40 ml. 10% sodium hydroxide solution were added in small amounts alternatively over a period of four hours of refluxing. The cooled solution was acidified with hydrochloric acid which precipitated the impure 5-methoxysalicylic acid. This acid was filtered and refluxed with 10% sodium hydroxide solution to hydrolyse ester impurities. The acid was recovered by acidification and after recrystallization from benzene and from water the yield was 2.8 gm. (37% of theoretical) with melting point 145.7 - 146.2° C. (literature values, 143.5° (14), 145 - 146° C.).

4-Methoxysalicylic acid was prepared by methylating 4-hydroxysalicylic acid (12). The same method was used as in the preparation of 5-methoxysalicylic acid. 4-Hydroxysalicylic acid was an Eastman Organic Chemical. The yield was 1.5 gm. (20% of theoretical) with melting point 155.9 - 156.3° C. (literature values, 154°, 157° C. (12)).

5-Methylsalicylic acid was prepared by reacting p-cresol with carbon tetrachloride and potassium hydroxide in the presence of copper (39). A mixture of 66 gm. (.61 mole) p-cresol, 300 gm. (2 moles) carbon tetrachloride, 200 ml. 30% potassium hydroxide solution (1.5 mole) and 3 gm. copper (B.D.H.

"precipitated") were stirred under reflux for two days. The mixture was acidified with hydrochloric acid and the excess carbon tetrachloride evaporated. A layer of excess p-cresol containing a large part of the desired product remained on the surface of the solution. The p-cresol layer was poured off and when the aqueous solution cooled crude 5-methylsalicylic acid precipitated and was filtered. The remaining product in the p-cresol layer was obtained by extracting with boiling water. The p-cresol could be separated from the aqueous solution by filtering through a wet filterpaper in a heated funnel. Yield of crude product after five extractions was 20 gm. (65% of theoretical). After two recrystallizations from water 8 gm. pure product were recovered with melting point 149.6 - 150.6° C. (literature values, 146 - 147° (39), 151°, 152°, 153° C.)

4-Nitrosalicylic acid was prepared by treating 4-nitroanthranilic acid with nitrous acid. A solution of 9.1 gm. (.05 mole) 4-nitroanthranilic acid (prepared by Prysiazniuk (29)) in 33 ml. concentrated sulfuric acid and 45 ml. water was cooled to 5° C. or less and stirred with a magnetic stirrer. A solution of 4 gm. sodium nitrite in 10 ml. water was added in small amounts over a period of eight to ten minutes. After stirring the solution for another ten to fifteen minutes, it was poured into 200 ml. boiling water. The solution was boiled briskly and cooled. 5-Nitrosalicylic acid precipitated on cooling, and after two recrystallizations from aqueous alcohol

3 gm. were recovered (33% of theoretical) with melting point 234.8 - 235.3 ° C. (literature values, 226°, 229 - 230°, 235° C.).

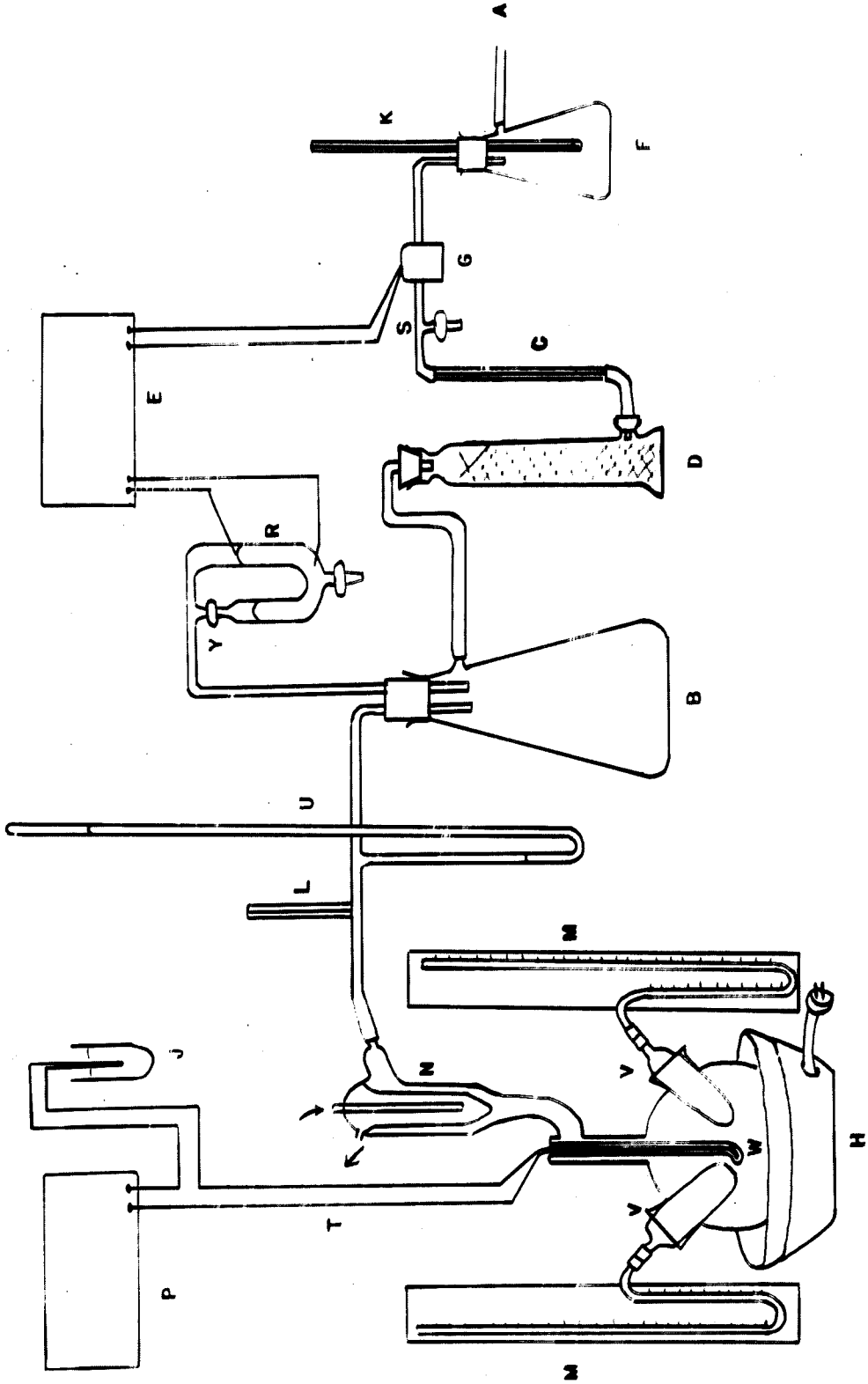
Apparatus

Apparatus for Manometric Runs

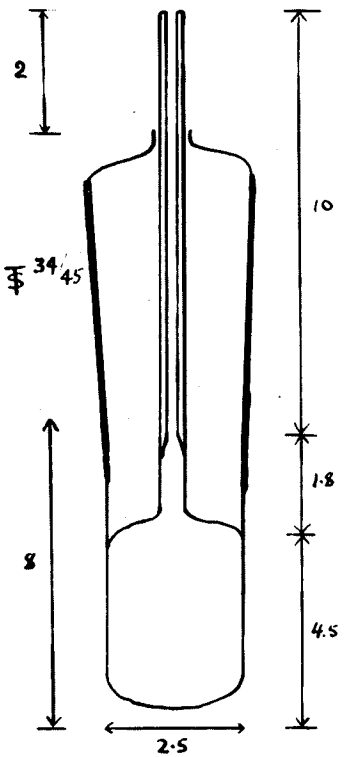
The rates of decarboxylation for most of the acids were followed manometrically in a system as shown on page 19.

The reaction vessel, as drawn on page 20 (dimensions in cm.), was built out of a 34/45 ground glass joint designed to hold 5 ml. of solution and about 15 c.c. vapour to be thermostated entirely throughout a run. The tube leading out of the reaction chamber and connected to a manometer was of 2 mm. capillary tubing so that a minimum volume of gas was exposed to variations in room temperature. Near the reaction chamber 6 mm. tubing, 2 cm. in length, was included to prevent condensed solvent from rising up the capillary and into the manometer.

The reaction vessel was kept at 200.0 ±.1° C. in a manostated thermostat, page 19. The thermostat consisted of a 2-litre flask containing boiling nitrobenzene manostated at 600 mm. pressure and heated with an electric heating mantle (H) regulated at 80 volts by an Autotransformer. The temperature in the thermostat was measured by an iron-constantan thermocouple (T) permanently placed in a thermocouple well (W). The difference in potential created by the hot and cold junction of the thermocouple, (the cold junction was kept in ice water in a Dewar flask (J)) was measured with a Tinsley portable potentiometer type 3184D (P). "Reference-Tables for Thermocouples"



THERMOSTAT & MANOSTAT FOR MANOMETRIC RUNS



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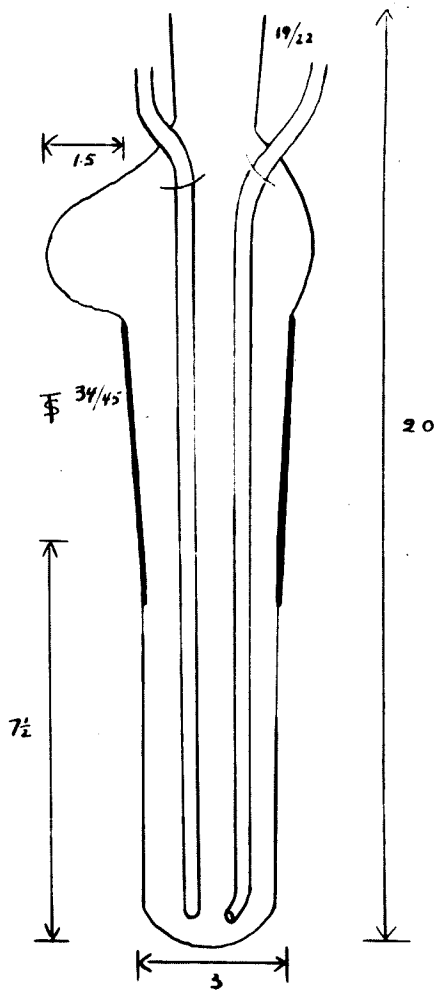


B

REACTION VESSELS · A, MANOMETRIC B, GRAVIMETRIC ·

(26) were used to convert potential difference to temperature.

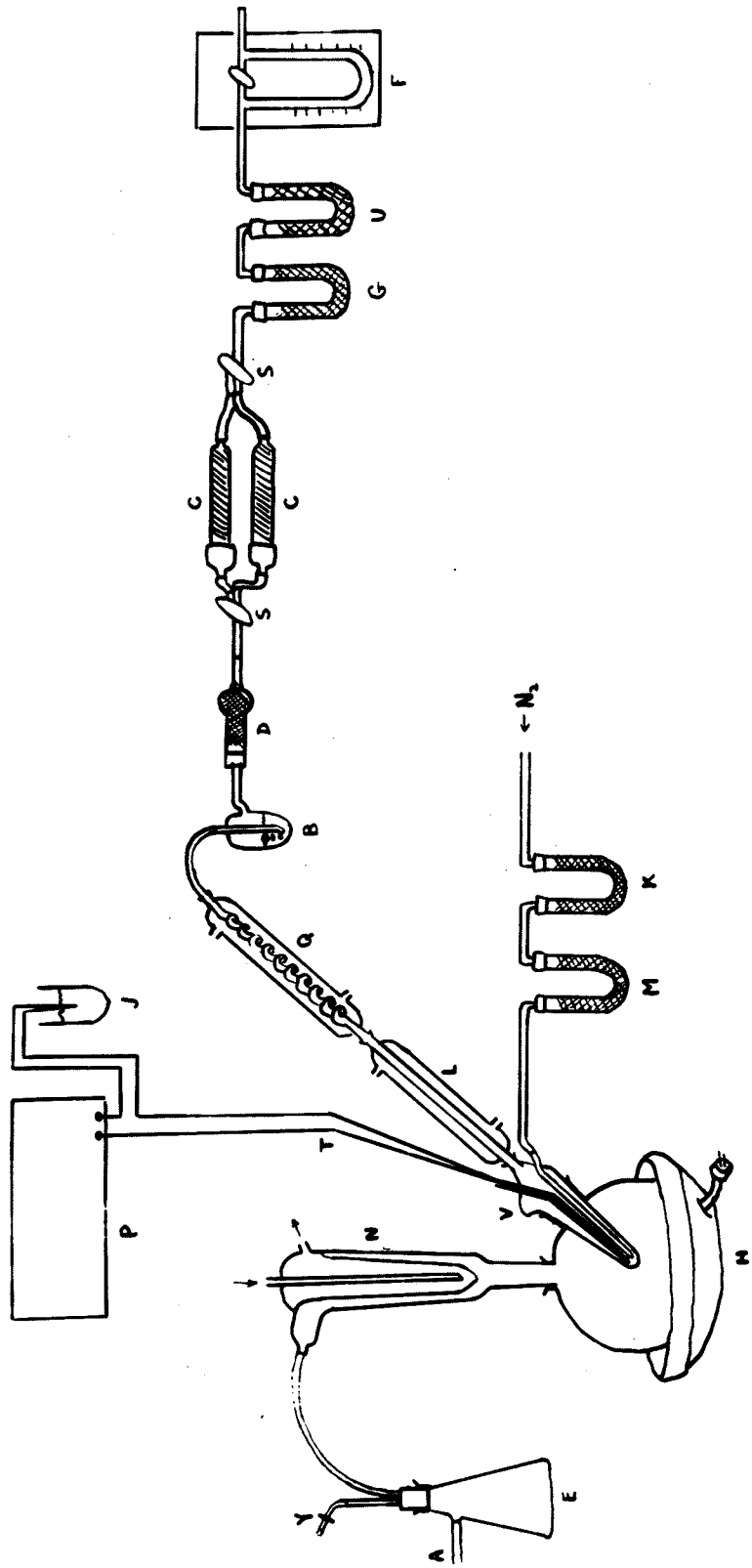
To obtain a constant and reproducible temperature in the thermostat, it was necessary to manostat the thermostating liquid, and preferably near atomospheric pressure. A manostating system as shown on page 19 was connected through a condenser (N) to the thermostat. The source of low pressure for the manostat was a water aspirator (A), kept in constant operation during a run connected to a flask (F) provided with a capillary leak (K). When the manostat regulator (R) activated the electronic relay (E), the valve (G), a Honeywell solenoid gas valve model V495, opened the system to the low pressure flask and the pressure in the thermostat was decreased accordingly. To avoid surging and excess overshooting a ballast flask (B) and a capillary (C) were inserted between the thermostat and the low pressure flask. The manostat was found to function more satisfactorily if the system was provided with a small leak (L). The pressure in the system could be read on the manometer (U). A drying tower (D) filled with Drierite placed between the water aspirator and the system kept water vapour from entering the thermostat. The system was opened to the atmosphere through a stopcock (S). The manostat regulator could be adjusted to any pressure regulation, by evacuating the system with the regulator stopcock (Y) open, and at the desired pressure closing it again.

Apparatus for Gravimetric Runs

The rates of decarboxylation for some of the acids were followed gravimetrically to check the rate constants obtained by the manometric method. Since the gravimetric method is based on the measurement of the weight rather than the volume of carbon dioxide produced a less elaborate temperature controlling system was required to produce reproducible decarboxylation rates.

The reaction vessel, page 20, was similar to that used by Prysiazniuk (29) but of slightly modified design. The vessel was built from a 34/45 ground glass joint and was designed with a gas inlet as well as a thermocouple well. A cavity near the top held the sample pellet before a run was begun. A 19/22 ground glass joint connected the flask to a condenser.

The reaction vessel was kept at 200.0±.2° C. in a 1-litre thermostat, page 23, containing boiling nitrobenzene at 650 mm. pressure heated by means of a heating mantle (H), controlled by an Autotransformer set at 80 volts. The thermostat was connected through a condenser (N) to a low pressure flask (E) which in turn was evacuated by a water aspirator (A). The pressure was adjusted with adequate sensitivity by a leak controlled with a pinch clamp (Y). The temperature was determined in an identical manner to that described on page 18.



THERMOSTAT & ABSORPTION TRAIN FOR GRAVIMETRIC RUNS.

The absorption train, page 23, consisted of two condensers (L,Q), a n-butylphthalate bubbler (B), a drying tube containing indicating Drierite (D), a two-way stopcock (S), absorption tubes containing Caroxite (an indicating Ascarite) (C,C), another two-way stopcock (S), a Drierite U-tube (G), an Ascarite U-tube (U) and a flowmeter (F). The condensers were of the Liebig (L) and Graham (Q) types and, with the n-butylphthalate bubbler completely eliminated organic vapours from the train. n-Butylphthalate is suitable because of its low volatility and good solvent properties. The drying tube (D) served to remove water vapour which may have entered the system when the apparatus was opened. The gas stream could be directed to either absorption tube by means of the two-way stopcocks (S,S). The U-tubes (G) and (U)prevented atmospheric water vapour and carbon dioxide from entering the absorption tubes. The flow rate of gas through the absorption train for different runs could be compared by means of the flowmeter. Nitrogen, which was used to sweep the carbon dioxide out of the reaction vessel and along the train, was passed through Drierite (K) and Ascarite (M) U-tubes before entering the reaction vessel.

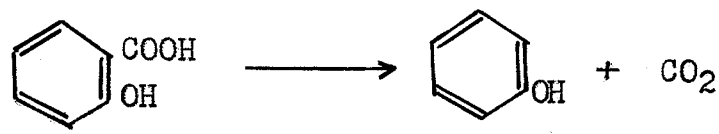
Procedure

Manometric

The reaction vessel was cleaned with hot chromic acid cleaning solution, water, acetone and ether and dried in a vacuum oven over-night. Before a run the vessel was allowed to cool while connected to a vacuum pump and dry nitrogen was admitted into the vessel after the pump was disconnected. The acid to be decarboxylated was weighed on a Bunge balance in a 10 ml. weighing bottle and 6 ml. quinoline were added from a 10 ml. syringe. While solution was being attained, the weighing bottle was stored in a desiccator until its use. A quantity of 5 ml. quinoline solution was injected into the reaction chamber in each run by means of a hypodermic syringe fitted with a 4-inch needle. For those acids which decarboxylated quickly the vessel was placed into the thermostat to heat up to 200° C. before the solution was injected. After about five minutes an open-end manometer of 2 mm. capillary was attached firmly to the capillary of the reaction vessel with a 3 cm. length Tygon tubing and the pressure readings taken as a function of time. An electric second counter was used to indicate the time elapsed from the beginning of heating. After at least three half lives of the run, a final pressure reading was taken.

As described, special precautions were taken to keep the quinoline solution and the reaction vessel dry. Quinoline is reported to be very hygroscopic (2) and it was found that rates of decarboxylation were accelerated if traces of moisture contaminated the solution. Since with our present system the initial concentrations could not be calculated explicitly, the final pressure reading on the manometer was taken as proportional to the initial concentration, i.e. the concentration at the time of connection of the manometer. The reported molarities were calculated on the basis of the weight of the acid and the volume of quinoline added. The maximum solubilities of some of the acids in cold quinoline were small, e.g. .02 M for 4- and 5-nitro- and 5-amino- salicylic acids, and thus only small changes in pressure with time could be observed. Therefore precise temperature control was required for reproducibility, since pressure changes as a function of temperature were comparable in magnitude to pressure changes due to decarboxylation.

The kinetics governing the decarboxylation of salicylic acid in quinoline was found to be first order. One molecule of salicylic acid decomposes to yield phenol and carbon dioxide.



For the reaction,

$$\text{Acid} \longrightarrow \text{Phenol} + CO_2$$

we have the following differential proportionality:

$$-\frac{d[A]}{dt} \propto [A]_t \propto \frac{dP}{dt}$$

where $[A]_t$, the concentratation of Acid at time t and P is the pressure of CO_2 at time t. But,

$$[A]_t \propto P_\infty - P_t$$

where P_∞ is the final pressure reading. Then,

$$\frac{dP}{dt} = k(P_\infty - P_t)$$

where k is the specific rate constant. On integration,

$$\log_{10}(P_\infty - P_t) = -\frac{k}{2.303}\, t + \log_{10}(P_\infty - P_o)$$

where P_o is the initial pressure.

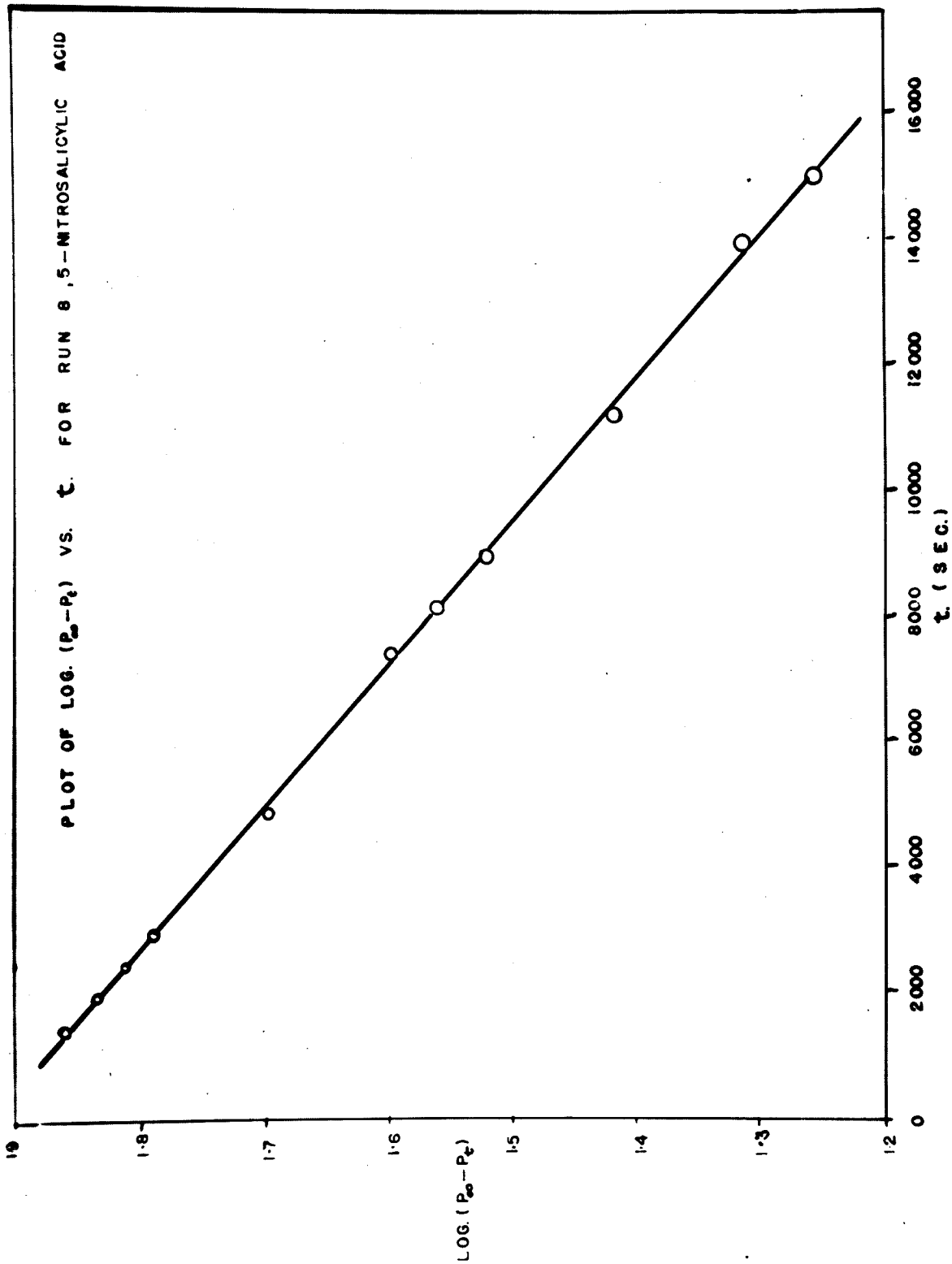
The slope of the plot $\log_{10}(P_\infty - P_t)$ *vs.* t is equal to -k/2.303. The rate constant, k, for each run was calculated from the slope of the best straight line through the points of the $\log_{10}(P_\infty - P_t)$ *vs.* t plot. Table II lists the pressure readings for a typical manometric run. The plot of $\log_{10}(P_\infty - P_t)$ *vs.* t for this run is shown on page 29.

Table II

TYPICAL MANOMETRIC RUN NO. 8

.012 M. 5-Nitrosalicylic Acid in Quinoline @ 200° C.

Time (sec.)	Pressure (mm.Hg)	log (P_∞-P)
1500	17.0	1.862
2000	22.0	1.837
2500	24.4	1.815
3000	27.8	1.791
3600	32.2	1.760
4900	40.0	1.696
7400	49.8	1.600
8200	53.4	1.559
9000	56.6	1.519
11250	63.6	1.415
13900	68.6	1.322
15000	71.6	1.255
t_∞ (8 hrs.)	89.5 (P_∞)	


PLOT OF LOG. ($P_\infty - P_t$) VS. t. FOR RUN 8, 5-NITROSALICYLIC ACID
LOG. ($P_\infty - P_t$)
t. (SEC.)
1·9
1·8
1·7
1·6
1·5
1·4
1·3
1·2
0
2000
4000
6000
8000
10000
12000
14000
16000

Gravimetric

The acid to be decarboxylated was shaped into a pellet with a hydraulic pellet press. The pellet was weighed on a Bunge balance and placed into the cavity of the reaction vessel, page 20. The reaction vessel was placed into the thermostat, page 23 and nitrogen was slowly passed into the vessel to sweep out atmospheric carbon dioxide and moisture. Then 10 ml. quinoline were introduced into the vessel with a 10 c.c. syringe and the absorption train connected through the two condensers. The thermocouple was inserted into the well in the vessel and the desired temperature was obtained quickly by adjusting the pressure in the thermostat and the flow rate of nitrogen entering the vessel. When the temperature remained constant at 200° C. the vessel was turned so as to bring the cavity up causing the pellet to drop into the solvent. The gas stream was directed into the weighed absorption tube by means of the two-way stopcock and the timer turned on. The absorption tubes were weighed periodically.

It was necessary to have a good condensing system above the reaction vessel since a fast flow of nitrogen was used to minimize the time delay in the movement of carbon dioxide from vessel to absorption tube. Hot quinoline quickly dissolved the pellet of acid after it dropped into the solvent. The absorption tubes weighed about 40 gm. and increases of weight of 3 to 10 mg. due to absorbed carbon dioxide were weighed on

a Bunge balance. The concentration of the solution in each run was calculated on the basis of the acid weighed and the quinoline added as solvent. However this concentration was checked by having the run go to completion. The number of moles of carbon dioxide recovered were usually over 90% of the number of moles of acid originally in the pellet.

For the kinetics we have as before,

$$\log_{10}(X_\infty - X) = -\frac{k}{2.303}\, t + \log_{10} X_\infty$$

where X stands for the moles of carbon dioxide weighed at time t, and X_∞ stands for initial number of moles of acid (in our calculations the accumulated moles of carbon dioxide produced were used for X_∞), and k is the specific rate constant.

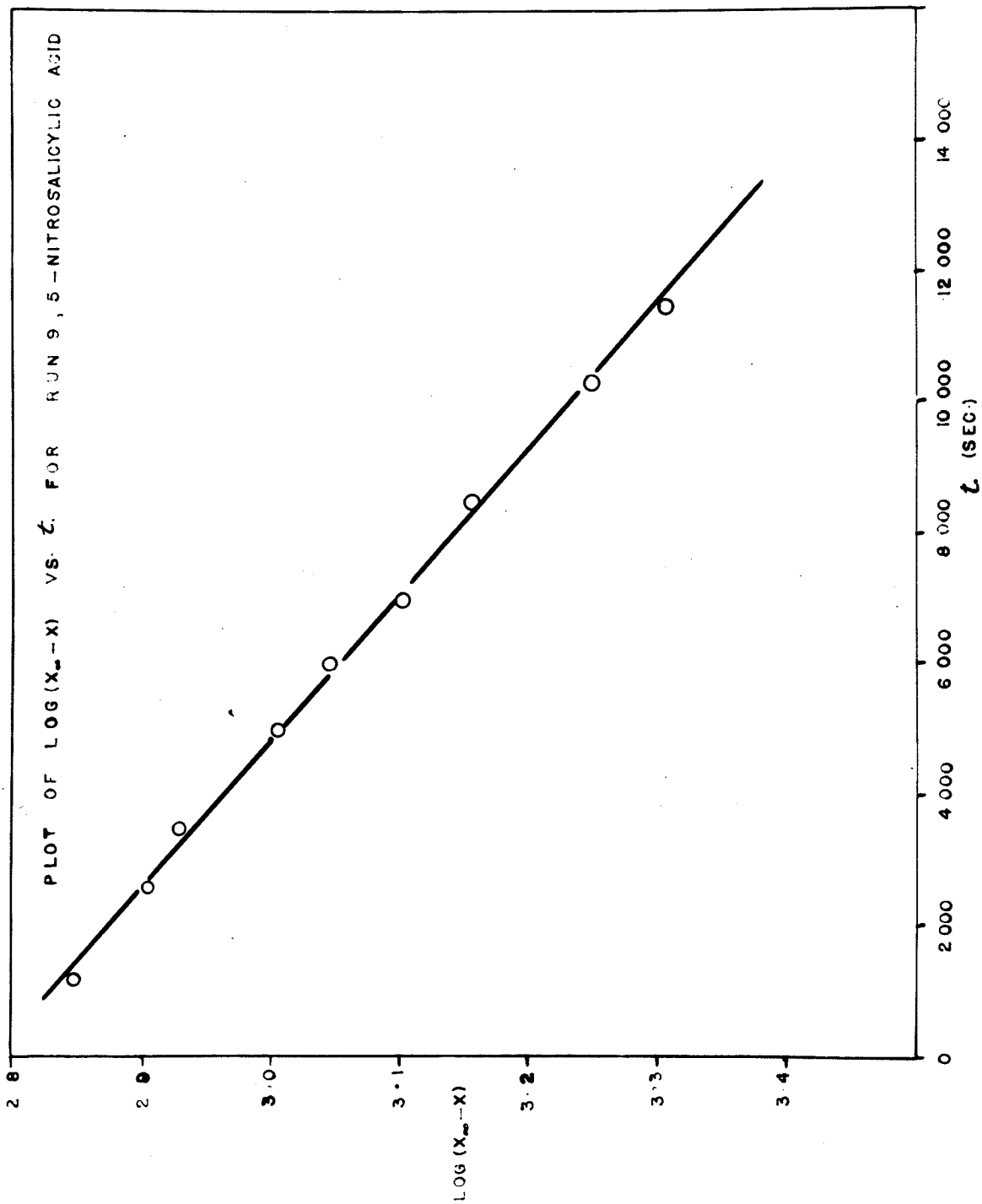
The rate constant for each run was calculated from the slope of the best straight line through the points of the $\log_{10}(X_\infty - X)$ *vs.* t plot. Table III lists the carbon dioxide weights for a typical gravimetric run. The plot of $\log_{10}(X_\infty - X)$ *vs.* t for this run is shown on page 33.

Table III

TYPICAL GRAVIMETRIC RUN NO. 9

.165 M. 5-Nitrosalicylic Acid in Quinoline @ 200° C.

Time (sec.)	CO_2 Weights (gm.) (X)	Total CO_2 (mole) (X x 10^4)	$\log(X_\infty - X)$
1200	.0090	2.04	-2.849
2600	.0073	3.71	-2.904
3500	.0046	4.76	-2.929
5000	.0064	6.21	-3.003
6000	.0039	7.10	-3.043
7000	.0045	8.22	-3.101
8500	.0048	9.20	-3.158
10300	.0058	10.5	-3.250
11500	.0029	11.2	-3.308
t_∞ (10 hrs.)	.0217	16.1	


PLOT OF LOG $(X_\infty - X)$ VS. t FOR RUN 9, 5-NITROSALICYLIC ACID
LOG $(X_\infty - X)$
2·8
2·9
3·0
3·1
3·2
3·3
3·4
0
2 000
4 000
6 000
8 000
10 000
12 000
14 000
t (SEC.)

RESULTS AND OBSERVATIONS

Tables IV and V list the observed rates of decarboxylation of salicylic acid and thirteen substituted salicylic acids.

The decarboxylation rate of salicylic acid in quinoline was found to be first order with respect to the acid. For most acids the plot of $\log_{10}(P_\infty - P_t)$ *vs.* t was linear over a period of two or three half lives. For some acids, *e.g.* 5-hydroxy- and 5-methyl- salicylic acid a gradual increase in rate was noticeable after about one half life of the run.

Quinoline was chosen as solvent when decarboxylation of salicylic acid in nitrobenzene was found to be too slow for a study of the effect of electron-releasing as well as electron-withdrawing substituents on the rate of decarboxylation. However the few trials performed with salicylic acid in nitrobenzene showed that second order kinetics were obeyed and a rate constant of about 2×10^{-4} litre moles^{-1} sec.$^{-1}$ was obtained. The catalytic effect of quinoline on the rate of decarboxylation of salicylic acid was thus found to be about fifty fold.

It was found that decarboxylation in quinoline proceeded smoothly for all substituted salicylic acids and on the gravimetric runs better than 90% of the theoretical carbon dioxide was usually obtained. However the quinoline darkened considerably for some acids after the reaction had proceeded for

Table IV

FIRST ORDER DECARBOXYLATION RATES OF SUBSTITUTED SALICYLIC ACIDS IN QUINOLINE

	Manometric			Gravimetric				
Substituent	Run No.	Nominal Conc.(M)	k x 10^4 ($sec.^{-1}$)	Run No.	Nominal Conc.(M)	k x 10^4 ($sec.^{-1}$)	Average x10^4	Maximum Deviation
H	2	.054	1.11					
	3	.031	1.08	43	.256	1.05	1.08	2.8%
5-NO_2	7	.025	1.11					
	8	.012	1.02	9	.165	1.05	1.06	4.8%
5-Cl	5	.050	1.67					
	6	.035	1.64	19	.138	1.58	1.63	3.1%
5-Br	20	.059	1.37					
	12	.039	1.41	10	.216	1.39	1.39	1.4%
5-CH_3	21	.043	1.25					
	23	.035	1.30	22	.186	1.35	1.30	3.9%
3,5-DiBr	14	.058	4.91					
	15	.028	5.13	13	.164	5.36	5.13	4.6%
5-CH_3O	26	.092	1.92					
	35	.080	1.96					
	24	.041	1.83	28*	.213	2.13	1.90	4.2%

* not counted into average

Table V

FIRST ORDER DECARBOXYLATION RATES OF SUBSTITUTED SALICYLIC ACIDS IN QUINOLINE

Manometric Runs

Substituent	Run No.	Nominal Conc.(M)	k x 10^4 ($sec.^{-1}$)	Average x10^4	Maximum Deviation
4-NH_2	31	.089	16.8		
	33	.084	15.7		
	30	.039	15.2	15.9	5.7%
4-CH_3O	27	.043	15.6		
	29	.037	16.5	16.2	3.7%
4-C_2H_5O	42	.061	16.2		
	39	.046	15.6		
	38	.027	16.3	16.0	2.5%
4-OH	52	.053	15.6		
	50	.046	15.5		
	49	.028	14.6	15.2	4.0%
5-NH_2	45	.033	2.04		
	46	.024	2.16		
	48	.013	2.02	2.07	4.3%
4-NO_2	54	.020	.822		
	53	.018	.833		
	55	.010	.810	.822	1.5%
5-OH	56	.061	1.64		
	57	.036	1.68	1.66	1.2%

some time. m-Iodosalicylic acid showed a faster rate than expected and since the odour of iodine was present after the run, which was indicative of a side reaction occurring in hot quinoline, the study of this compound was not pursued.

o-Anisic acid showed a decarboxylation rate of approximately that of salicylic acid (k, o-anisic acid = 1.1×10^{-4} sec.$^{-1}$; k, salicylic acid = 1.08×10^{-4} sec.$^{-1}$) after an "induction" period; i.e. for a gravimetric run at .2 M concentration of acid in quinoline evolution of carbon dioxide could be detected only after a period of fifteen minutes and for a manometric run at .066 M, pressure increases were produced only after one hour. Of interest is the observation that the quinoline solution changed colour through red to brown immediately on the addition of the pellet to the hot solvent. A solution of o-anisic acid in quinoline will not show this colour at room temperature.

Anthranilic acid showed little or no decarboxylation in quinoline.

DISCUSSION

Mechanism

The limited exploration as yet into the decarboxylation of salicylic acid in nitrobenzene indicates that a mechanism similar to that for anthranilic acid in nitrobenzene could be possible. At least the second order kinetics observed are consistent with the mechanism proposed for anthranilic acid.

However decarboxylation of salicylic acid in quinoline has been found to be first order with respect to the acid, and accelerated by electron-releasing substituents in para position.

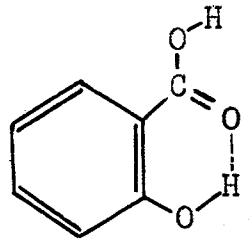
According to the reaction schemes for decarboxylation as classified by Brown (page 5) first order kinetics could be shown by acids decarboxylating spontaneously from the anion. However the known examples of these acids have strong electron-withdrawing groups influencing the carbon-carbon bond to be broken in the decarboxylation. Moreover Corey (8) has shown that phenols and carboxylic acids are inappreciably ionized in pyridine (the basicity of pyridine is only slightly less than that of quinoline (13)). The decarboxylation of the mono-anion of malonic acid was found by Yankwich (page 10) to be much less catalyzed by quinoline than the di-acid. From these three pieces of evidence it can be concluded that decarboxy-lation from the anion would be hindered by electron-releasing groups and by the effect of quinoline. The reverse is found

to be the case in the decarboxylation of salicylic acid in quinoline.

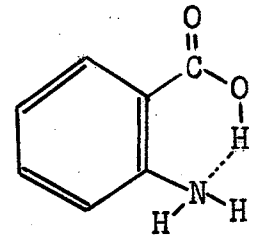
Returning to Brown's reaction scheme (b) (page 5), first order kinetics could also be observed for zwitterionic or hydrogen-bonded forms of the acid. But where the hydrogen of the carboxyl is either transferred completely as in the zwitterion or only partially as in the hydrogen-bonded form, the net effect is that of decomposition occurring from the anion. However decarboxylation from the anion is hindered by electron-releasing substituents and quinoline (as concluded from work done by Yankwich). It has been found that these two effects aid the decarboxylation of salicylic acid and on this basis Brown's reaction scheme (b) is also ruled out as a possible mechanism for the decarboxylation of salicylic acid in quinoline.

From evidence by Yankwich (37,38) the carboxyl of malonic acid must be in the free acid form for quinoline-catalyzed decarboxylation to occur. A consideration of the probable hydrogen bonding in salicylic acid and anthranilic acid may explain the observed catalytic effect on the decarboxylation of the former but not the latter. In salicylic acid phenolic hydrogen bonding is known to take place, but in anthranilic acid it is probable that the carboxyl hydrogen chelates with the nitrogen of the amine (23).

Thus:



Salicylic Acid

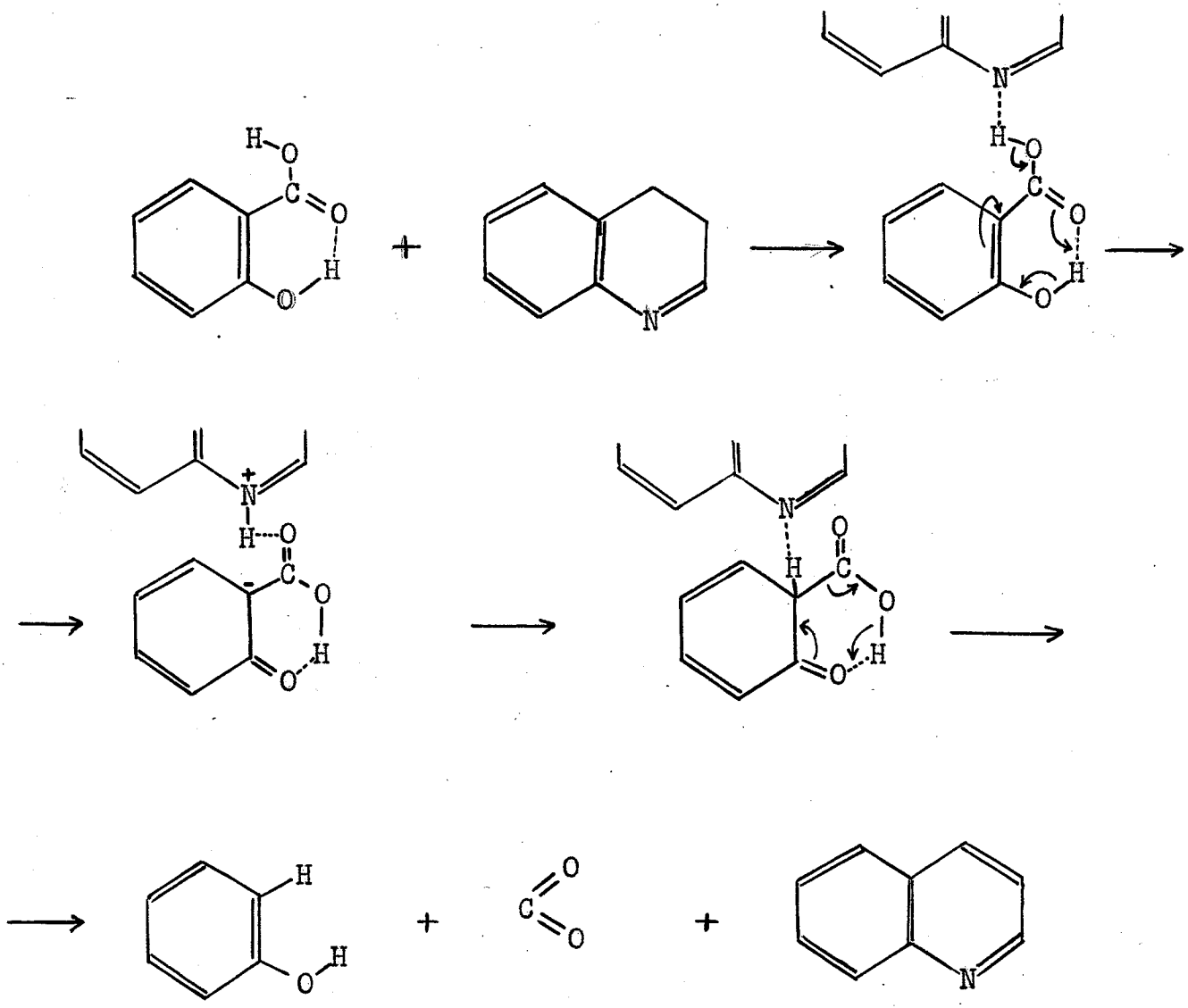


Anthranilic Acid

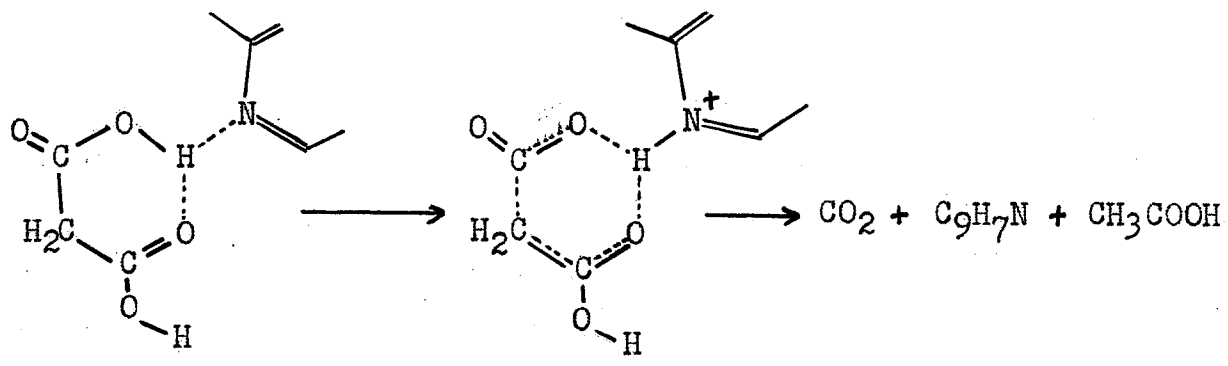
If in fact the carboxyl must exist as the free acid for quinoline to be effective in decarboxylation, salicylic acid should decarboxylate more readily in quinoline than anthranilic acid,which is found to be the case.

Since electron-donating substituents favour the decarboxylation of salicylic acid in quinoline the reaction scheme (c) (page 7), demanding a high electron density on the ∝ carbon of the free acid, seems the most likely mechanism to apply to this system. This mechanism would show first order kinetics when either the solvent donated the proton in the rate-determining step, or the proton was donated internally. For salicylic acid in nitrobenzene second order kinetics indicates the probability of a bi-molecular mechanism in action with one acid molecule playing the part of proton donor in the replacement reaction. For salicylic acid in quinoline first order kinetics indicate either proton donation occurring internally or by a solvent molecule. Although protonated quinoline would be an effective proton donor, the concentration of this species in quinoline should be very small corresponding to slight ionization

of the acid molecule. This leaves one possibility, namely that the proton must be donated internally by salicylic acid in quinoline. A mechanism whereby this could occur is outlined in the following equations:



This mechanism might be placed in the category of the so-called four-centre-type reaction defined by Hine (19) as those reactions "in which the atoms in the reactant(s) simply change their configuration to that of the product(s) without electron pairing or unpairing and without the formation or destruction of ions. There are four (or more) key atoms, each of which is simultaneously forming a new bond and breaking an old one in the transition state." A similar mechanism has been suggested by Yankwich (10) for the decarboxylation of free malonic acid in quinoline and by various authors for the decomposition of β-keto acids (4) although in the latter case only primary and not tertiary amines markedly catalyse decarboxylation. However the role played by quinoline in decarboxylation has not been discovered as yet. Yankwich (10) has shown that hydrogen bonding between the carboxyl hydrogen and the nitrogen of quinoline occurs by measuring the shifts of the carbonyl absorption peak of malonic acid in quinoline-dioxane solutions. This evidence seems to suggest that if this hydrogen bonding or complexing aids decarboxylation, a molecule of quinoline stabilizes the transition state in the decarboxylation. It may occur in the following manner:



The decarboxylation of anisic acid cannot occur by the mechanism proposed since chelation between the carbonyl oxygen and the phenolic proton, which plays an important role in our mechanism, is not possible for anisic acid. Evidence has been reported for methoxy acids rearranging to form phenolic and ester products and electron-withdrawing groups, namely the nitro group, facilitated these rearrangements (28). The "induction" period observed for anisic acid in this investigation may imply a free radical reaction where salicylic acid is an intermediate and the rate of decarboxylation observed may have been that of salicylic acid itself.

The Hammett Equation

The Hammett equation was originally based on the effect of changing substituents on the acidities of aromatic acids and reactivities of aromatic side chains (15). The electrostatic, inductive and resonance effects of a substituent on a reaction site were combined into an experimentally determined constant, characteristic of the substituent from one reaction to another. The Hammett equation stated that the logarithm of the ratios of the dissociation constants (or rate constants) for the substituted to the unsubstituted acid (or reactant) was proportional to sigma, σ, the substituent constant:

$$\log_{10} \frac{k}{k_o} \propto \sigma$$

A proportionality constant rho, ρ, was included:

$$\log_{10} \frac{k}{k_o} = \rho \sigma$$

Sigma was defined as the logarithm of the ratio of the acid dissociation constants for the substituted to the unsubstituted benzoic acids in water at 25° C. This was equivalent to setting rho equal to unity for benzoic acids. Rho was called the reaction constant and could be interpreted as the susceptibility of the reaction rate to changes in electron density at the reaction site.

Slightly larger values for sigma have been found for strongly electron-withdrawing groups when in the para position

to phenols and amines due to strong conjugative interaction with the reaction site. A new series of sigma values has been determined by H.C. Brown which he called sigma plus, σ^+, substituent constants to be used for electrophilic replacement reactions occurring on the benzene nucleus, which are slightly larger for electron-donating groups due to strong conjugative interaction with the reaction site.

The data for the rates of decarboxylation of the substituted salicylic acids, Tables IV and V, were applied to the Hammett equation using Brown's substituent constants. Using the following form of the Hammett equation:

$$\log_{10}k = \rho\sigma^+ + \log_{10}k_o$$

A plot was made of the logarithm of the rate constant of the substituted salicylic acid versus sigma plus (Table VI & page 46).

A straight line which will go through or fall near all the points cannot be drawn for the Hammett equation plot, although in general the slope of rho is negative, i.e. electron release favours and electron withdrawal hinders decarboxylation of salicylic acid in quinoline if the α carbon is considered as the reaction site.

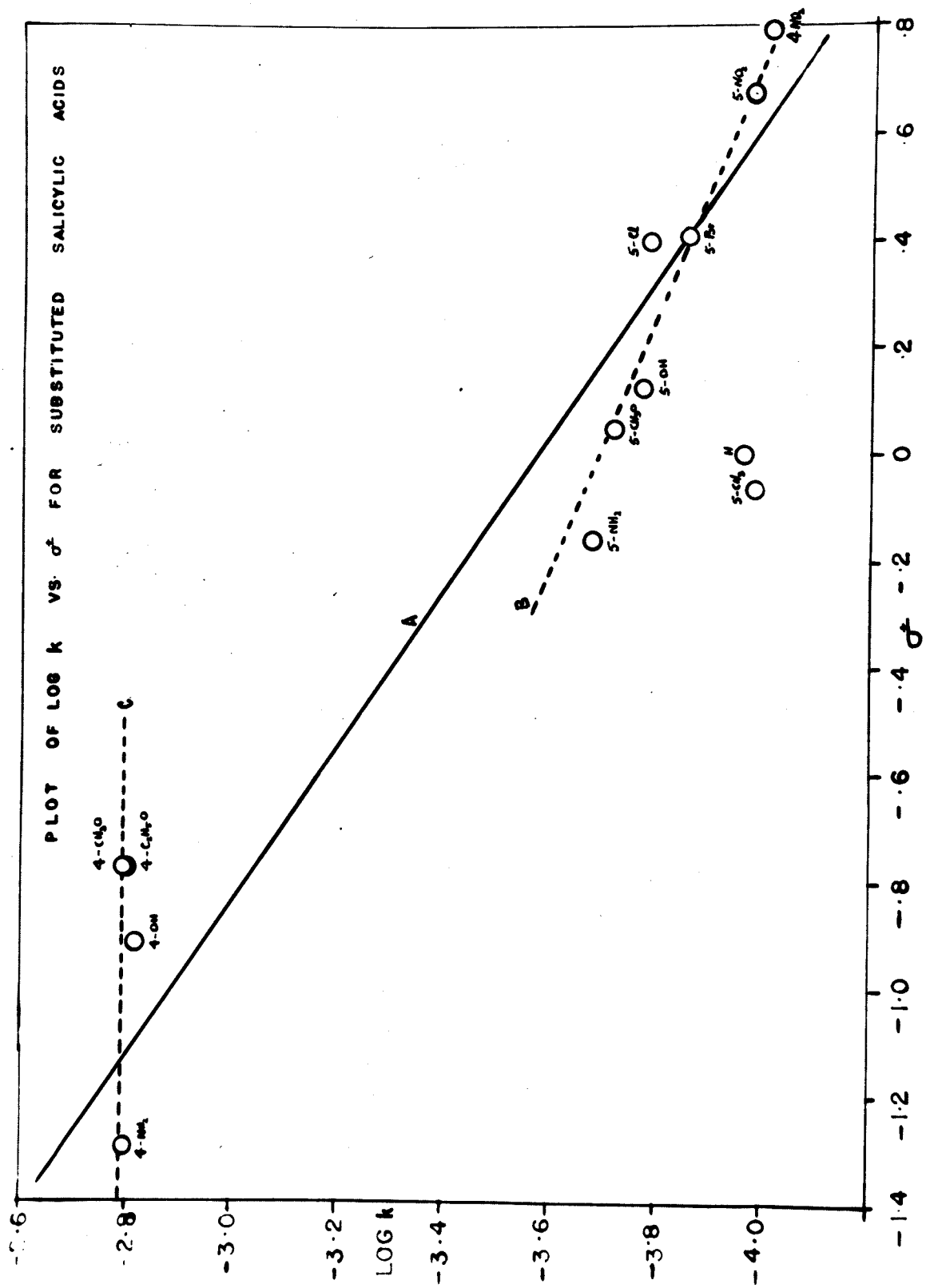
The best straight line for all the points as calculated by the least squares method (9) has a comparatively small value of rho, namely -.75 (line A), and the deviations of the points from this line are large. Since this line does not pass through

Table VI

DATA FOR THE HAMMETT EQUATION PLOT

Substituent	Log k	Brown's σ^{+} (6)
4-NH_2	-2.796	-1.3
4-OH	-2.816	-.92
4-CH_3O	-2.789	-.778
4-C_2H_5O	-2.794	-.78*
5-NH_2	-3.681	-.16
5-CH_3	-3.884	-.066
5-OH	-3.778	.121
5-CH_3O	-3.720	.047
5-Cl	-3.786	.399
5-Br	-3.855	.405
5-NO_2	-3.973	.674
4-NO_2	-4.083	.790
H	-3.965	0

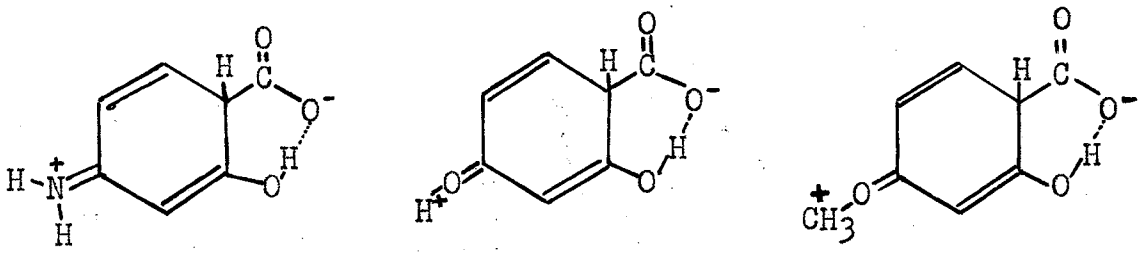
* σ^{+} for C_2H_5O has not been given by Brown; the value for CH_3O is used.


PLOT OF LOG k VS. σ⁺ FOR SUBSTITUTED SALICYLIC ACIDS
LOG k
σ⁺
A
B
C
4-NH₂
4-OH
4-CH₃O
4-C₆H₅O
5-NH₂
5-OH
5-CH₃O
5-Cl
5-Br
5-NO₂
5-C₆H₅
4-NH₂

the point for salicylic acid itself, and since the rates of decarboxylation of all the substituted acids, except 5-methylsalicylic acid, are in fact faster than anticipated by the Hammett equation the evidence suggests that both electron donation and electron withdrawal is effective in aiding decarboxylation. All the substituents under consideration are thought to have conjugative characteristics and in the proposed mechanism conjugation of a substituent with the reaction site probably has a pronounced effect on the rate of decarboxylation. Since 5-methylsalicylic acid decarboxylates at a rate similar to that of salicylic acid it seems conjugative effects are not in operation for this group in our system.

These observations suggest that proton attack on the α carbon may not be the only rate-determining step in operation in the decarboxylation of salicylic acid in quinoline but rather that bond-making and bond-breaking of the phenolic hydrogen to the two oxygen atoms and possibly the carbon-carbon bond-breaking may all be involved in the process. However proton bond-making and bond-breaking from phenolic to carbonyl oxygens only involves an electronic shift and seems an unlikely rate-determining step. But since the rates of decarboxylation of the strongly electron-donating substituents, p-amino, p-hydroxy and p-alkoxy do not fall on the line drawn through the meta substituents, (line B, slope -.47 by least squares method) and in fact appear to fall on a line of zero slope (line C, the rates are very similar for

all four substituents) the rate-determining step governing the rates of these acids may be different than that for the meta substituted acids and may involve a step not greatly affected by moderate changes in electron donation. Such a rate-determining step may be the breaking of the carbon-carbon bond in the decarboxylation process. On considering the following examples of possible transition or intermediate states:



the transfer of the proton as indicated on page 40 to the ∝ carbon may have been facilitated by strong conjugative electron donators to the extent that the rate-determining step becomes the breaking of the carbon-carbon bond. Since the carboxyl group in the above structures cannot take part in conjugation the cleavage of the carbon-carbon bond in these acids cannot be affected greatly by moderate changes in electron donation by the different groups if our predicted mechanism is correct.

In summing up the main features of the proposed mechanism for the decarboxylation of salicylic acid in quinoline it has been suggested that an internal replacement of the carboxyl group by a proton occurs in the decarboxylation process,

and that for 5-amino-, 5-methoxy-, 5-hydroxy-, 5-chloro-, 5-bromo-, 5-nitro-, 4-nitro- and 5-methyl- salicylic acids and salicylic acid itself the rate-determining step is that of the proton attack. But for 4-amino-, 4-hyroxy-, 4-methoxy- and 4-ethoxy- salicylic acid the rate-determining step may be the breaking of the carbon-carbon bond.

Further investigations into the mechanism of decarboxylation of salicylic acid in quinoline should test the validity of the proposed mechanism by determining the rate of decarboxylation of salicylic acid in various modifications of the present system. In this connection the following suggestions are made:

1. Salicylic acid decarboxylated in nitrobenzene containing progressively larger concentrations of quinoline would determine the order of the reaction with respect to quinoline.
2. Salicylic acid decarboxylated in substituted quinoline solutions would indicate the influence of changing electron density on the nitrogen atom on the rate of decarboxylation.
3. Salicylic acid with inert substituents in the 5 position (e.g. 5-methylsalicylic acid) decarboxylated in quinoline and 2 or 8 substituted quinoline would determine the effect of steric hindrance on decarboxylation.
4. An isotope effect if observed for the decarboxylation of deuterated salicylic acid in quinoline would be consistent with the mechanism proposed for the decarboxylation of salicylic acid in quinoline.

5. An isotope effect if observed in the decarboxylation of salicylic acid with C^{14} as carboxyl or α carbon, would substantiate the suggestion that the breaking of the carbon-carbon bond was part of the rate-determining step.

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