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*I hereby recommend that the thesis prepared under my supervision by* Samuel George Dent, Jr.

*entitled* Benzoxazones and Benzoxazadiones, Their Syntheses and Pharmacological Actions,

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# BENZOXAZONES AND BENZOXAZADIONES, THEIR SYNTHESES AND PHARMACOLOGICAL ACTIONS

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by

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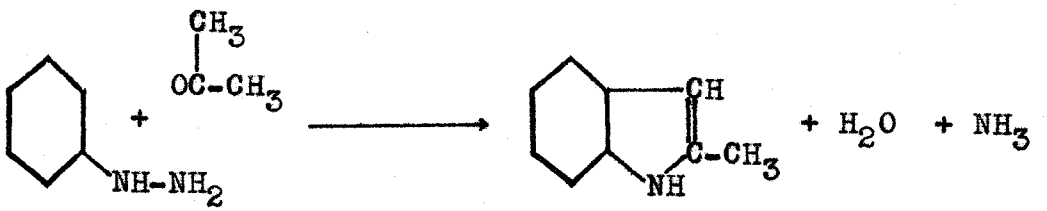
# ANALGESICS AND ANTIPYRETICS

Antipyretics (drugs which reduce abnormally high body temperature) and analgesics (drugs which characteristically relieve pain without producing stupefaction or unconsciousness), are some of the earliest and best known of the synthetic drugs. During the past seventy years, almost numberless compounds which possessed antipyretic and analgesic properties were introduced by drug manufacturers, but the number of really new and valuable products is small. The greater number of these compounds consist of insignificant variations in a few parent compounds. A few of these, however, have survived and proved their usefulness, not so much as antipyretics, but as analgesics. Several have also proved useful in the symptomatic treatment of acute rheumatic fever and gout. Since the amount of literature on the subject is so great, the author has made no attempt to give a complete survey, but rather a general view of the more important developments in the field.

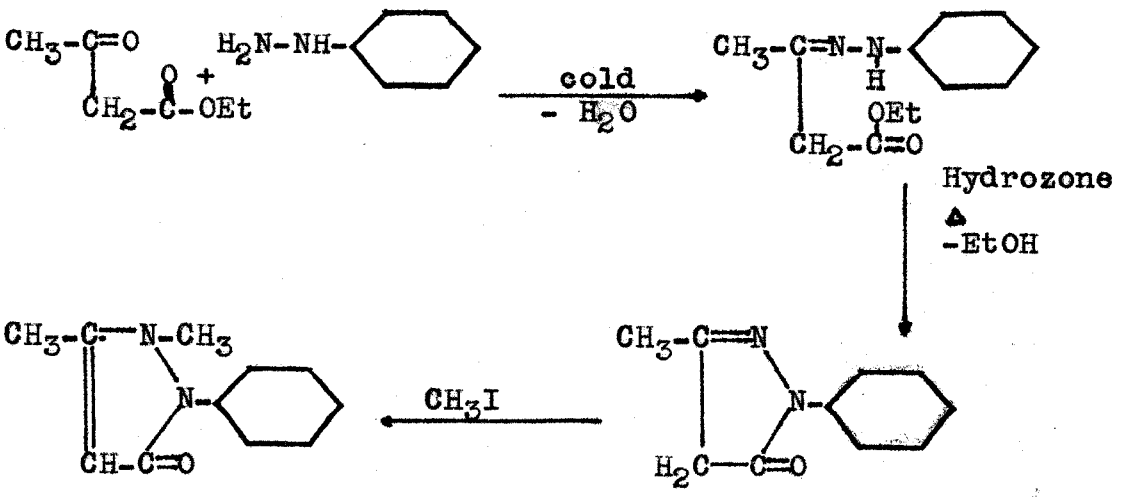
Until the latter part of the 19th century the only effective agent for the reduction of the body temperature of fevered patients was quinine. After Pelletier and Canentou had isolated quinine in 1820, it was many years before the constitution of this alkaloid was determined. However, it was known quite early that quinine yielded quinoline upon decomposition. It was found that quinoline itself has an antipyretic action, but could not be used as a drug, owing to

its toxic action. Efforts were therefore made to prepare non-toxic compounds to replace the then expensive quinine. Several compounds, derivatives of 6-methoxy-quinoline, were prepared and shown to possess antipyretic action, but were all too toxic for use.

This impetus towards the investigation of the quinoline group was given by König's synthesis of quinoline in 1879, which was followed in 1880 by Skraup's general synthesis. Following Fischer's discovery of phenylhydrazine, and its application to his famous indole synthesis,




Knorr, working in Fischer's laboratory, attempted to make a tetrahydro-quinoline derivative from phenylhydrazine and acetoacetic ester. The product of the reaction, however, was later shown by him to be a pyrazole derivative (1). The methyl derivative of this compound, produced with the intention of obtaining a substance resembling quinine, was a surprising success. Its trade name was Antipyrine. In the commercial process, phenylhydrazine was reacted with acetoacetic ester to form a hydrazone, which on heating lost the elements of alcohol, with the formation of phenyl-methyl-pyrazolone. This was then heated with methyl iodide and methyl alcohol at 100-150°C., to form antipyrine (2).



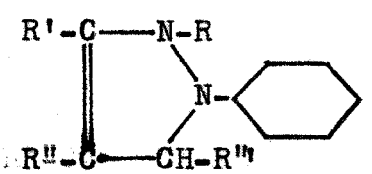

Phenyl-dimethyl-pyrazolone (Antipyrene)

Phenyl-methyl-pyrazolone

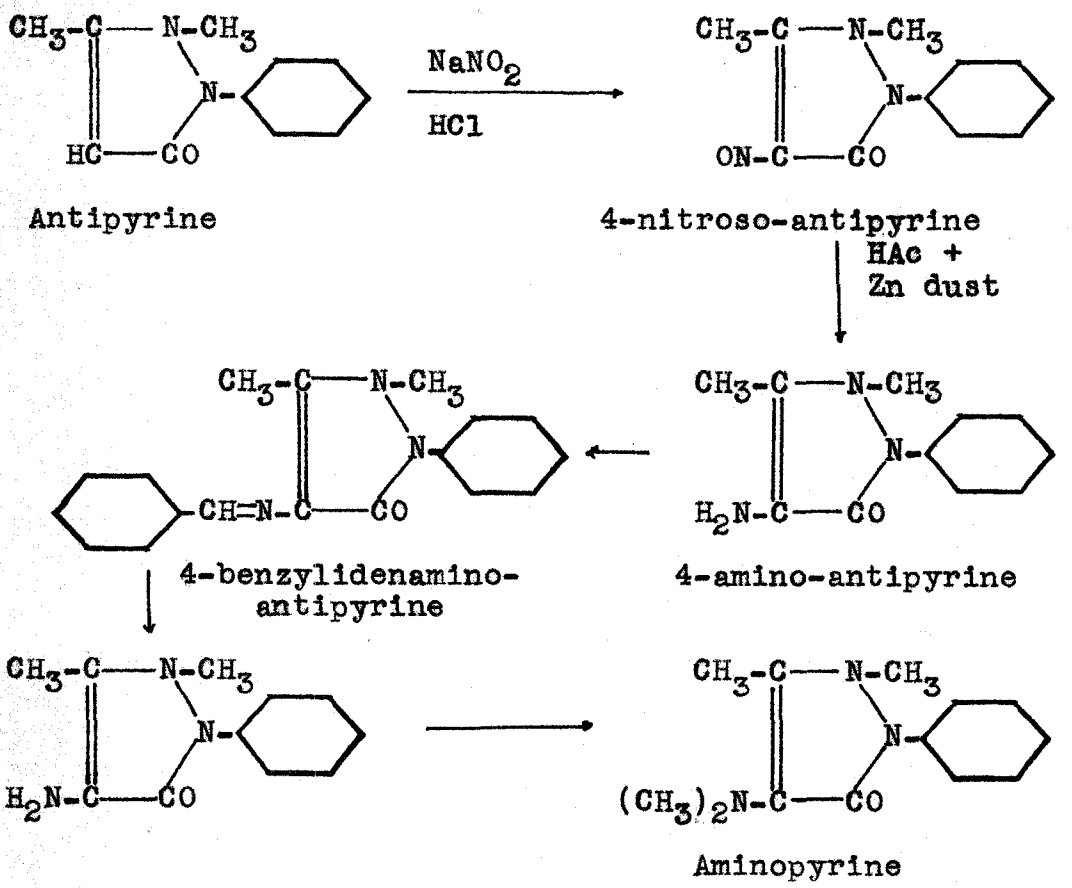
As might be expected, numerous variations of the above process are possible, and have been patented.

Antipyrene is a white, odorless, crystalline solid, m.p. 111-113, having a slightly bitter taste. It has a very strong antipyretic action, and is comparatively free from injurious effect on the haemoglobin. It also has a strong analgesic action, and is used widely in various analgesic mixtures sold to the public.

Many compounds related to antipyrene have been prepared by substituting different radicals for R, R', R", and R"', in the pyrazol ring:



Few of these, however, are of practical value. One of these, which has attained some commercial success, is Pyramidon or Aminopyrine (4-dimethylamino-antipyrine), first synthesized by Stoltz in 1893. It was prepared by treating an acid solution of antipyrine with sodium nitrite, to form the nitroso derivative. This in turn was reduced to the amine with zinc dust and acetic acid, purified by isolation as the benzylidene derivative, followed by hydrolysis with HCl, and the amino group methylated with methyl iodide or dimethyl sulfate.




Since the direct methylation of aminopyrine is difficult

and gives poor yields, many alternate methods have been worked out for alkylating the amino group.

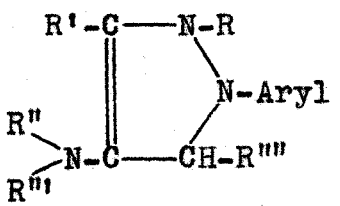
The two main systemic actions of aminopyrine and antipyrine are analgesia and antipyresis. In this respect they resemble the other common drugs of this nature (salicylates, acetanilid and acetophenetidin). In addition, antipyrine has some mild local anesthetic and antiseptic properties.

The mechanism of the antipyretic action of all of the common antipyretics is the same. They lower the body temperature of febrile patients only. The normal regulation of body heat requires a delicate balance between heat production and heat loss. The central nervous system, especially the hypothalamic nuclei, seems to play the dominant role in the regulation of body temperature, through its control of the peripheral mechanisms such as blood vessels or sweat glands which are concerned with the production and loss of body heat. The hypothalamus is thought to be the body's thermostat. In fevered patients, this thermostat is set at a higher level. Antipyretic drugs reset it at a lower level. As proof of this theory, it has been shown that high section of the spinal cord prevents the lowering of body temperature of fevered animals through the use of antipyretics.

The analgesic action of these drugs, however, is not as well understood. This action is attributed to a central depressant action located in the optic thalami. The fact that the site of action is not cortical is indicated by the

lack of mental disturbance, anesthesia, or changes in sensations other than pain sense, after the patient receives an analgesic dose of any of the common analgesics. The types of pain which are relieved by these drugs are headache, myalgia, arthralgia, and other pains arising from integumental structures rather than from the viscera. No local anesthesia of nerve endings is obtained with these drugs. None of these synthetic analgesics possess the analgesic action of morphine. Of the synthetic analgesics, Aminopyrine has the strongest action.

As was the case with Antipyrine, numerous compounds related to Aminopyrine have been prepared. These may be considered as derivatives of aminopyrine through substitution of different groups for the Aryl, R, R", R''', and R"", in the following formula:




None of these derivatives have proven superior to aminopyrine in clinical use.

Antipyrine is very extensively used. Although introduced as an antipyretic, it is used now more extensively as an analgesic. It is a constituent of many of the patent

medicines sold to the public (frequently under misleading trade names) for the relief of pain. Used in small amounts, it seldom causes any harmful reactions, except in a few allergic patients, in whom it causes a pigmentation of the skin (like birthmarks) similar to that seen with phenolphthalein (a widely used laxitive).

Aminopyrine is an effective antipyretic and analgesic, and was at one time widely used. Recently however, it has been suspected of causing the serious and often fatal disease known as agranulocytosis in patients who show a hypersusceptibility towards it. For this reason its use is largely restricted.

Following the success of antipyrine, many phenylhydrazine derivatives were prepared and tested. Most of these were without practical value due to their toxicity.

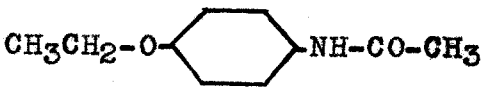
The discovery in 1886 by Cahn and Hepp that aniline and acetanilide have powerful antipyretic and analgesic properties opened a new field of investigation for cheaper antipyretics. It was found that while aniline and its salts were toxic in small doses because aniline destroys the hemoglobin forming methemoglobin, the introduction of an alkyl or acyl group in place of an amino-hydrogen, greatly reduced this toxicity.

Through the acetylation of aniline, acetanilide $C_6H_5NH\text{-}CO\text{-}CH_3$, is produced. It has marked antipyretic properties, and also acts as an analgesic. Although it is much less toxic than aniline, its physiological effect is

due to the slow liberation of aniline, and in time symptoms of aniline poisoning become apparent. It is only used now because of its cheapness. Other compounds related to acetanilide were tried. Their action varied directly with their ease of hydrolysis, since they all depended on the liberation of free aniline for their physiological effect. Acidic groups were also added to the molecule in an effort to obtain more soluble derivatives, but since the sparing solubility of acetanilide does not deter its therapeutic action, these attempts were valueless. Moreover, this is in line with the general pharmacological observation that acidic groups generally cause a compound to be inert.

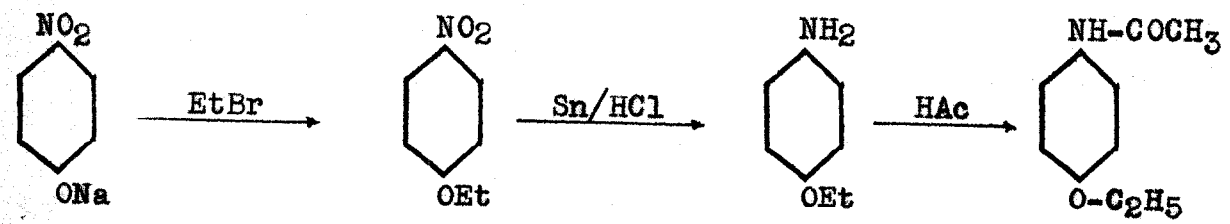
After the discovery by Schmiedeberg in 1878 that aniline and its simple derivatives were converted partially into p-aminophenol in the body, derivatives of this compound were prepared and tested for their antipyretic and analgesic action. Although p-aminophenol itself is less toxic than aniline, it is still harmful in moderate doses. This toxicity was reduced by the substitution of a hydrogen of the OH or $NH_2$ group--- the reduction being greater if the $NH_2$ group is substituted. This reduction of toxicity proved to be greater if the group substituted is alkyl -- less if acyl or aryl. If two H's are substituted, the reduction in toxicity is greater if the groups substituted are alkyl and acyl, than if both of these radicals are of the same type. The toxicity and therapeutic qualities were found to diminish with the increasing molecular

weight of the introduced group. The most useful derivative tested, from the standpoint of toxicity and therapeutic actinn was p-ethoxy-acetanilide




or Phenacetin as it is more commonly called. With larger groups, particularly aromatic groups, the compound became so resistant that the therapeutic action was reduced almost to nothing. The substitution of halogen atoms in the ring did not modify the antipyretic or toxic action of the original substance.

In the original synthesis of phenacetin, p-nitrophenol was converted to the sodium salt, treated with ethyl bromide, and the product reduced with tin and HCl. The para-phenetidine thus formed was then acetylated by boiling with glacial acetic acid.



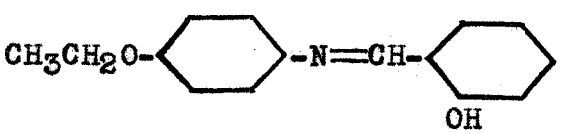

Many different procedures for the preparation of phenacetin are of course possible, and many of them have been patented. The most economical of these make use of by-products of the dye-stuffs industry.

The two chief systemic actions of acetanilide and phenacetin are antipyresis and analgesia. In these actions they differ little from the other drugs of this nature such as antipyrine and aminopyrine. Acetanilide and phenacetin are the only two aniline derivatives which have survived the past 50 years of clinical trial, and are second only to the less toxic salicylates in popularity.

Poisonings due to the aniline derivatives usually result from the medical misuse of these drugs, such as the indiscriminate self-administration of proprietary drug mixtures (usually headache powders) by the laity. Poisoning may be acute or chronic and death may result from either. In either case, the symptoms are those due to aniline poisoning, such as cyanosis (due to alterations of hemoglobin to methemoglobin and sulfhemoglobin), anemia, weakness, skin reactions, collapse and coma.

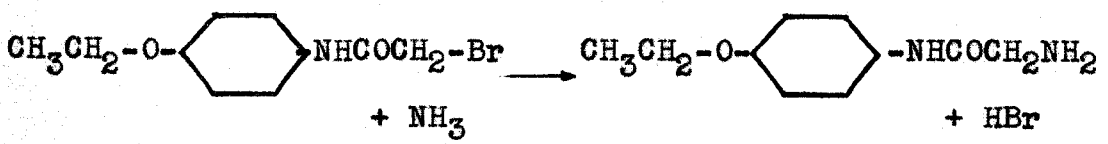
The phenyl-urethanes have been tested for their pharmacological action. Most of them showed some feeble but uncertain antipyretic action, and the lack of any hypnotic effect.

Among other derivatives of phenetidine are several condensation products with aldehydes, such as salicyl-aldehyde:




None of these have met with any clinical success.

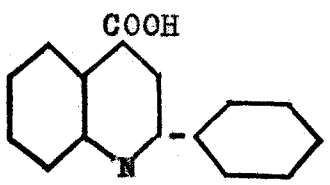
A soluble derivative of phenacetin was first prepared by Schmide and Majert in 1890, by the action of ammonia on brom-acetyl phenetidine:




The amino-phenacetin is known as Phenocoll. Its salts are soluble in water, and consequently its actions appear promptly but disappear rapidly also. Its salt with salicylic acid (insoluble) is reported to be stongly antipyretic and analgesic.

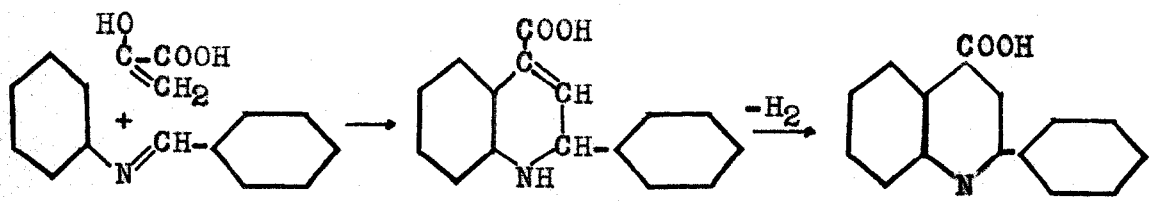
Several phenetidine derivatives have been prepared in which the hydrogen of the hydroxyl group has been replaced by more complex groups, but none of these appears to have had much clinical success.

Since 1900 several quinoline derivatives have been introduced for the treatment of gout, neuralgia of the sciatic nerve, and for urinary antisepsis. They also have antipyretic and analgesic actions similar to the other drugs of that nature. The simplest of these derivatives is Cinchopen, or

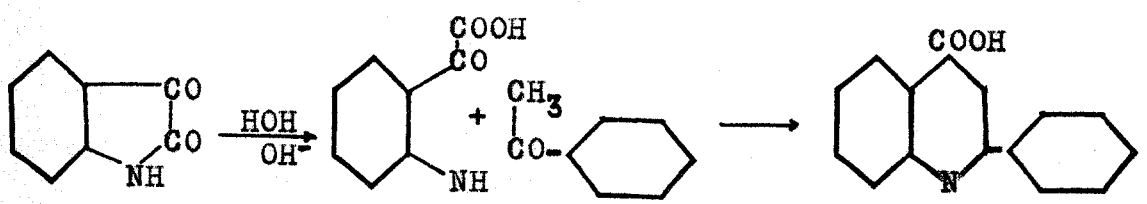



2-phenyl-quinoline-4-carboxylic acid

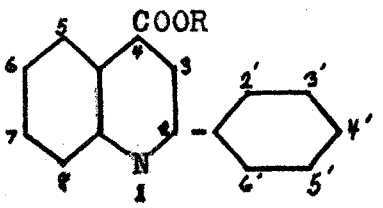
This compound was synthesized in 1887 by Doebner and Giesecke (3) through the condensation of o-amino benzaldehyde with acetophenone; although a better method is to heat benzylidene-aniline with pyruvic acid, and dehydrogenate the product to cinchopen:



One commercial process (4) makes use of isatin (from the dyestuffs industry) by condensing this compound with aceto-phenone in strongly alkaline solution, to form cinchopen directly:



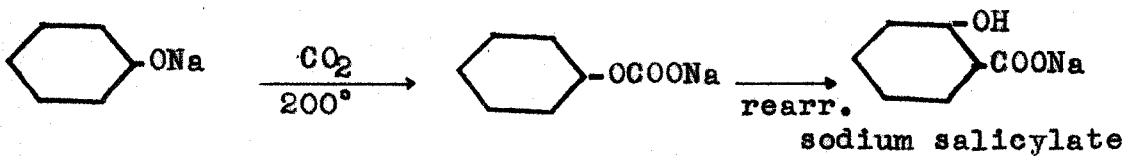
Due to its acid character and bitter taste, cinchopen is usually converted into its sodium salt before administration, in order to avoid gastric disturbance. Its ethyl ester -- Neocinchopen -- is non-irritating, while possessing the same properties as cinchopen. Many cinchopen-type compounds have been patented:




as well as various fused-ring compounds, but none of these has any advantage over cinchopen or neocinchopen.

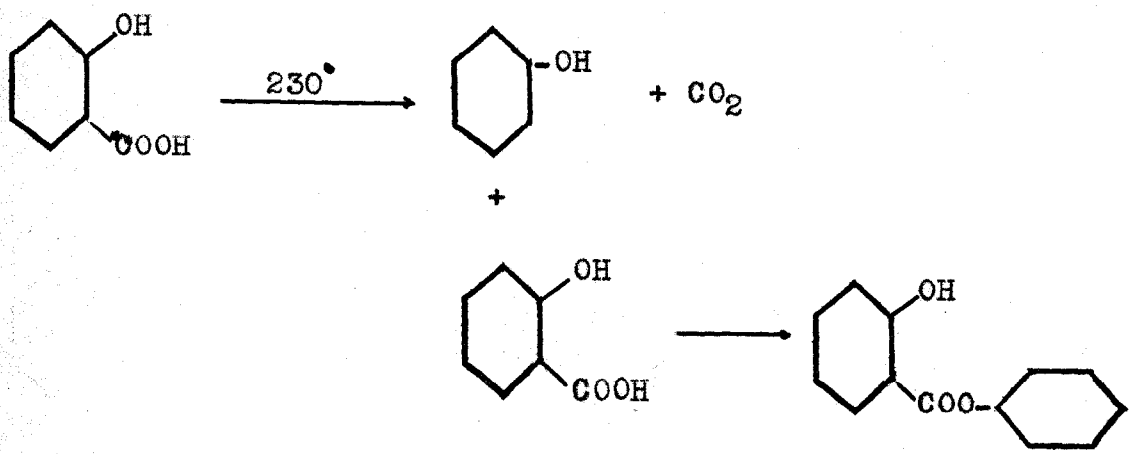
In spite of the useful pharmacological properties possessed by cinchopen, it causes severe toxic reactions in certain individuals. Under certain conditions it causes a toxic cirrhosis of the liver which is usually fatal. Since it is a constituant of dozens of proprietary drug mixtures, the indiscriminate use of these drugs for the symptomatic treatment of gout is dangerous.

The use of the salicylates for the relief of fevers dates from ancient times. The usual form was an extract of willow bark, (of the genus Salix) which contained the bitter glucoside, salicin ($C_{13}H_{18}O_7$) which on hydrolysis yielded dextrose and saligenin, or salicyl alcohol. Sodium salicylate was first introduced into clinical therapeutics by Buss in 1875, who used it on patients suffering from typhoid, tuberculosis, diphtheria and rheumatic fever. Salicylic acid had been first synthesized by Kolbe and Lautemann (5), by the action of carbon dioxide on phenol in the presence of sodium:



Salicylic acid is so irritating that it can only be used externally and therefore various derivatives of this acid have been synthesized for systemic use. These are grouped into two large classes; those which are esters of salicylic acid through substitution of the H in the carboxyl group, and those which are salicylate esters of organic acids in which the carboxyl group of salicylic acid is retained and substitution is made in the OH group.

Phenyl salicylate (Salol) introduced by Nencki in 1886, was the first synthetic organic ester made up of two physiologically active components to be used in medicine. It was prepared by heating salicylic acid to 230°, whereupon $CO_2$ was eliminated and the resulting phenol condensed with the remaining salicylic acid:




Nencki's idea was to convert substances (phenol in the case of salol) which were too toxic for ordinary use into esters from which the active component is liberated so slowly that

it produced no injurious side reactions. Salol, introduced as an intestinal antiseptic, has not proven as effective as was anticipated. It is often excreted unchanged. Moreover, decomposition in the intestines is so slow and incomplete, and the absorption of the phenol liberated is so rapid that effective germicidal concentrations are not established. It has proven of value, however, as an enteric coating for pills. In spite of the failure of salol itself, Nencki's "Salol principle" has proved of value in the preparation of many new medicinals, as for example, the aniline derivatives mentioned earlier.

Due to the gastric irritation and unpleasant taste of salicylic acid and its simple salts, less soluble derivatives, e.g., esters, have been introduced. It was believed that these compounds would pass through the stomach unchanged, and thus avoid the nausea caused by salicylic acid. While it was found that they did pass through the stomach largely unchanged, the nausea, probably of central origin, remained.

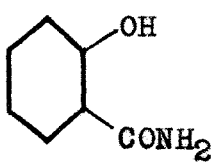
Acetyl salicylic acid, introduced into therapy by Dreser in 1899, is prepared by the acetylation of salicylic acid with acetic anhydride. It is perhaps the most widely used analgesic and antipyretic at the present time, and is sold under the name Aspirin. Its calcium salt is soluble in water.

Derivatives of salicylic acid with dibasic acids such as succinic acid (Diaspirin), anhydromethylene citric acid (Novaspirin) have been introduced. In general they act exactly

like aspirin. Diplosal is the salicyl ester of salicylic acid, prepared by treating salicylic acid with phosgene, phosphorus trichloride, or thionyl chloride. It behaves qualitatively like salicylic acid.

Compounds formed by the replacement of the hydrogen in the carboxyl group of salicylic acid are more readily absorbed from the skin and are better for external use (counter-irritants) than is salicylic acid itself. These include methyl salicylate (Oil of Wintergreen), as well as esters of other alcohol such as; ethyl alcohol, ethylene glycol, methoxy-methyl alcohol, and many others.

Another type of salicylic acid derivative comprises those in which it is combined with basic radicles. Salicyl-amide




is more soluble than salicylic acid, and has a more marked analgesic action. Many compounds have been prepared in which salicylic acid is combined with substances having anti-pyretic and analgesic properties, such as aniline and aniline derivatives.

From the observation of the physiological action of the various salicylates, it is possible to make several generalities.

The characteristic actions of the various derivatives are due to their salicylic acid content. The variations in the solubility and tendency to cause local irritation are the main factors which determine the degree of usefulness of these compounds. The ortho-position of the OH group seems to be essential for the typical action of salicylic acid; this action being absent in the meta and para-hydroxy benzoic acids. The toxicity of salicylate acid derivatives and their therapeutic potency depends to a large extent on the amount of salicylic acid liberated in the body, and the rate at which it is liberated. This depends to a great extent on the solubility and stability of the compound.

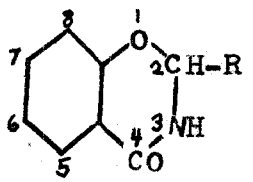
The salicylates in general show some bacteriostatic action against moulds and fungi, and some (salicylic acid in particular) are quite irritating to the skin and mucosa. In general, however, they are quite safe to use. They are used commonly as antipyretics or analgesics, and in the symptomatic treatment of rheumatic fever. They are absorbed readily from the gastro-intestinal track, including the rectum, and other Mucosal surfaces of the body, and shortly after absorption, can be found in nearly every tissue and fluid of the body. The wide use of salicylates in medicine and their indiscriminate employment by the laity for every ailment has been the cause of numerous cases of toxic reactions. Fortunately, most of these were mild. Moreover the toxic reactions which do appear, generally go away when medication ceases. In this respect the salicylates are far safer than any of the other analgesics and antipyretics previously discussed.

# PART II

## DISCUSSION

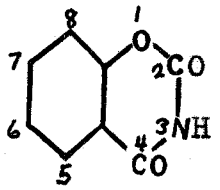
As has been pointed out earlier, salicylamide, while possessing a stronger analgesic action than salicylic acid, is not used in medicine due to the gastric distress which it causes. This may be due in part to its possessing a greater solubility than salicylic acid. The author, therefore, thought it worthwhile preparing a series of derivatives of salicylamide which were more insoluble, and which would decompose slowly with the liberation of salicylamide.

Two series of compounds were chosen, each containing a benzene ring and a heterocyclic ring containing carbon, oxygen, and nitrogen. The first of these, the dihydrobenzoxazones:




are prepared through the condensation of salicylamide with an aldehyde, are in general, white, crystalline solids which are insoluble in water.

The second series of compounds were derivatives of O,N-carbonyl salicylamide;



in which the hydrogen of the NH-group was to be replaced by various groups.

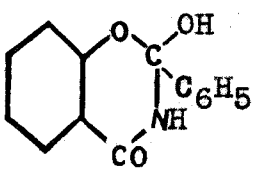
## THE BENZOXAZONES

Most of the early work on benzoxazones was done in researches on the labile isomerism among the acyl derivatives of salicylamide.

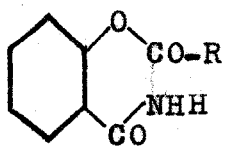
Titherley and Hicks (6) found that during the benzoylation of salicylamide, two mono-benzoyl derivatives were produced. One of them, the O-benzoyl salicylamide (m.p. 144°) is labile and is readily converted into the other, a stable compound melting at 208°, which was identical with the product obtained by Gerhardt and Chiozza (7) by heating benzoyl chloride and salicylamide.

Awers (8) regarded Gerhardt's salicylamide as the N-benzoyl derivative, and held that the isomeric change observed by Titherley and Hicks involved the transport of the benzoyl group. He cited some work which he had done on the acyl derivatives of salicylamide, the O-acetyl derivative of which immediately passes into the N-acetyl isomer due to its instability.

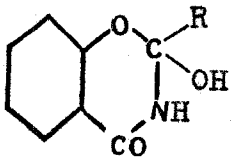
McConnan and Titherley (9) however, demonstrated that the simple N-benzoyl formula could not be accepted, and that acyl salicylamides in general exhibit remarkable labile isomerism. It was demonstrated that Gerhardt's benzoyl salicylamide is tautomeric, and can behave as if the benzoyl were attached to both N and O. In order to account for the conflicting evidence as to the constitution of Gerhardt's benzoylsalicylamide and acyl salicylamides in general, they put forth the hypothesis of cyclic tautomerism, in which the alternate tautomeric forms are an open chain and a ring. Gerhardt's compound by this hypothesis was represented as the ring derivative:



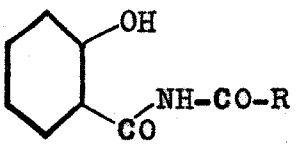

They assumed that among the labile O-acyl salicylamides that the CO of the acyl group reacts with the hydrogen of the $CONH_2$ group forming a cyclic hydroxy-derivative which may be tautomeric. A compound results which if stable remains as such (B), or if unstable may undergo one of two changes: 1. the hydroxyl hydrogen may wander back to the nitrogen atom (giving A), or 2. may wander to the phenolic oxygen atom (giving rise to C):




(A)

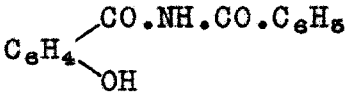



(B)

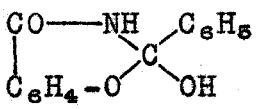


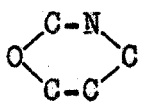

(C)

Varying degrees of stability of types A, B, and C might be expected, according to the nature of R, and according to whether the residual H of the NH-group is further substituted. Taking mono-benzoyl salicylamide as an example; form A exists as a labile compound (m.p. 144°) which, stable at 15°, passes on heating or in ionizing solvents easily into B or C, forming a stable derivative (m.p. 208°) which is tautomeric and may equally well possess the open chain




or the closed chain formula




Since the ring  was at the time known as the metoxazone ring, they called this type of tautomerism "Metoxazone Tautomerism," and by it explained the ease of mobility of the acyl groups in salicylamide derivatives. It may be observed in passing that the alkyl derivatives, unlike the acyl derivatives, are stable.

This scheme of reversible change involved ring production in one of its tautomeric forms, and is thus analogous to lactone tautomerism which is shown by certain di-aldehydes such as succinaldehyde and phthalaldehyde.

In order to prove his hypothesis of "Metoxazone Tautomerism", Titherley (10) attempted to prepare the cyclic hydroxy-derivative by oxidizing phenyl-benzometoxazone (as it was then called). In this research, he not only studied the preparation of phenyl-benzometoxazone by the condensation of salicylamide with benzaldehyde, but he also elucidated this reaction mechanism, and reported many of its reactions.

The condensation of amides with aldehydes was first studied by Roth (11), who attempted to prepare the amide of cinnamic acid by heating acetamide with benzaldehyde. The product was benzylidenediacetamide:

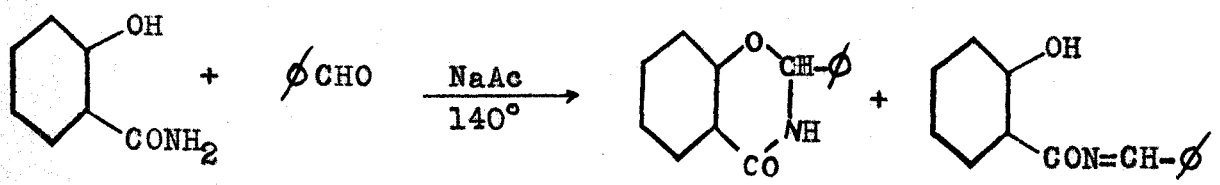
$$C_6H_5\text{-}CH(NH\text{-}CO\text{-}CH_3)_2$$

Similar compounds have since been prepared by the condensation of aryl and alkyl aldehydes with amides of monobasic acids by Schuster (12), and Hoffmann and Meyer (13) to mention only a few. In each case, the reactions proved to be of the type:

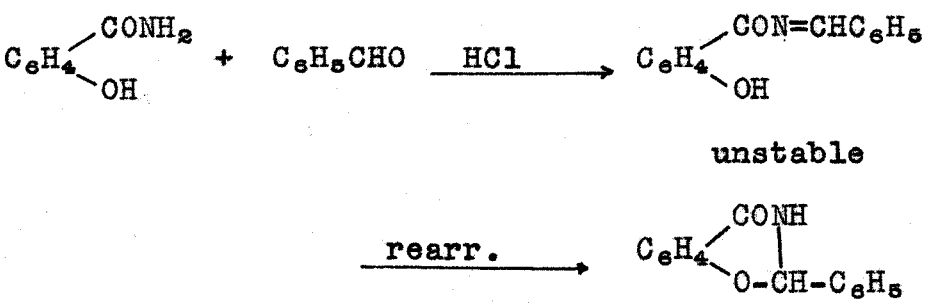
$$RCH{=}O + \begin{matrix} H\text{-}NH\text{-}COR' \\ H\text{-}NH\text{-}COR' \end{matrix} \longrightarrow RCH\begin{matrix} NHCOR' \\ NHCOR' \end{matrix} + HOH$$

The condensation of formaldehyde with amides gave N-methylol compounds $R\text{-}CO\text{-}NH\text{-}CH_2OH$ (Einhorn (14)), from which methylene compounds could be obtained by further action of amides $CH_2{:}(NH\text{-}CO\text{-}R)_2$ .

Cebrian (15) attempted to condense benzaldehyde with salicylamide using sodium acetate as the condensing agent, and obtained two products; one of which was insoluble in alkali and gave no ferric chloride reaction, and the other, the quantity of which varied with the conditions of the experiment, was soluble in alkali and gave a positive ferric chloride reaction



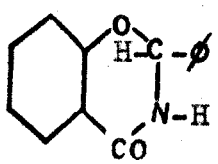

Titherley (10) attempted the same reaction, but used alcoholic HCl instead of sodium acetate as condensing agent, and also ran his reaction at 60°. The only product obtained in this case was the compound which was insoluble in alkali, and which gave no ferric chloride test. He put forth the following mechanism to explain the observed reaction:



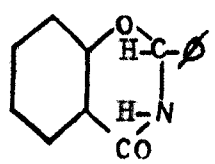

There might be an alternate mechanism. The metoxazone

might be formed first and rearrange to the benzylidene form. However, if the metoxazone was formed first, N-methyl salicylamide should react to give a metoxazone, but since it does not, this mechanism is ruled out. Also phenyl benzometoxazone shows no tendency to rearrange to benzylidene salicylamide.

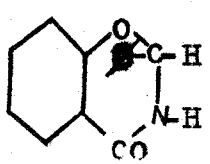
The free synthetic benzylidene compound obtained by Cebrian is stable to HCl and sodium acetate, but the compound obtained by the rearrangement of the metoxazone (with pyridine and KOH), can be recycalized on melting or heating with certain solvents. The existence of the two compounds is intelligible on the assumption that they are geometric isomerides (like the oximes). One is amorphous and cannot be recrystallized, while the other can be obtained in a crystalline form. On the assumption that the syn form is obtained from the cyclic compound, the stable form is called the anti form. Also, since the metoxazone has an asymmetric carbon atom as well as an asymmetric nitrogen (Werner-Hantzsch theory), two pairs of enantiomorphs are possible:



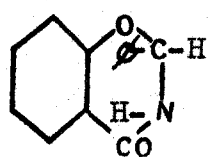
d-syn



l-syn



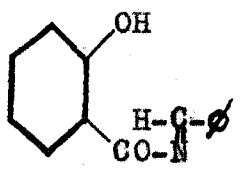
d-anti



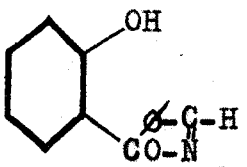
l-anti

However, only one inactive compound is known (m.p. 169°).

The difference in stability between the two isomeric benzylidenes:



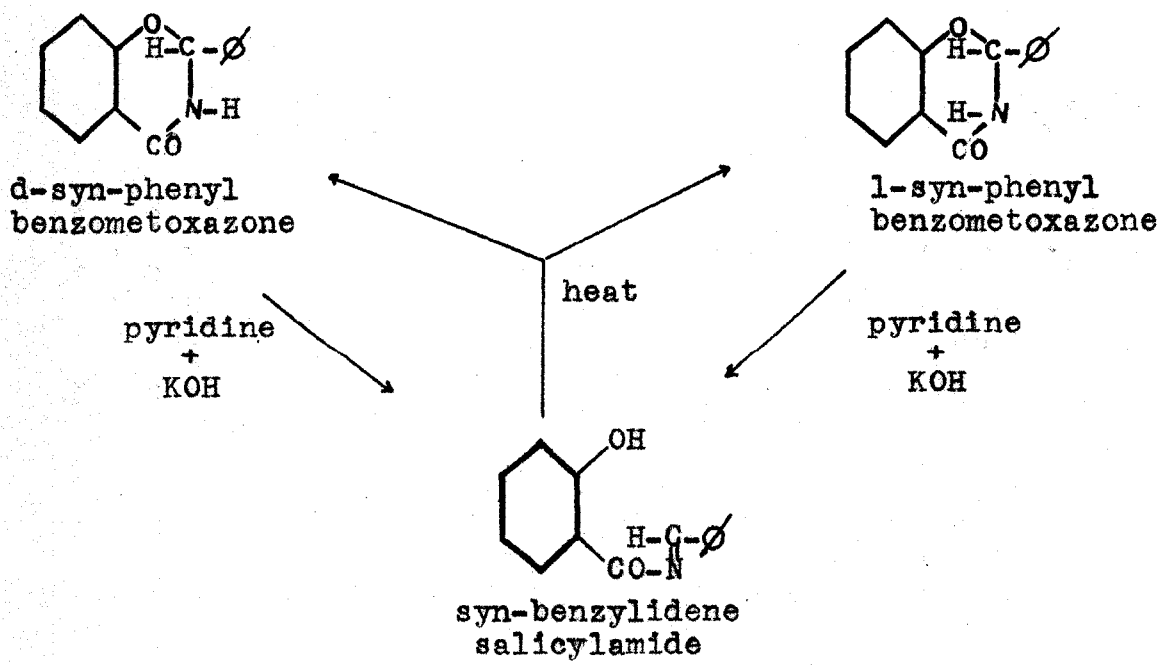
I



II

is explained on the grounds of "steric hindrance" exercised by the large phenyl group which prevents rearrangement in II. (I) is therefore syn and the phenyl benzometoxazone is d & l syn (configuration A).

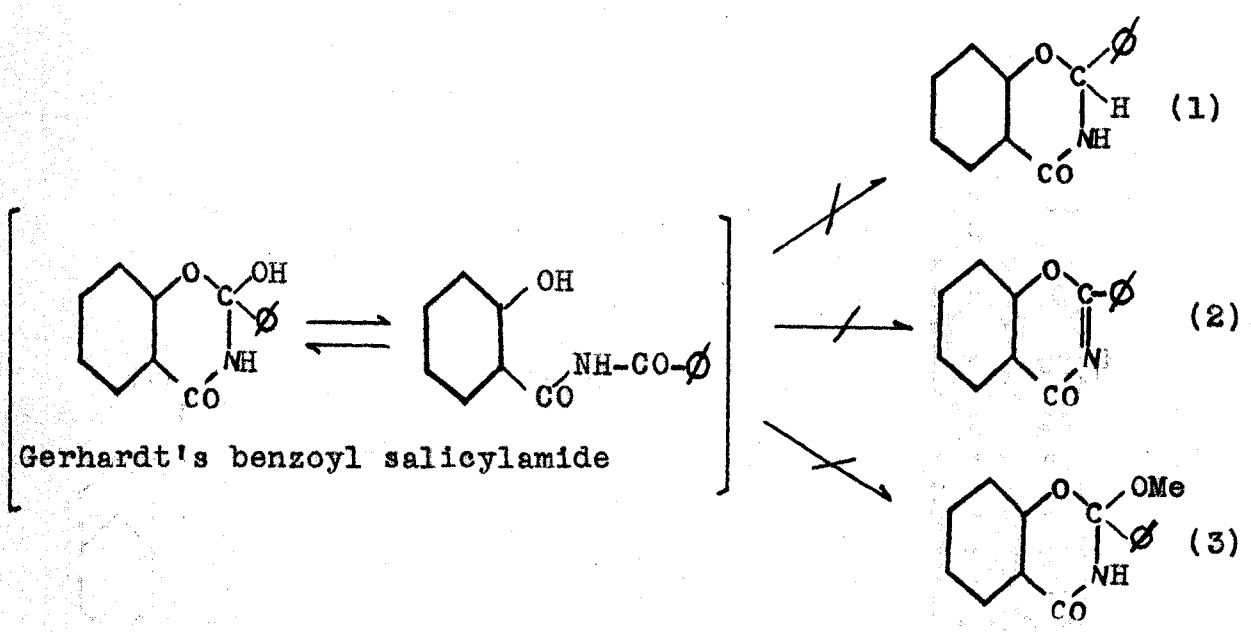
The preceeding reactions may be summarized as follows:



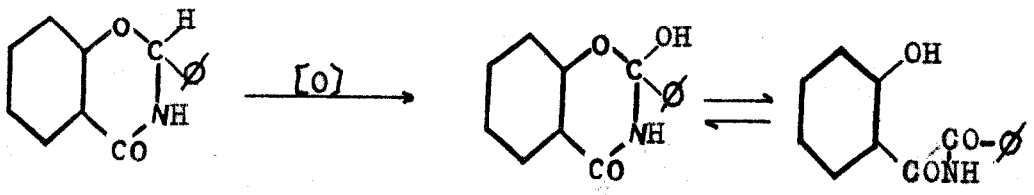
Salicylamide + benzaldehyde

- HCl → only syn-benzylidene salicylamide produced
- NaAc at higher temperatures → syn+anti-benzylidene salicylamide produced

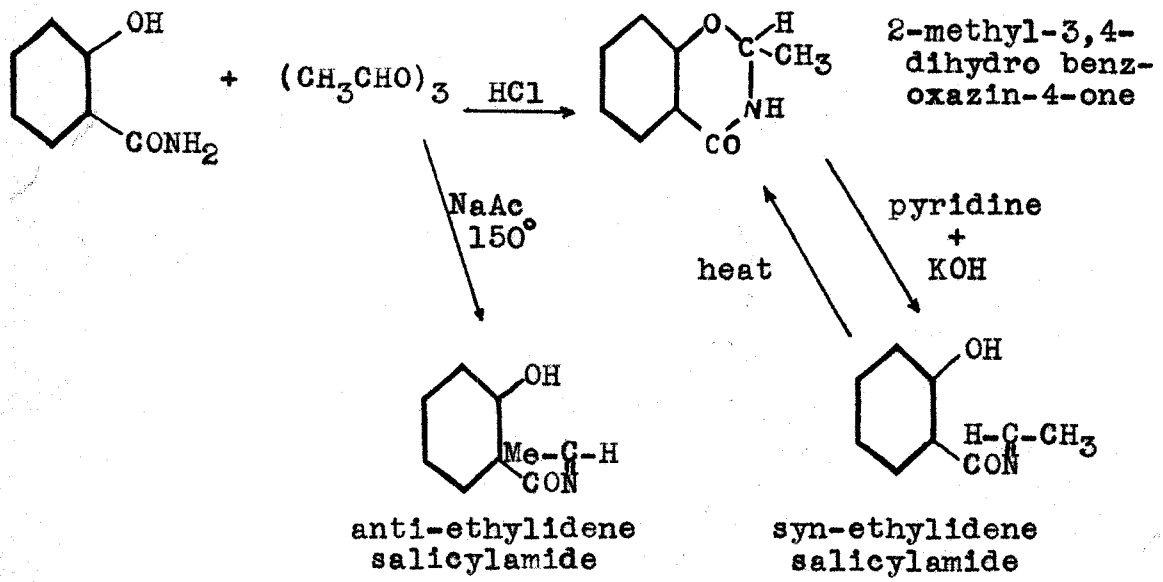
Titherley also found that N-benzoyl salicylamide (Gerhardt's salicylamide) could not be (1) reduced to phenyl benzometoxazone, (2) dehydrated, or (3) methylated to methoxyphenyl benzometoxazone:



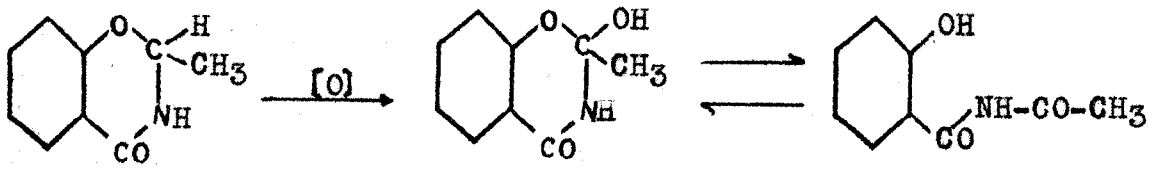

However by dissolving phenyl benzometoxazone in cold concentrated sulfuric acid and oxidizing it with an acetic acid solution of chromic acid, Titherley was able to obtain a good yield of N-benzoyl salicylamide, thus substantiating his theory of "Metoxazone Tautomerism:"



Later work has confirmed rather than disproved Titherley's theory. Hicks (16) investigated the 2-methyl benzoxazone (note name change) in connection with the problem of the tautomerism and labile isomerism of the acetyl salicylamides. He prepared this derivative through the reaction of salicylamide with paraldehyde in the presence of HCl, and from it prepared the syn-ethylidene salicylamide by treating it with pyridine and concentrated alkali. Hicks also prepared the anti-ethylidene salicylamide by heating paraldehyde with salicylamide in the presence of sodium acetate at 150° in a sealed tube.

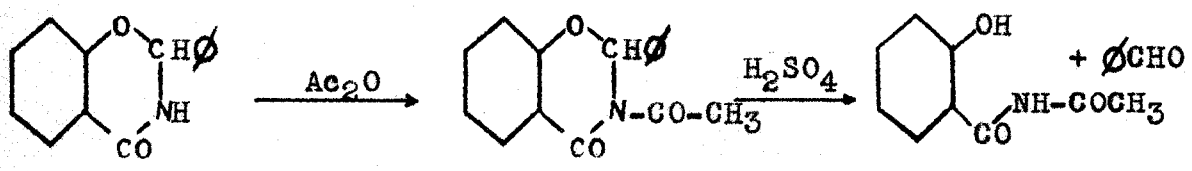


Hicks was able to oxidize the methyl-derivative to N-acetyl salicylamide, thus proving the relationship between these two compounds.




More recently still, Moucka and Rögl (17) prepared the i-propyl and the i-butyl derivatives and carried them through the above reactions, obtaining the syn and anti-derivatives and the corresponding acyl derivatives of salicylamide.

The 2-phenyl dihydrobenzoxazone which had been prepared by Titherley was also investigated by Keane and Nicholls (18). They were able to prepare the acetyl derivative by treating the compound with acetic anhydride. By treating this compound with concentrated sulfuric acid, they were able to decompose it into N-acetyl salicylamide:

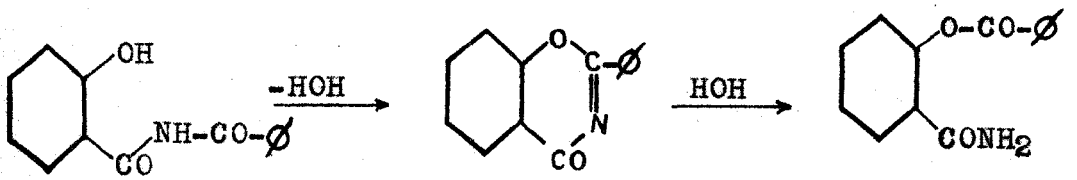



I II III

They also found that by heating phenyl-benzoxazone (I) with

water over a long period of time, it would be decomposed into its constituents (benzaldehyde + salicylamide). In the presence of acid, this decomposition was speeded up, while alkaline hydrolysis proved to be most rapid of all. On heating (I) with aniline, it decomposes with the formation of benzylidene-aniline and salicylamide.

In his criticism of the metoxazone theory of labile isomerism, Auwers (19) attributed the change of N-benzoyl salicylamide I, to O-benzoyl salicylamide III, (by boiling in acetic acid) to the intermediate formation of the unsaturated ring II, by loss of water, which then immediately decomposed this hypothetical ring, yielding the O-benzoyl derivative:

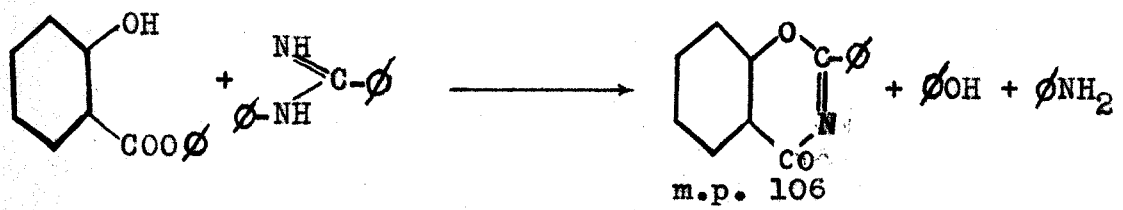



I II III

In order to test the validity of Auwers' contention, Titherley (20) attempted to prepare this unsaturated derivative in order to compare its properties with those which Auwers had attributed to his hypothetical compound.

Titherley first attempted to prepare this ring from phenyl-dihydrobenzoxazone by eliminating two atoms of hydrogen, but this was not successful. He then tried to remove a molecule of water from O and from N-benzoyl salicylamide using

phosphoric oxide and zinc chloride, but both of these attempts were unsuccessful. He was, however, successful when he reacted phenyl salicylate with phenyl benzamidine.

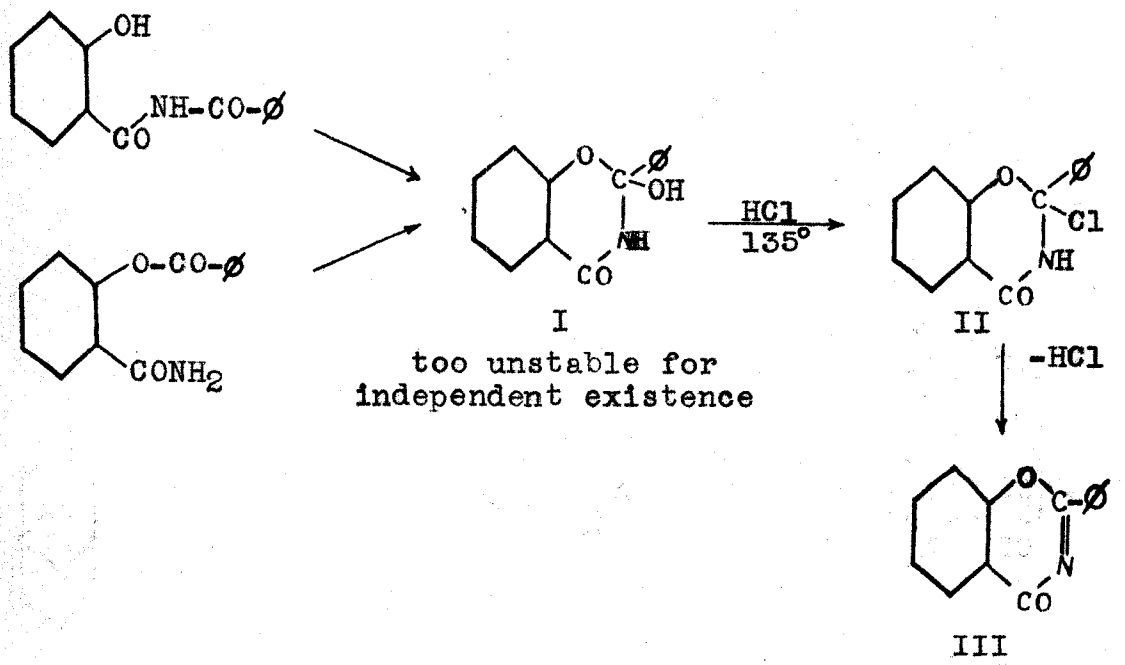



m.p. 106

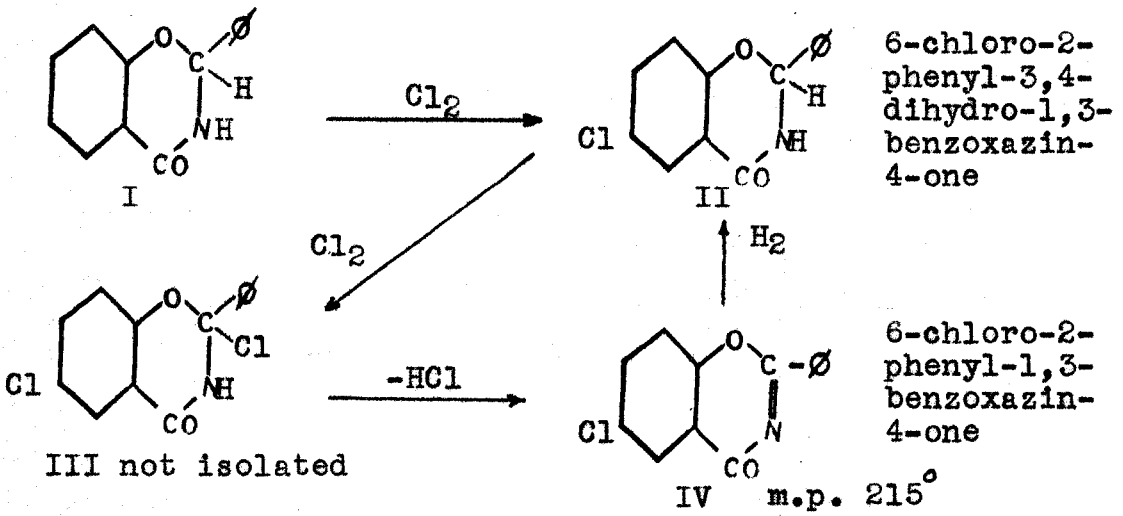
Titherley found the compound to be markedly additive in its properties. In the presence of pure water or dilute alkalies, it was unaffected, but in the presence of hydrogen ions, it rapidly added one molecule of water, yielding N-benzoyl salicylamide quantitatively. This effectively disposed of Auwers' contention which involved a hydrolytic rupture at the double bond. Moreover, the rupture of the unsaturated ring between the O and C atoms was discounted due to the stability of the ringin the presence of hydroxyl ions which would favor such a rupture. Titherley thus proved that the mechanism of the isomeric changes observed in acyl salicylamides did not involve the intermediate formation of such an unsaturated ring.

In further investigations of this same unsaturated compound, Titherley found that it could be made in good yield from either N or O-benzoyl salicylamide by boiling it in toluene or anisole (with an arrangement for the removal

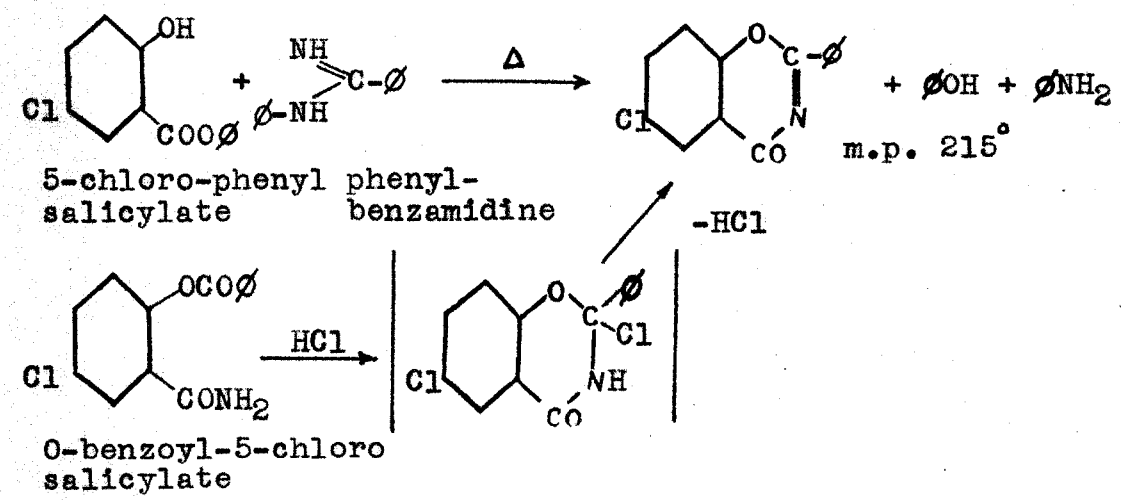
of water) in the presence of HCl -- the proportion of which could be varied greatly. He attributed the loss of water not to a direct dehydration but to the intermediate formation of a chloro-compound:




In further investigations of this same reaction, Titherley and Hughes (21) attempted to obtain 2-chloro-2-phenyl-3,4-dihydro-1,3-benzoxazin-4-one (II), through the chlorination of 2-phenyl-dihydrobenzoxazone, but instead, obtained 6-chloro-2-phenyl-dihydrobenzoxazone, which on further chlorination yielded 6-chloro-2-phenyl-1,3-benzoxazin-4-one, through loss of HCl:



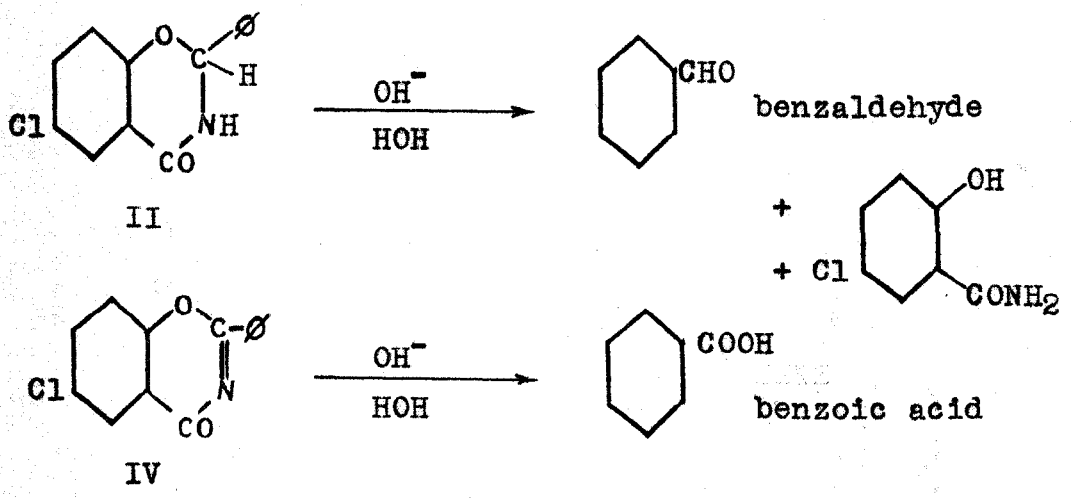

(II) was proven by synthesis from 5-chloro-salicylamide and benzaldehyde, using HCl as a catalyst. (IV) was prepared by two methods, thus proving its structure:




They were also able to reduce IV to II, using hydrogen and a platinum catalyst. This was to be expected in view of

the additive properties of compounds of that type, which had been the subject of one of Titherley's earlier investigations.

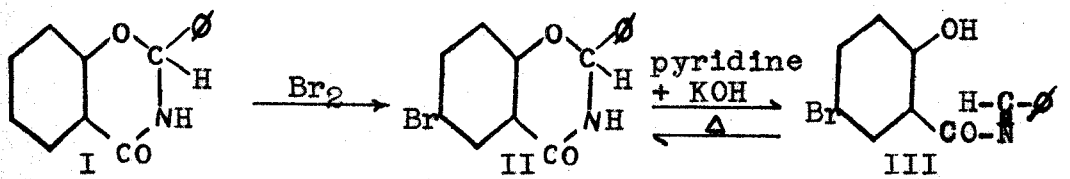
Titherley and Hughes found that II on alkaline hydrolysis yielded benzaldehyde, while IV under the same circumstances yielded benzoic acid:




Also in line with their earlier work, Titherley and Hughes found that IV would add water in the presence of hydrogen ions to form the 2-hydroxy derivative, which in turn would rearrange to N-benzoyl-5-chloro salicylamide.

Later, Hughes and Titherley (22) attempted to carry out these same reactions using bromine instead of chlorine. They found that while one atom of bromine could easily be substituted into the benzene ring of the phenyl-benzoxazone, it was impossible to form the intermediate 2-bromo derivative through the substitution of the hydrogen atom on the 2-carbon, as had been the case when they used chlorine in their earlier

investigation. By treating this bromo-derivative with pyridine and KOH, they were able to prepare the syn-benzylidene bromosalicylamide, which on heating was reconverted to the bromobenzoxazone:



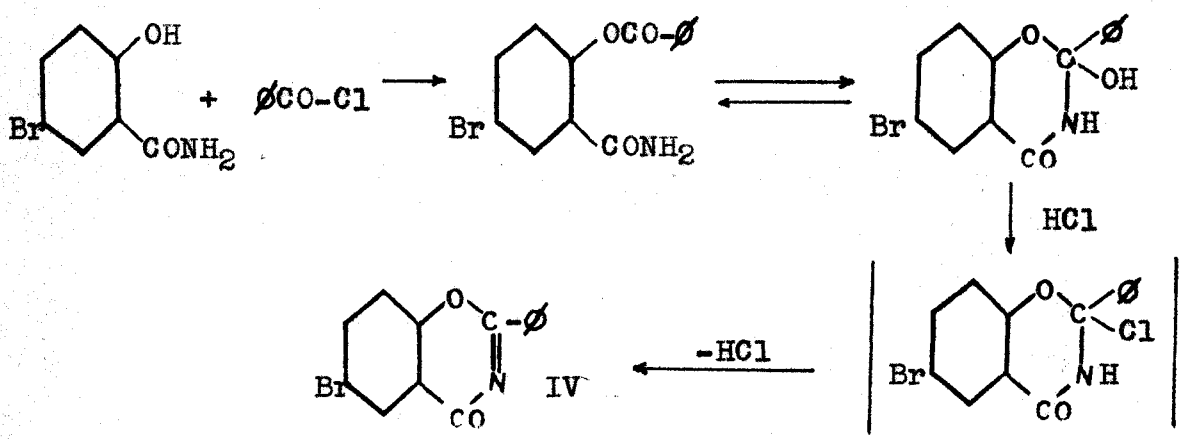

I 2-phenyl-3,4-dihydro-1,3-benzoxazin-4-one

II 6-bromo-2-phenyl-3,4-dihydro-1,3-benzoxazin-4-one

III syn-benzylidene-5-bromo-salicylamide

They were able to prove the identity of II by its independent synthesis from 5-bromo salicylamide and benzaldehyde, using HCl as a catalyst.

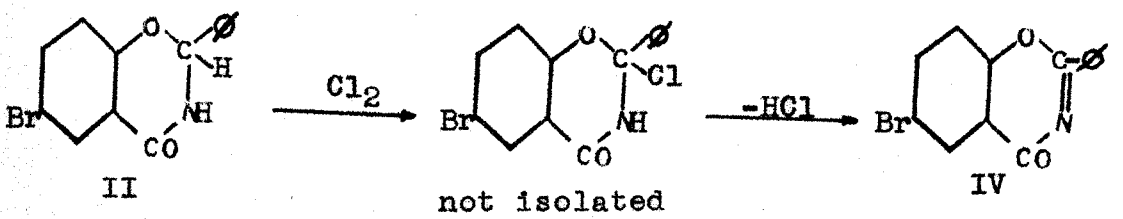
By treating 5-bromo salicylamide with benzoyl chloride at low temperature, they were able to obtain O-benzoyl-5-bromo salicylamide, from which they were able to remove a molecule of water, by heating it at a high temperature in the presence of HCl, using a solvent which was immicible with water:




IV

(IV) was found to take up a molecule of water in the presence of acid (as did its analogues) to form the N-benzoyl derivative.

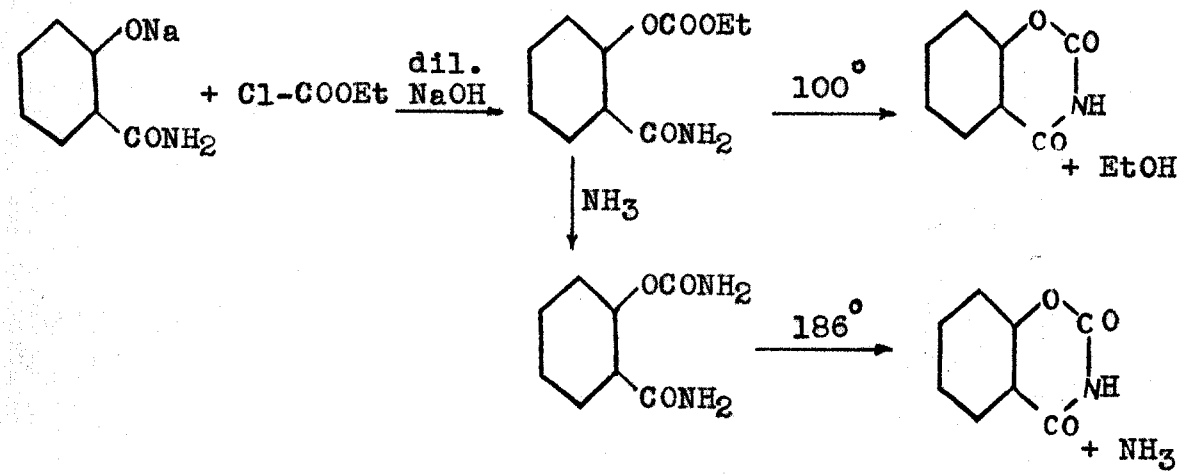
They were able to prepare IV from II by reacting it with chlorine. As before, an unstable intermediate was formed which was converted into IV through the loss of HCl:



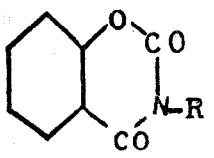

II not isolated IV

## DERIVATIVES OF O,N-CARBONYL SALICYLAMIDE

The preparation of O,N-carbonyl salicylamide was first reported by Bogisch (23). He found that similar to sodium phenolate, sodium salicylamide when reacted with ethyl-chloroformate gave a carbonic ester which when treated with ammonia is converted into carbamic salicylamide. Both the amide and the ester on heating will give the condensation product, carbonyl salicylamide; the former at 186° with splitting off of ammonia, and the latter at 100°, with the splitting off of alcohol:

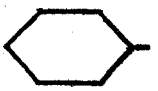



He found the hydrogen of the imido group sufficiently acidic to allow it to be easily replaced by metals. The potassium salt was used in the preparation of various derivatives, such as:

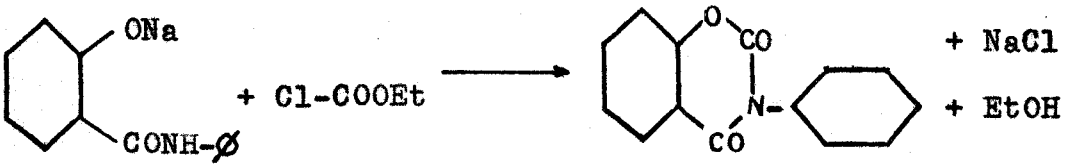


Where R is:

| | |
|---|---|
| $CH_3CO-$ | $-CH_2COOH$ |
| $CH_3CH_2-$ | $-CH_2CONH_2$ |
| $C_6H_5-CH_2-$ | $-CH_2COOEt$ |

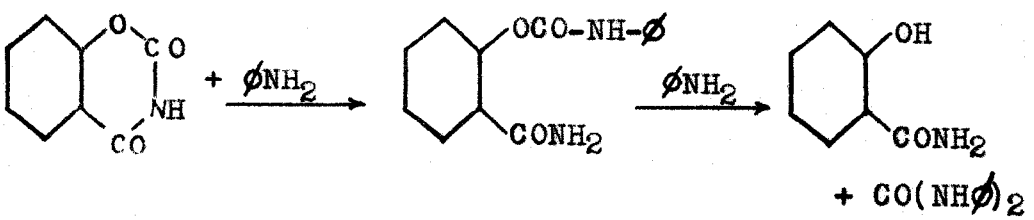


The reactions were usually carried out by heating the salt of carbonyl salicylamide with the alkyl, or acyl halide in a sealed tube to 150°. The N-phenyl derivative, however, was prepared from salicylanilide and ethyl chloroformate in dilute NaOH solution:

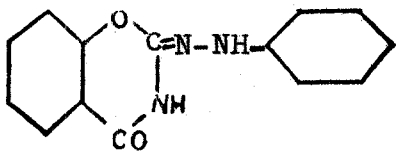



He found that the N-substituted carbonyl salicylamides could be decomposed to the N-substituted salicylamides on heating with ammonia. It is thus evident that these compounds can be used in the preparation of pure primary amines, as is Gabriel's phthalimide synthesis.

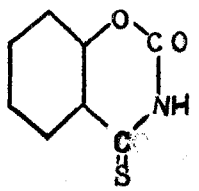
On long heating with aniline, carbonyl salicylamide is decomposed into salicylamide and diphenyl urea, phenylcarbamic salicylamide being formed as an intermediate product:




With phenylhydrazine, carbonyl salicylamide gives a phenylhydrazone:




When heated with $P_2S_5$ to 175°, carbonyl salicylamide yields a thio-derivative:



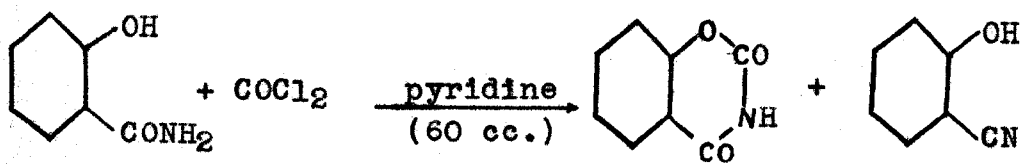
Bogisch attempted to reduce carbonyl salicylamide to a hydrocarbon, but without success.

Later, Einhorn in his study of the reactions between acid amides and phosgene, studied the reaction between salicylamide and phosgene, in which some carbonyl salicylamide is produced. At that time, he was attempting to elucidate the mechanism of the reaction between acid amides and phosgene.

Schmidt (24) observed that when benzamide was heated

with phosgene under pressure to 160-170°, ammonium carbonate, cyaphenine (2,4,6-triphenyl-1,3,5-triazine), benzoyl chloride, dibenzoyl urea, and benzonitrile were produced. At ordinary temperature, however, only benzoyl chloride, and benzonitrile were produced.

Using a phosgene-pyridine mixture, which they had found would remove water from many organic compounds at a low temperature, Einhorn and Mettler (25) reacted benzamide with phosgene-pyridine and obtained only benzonitrile. Salicylamide, on the contrary, gave along with salicylnitrile, a small quantity of carbonyl salicylamide:




10 gm. 8 gm. 0.4 gm. 6.5 gm.

There were, however, several viewpoints to be taken about the reaction mechanism. One of these, which found some confirmation in a technical process (26) for the preparation of benzal chloride from benzaldehyde in a phosgene-pyridine solution, was that a hypothetical compound $C_6H_5-CCl_2-NH_2$, was produced at some stage of the reaction. This compound of course would be expected to subsequently give off HCl, producing benzonitrile. Such amide chlorides had been prepared by Wallach (27) who reacted some acid amides with $PCl_5$. However, with benzamide he obtained a

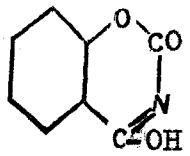
phosphorus-containing intermediate compound.

In accordance with Schnidt's observation that dibenzoyl urea is formed from benzamide and phosgene, it may be assumed that the chlorine, instead of replacing the oxygen of the carbonyl group, replaces the hydrogen of the amide group, producing an intermediate benzoyl-derivative of isocyanic acid $C_6H_5$-CO-N:CO. This under the existing reaction conditions would be expected to decompose into carbon dioxide and benzonitrile. In support of this contention is Schiff's observation (28), that benzoyl chloride when reacted with potassium cyanate yields benzonitrile.

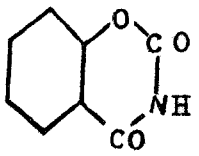
Although Einhorn and Mettler were unable to isolate any of the intermediate products which would have enabled them to decide upon the correct reaction mechanism, they nevertheless concluded that the latter mechanism was the more probable.

In investigating practical methods for the synthesis of carbonyl salicylamide (salicylamide + phosgene-pyridine gave 3% of carbonyl salicylamide; salicylamide + phosgene in 5% NaOH gave 44% yield), they repeated the procedure of Bogisch, reacting salicylamide with ethyl chloroformate in pyridine solution (instead of dilute NaOH). They reported that this method gave the most satisfactory yield.

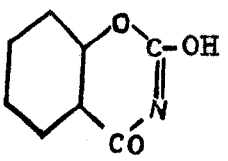
Carbonyl salicylamide, which can be assigned the possible formulas:



I



II



III

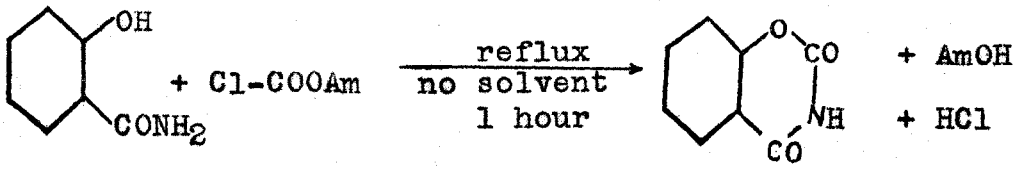
is probably an equilibrium mixture of the three forms, although II is the generally accepted formula.

Einhorn and Mettler found carbonyl salicylamide to be very resistant to bases at ordinary temperatures, but at high temperatures it was more readily attacked. They confirmed Bogisch's observation that with aniline (at 200°), carbonyl salicylamide gave diphenyl urea and regenerated salicylamide.

In addition to replacing the imido hydrogen with metals in order to prepare derivatives, they were able to replace it directly by reacting carbonyl salicylamide with benzoyl chloride in pyridine solution. Finally, with chlorine they were able to prepare carbonyl salicyl-chloramide.

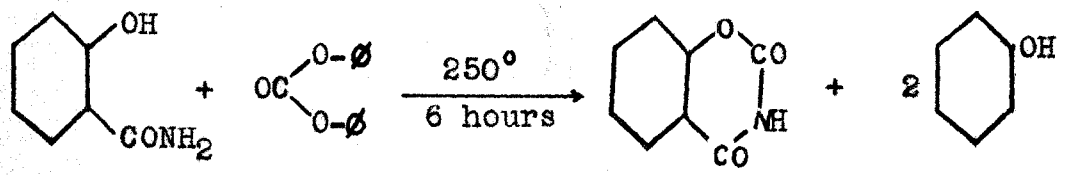
Einhorn and Schmidlin (29) also investigated various reactions for the purpose of preparing carbonyl salicylamide, but all of these reactions were of theoretical interest only. In these reactions, salicylamide was heated with various carbonyl-containing compounds, but in all cases the yields of carbonyl salicylamide, whether reported or implied, were poor.

In one case, they merely heated salicylamide with amyl chloroformate:



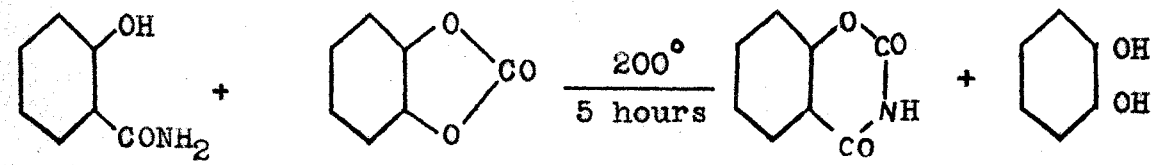

3 gm. 4.5 gm. 1.5 gm.

In another procedure, they heated salicylamide with diphenyl carbonate, to obtain carbonyl salicylamide:

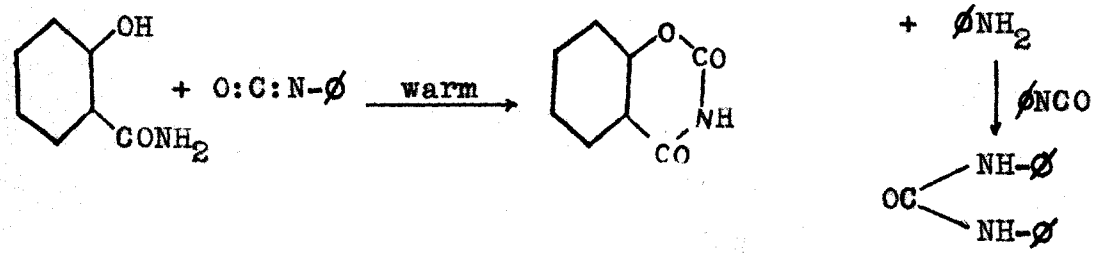



3.8 gm. 6 gm.

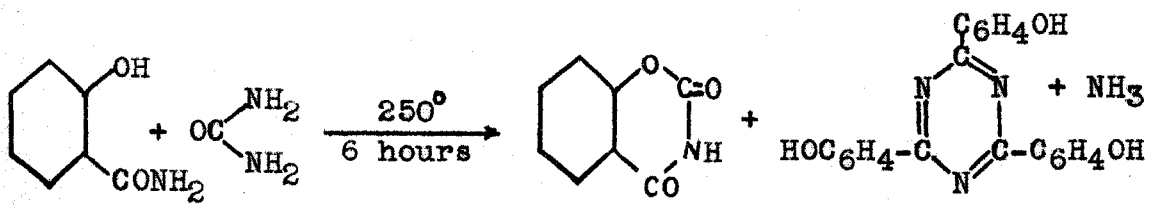
Pyrochatechin carbonate also reacts with salicylamide to produce some carbonyl salicylamide:




The reaction between salicylamide and phenyl isocyanate was found to produce some carbonyl salicylamide as well as diphenyl urea:



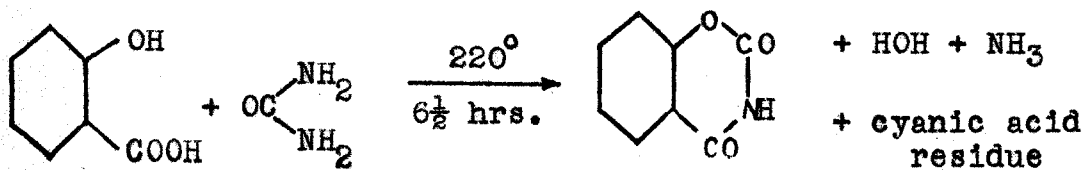
In the reaction between salicylamide and urea, they obtained some carbonyl salicylamide and an appreciable quantity of the so-called polynitrile of salicylic acid.




15 gm. 8 gm. 2.5 gm. sym-trihydroxyphenyl-triazine 4.5 gm.

This latter compound had been prepared by Limpricht (30), who obtained it by heating salicylamide to 270°. He reported it as salicylnitrile, but Mettler and Schmidlin were able to show that it was trimolecular.

In conclusion, they were able to obtain a small quantity of carbonyl salicylamide by melting together salicylic acid and urea:



From the previous discussion of the properties and reactions of the dihydro-benzoxazones, and the N-substituted carbonyl salicylamides, it is apparent that the physiological action of the two series of compounds should be quite different. Since the esters of salicylic acid are only partly hydrolyzed before absorption takes place, a considerable proportion of the unchanged compounds appears in the circulation and tissues. We can thus expect a regular gradation in properties among homologues. Other properties, such as solubility, resistance to hydrolysis, etc., should affect the speed and duration of their analgesic action.

Due to the large number of aldehydes, ketones, aliphatic and aliphatic-aromatic halides commercially available, the author thought it worthwhile and possible to prepare a large number of dihydro benzoxazones and carbonyl salicylamide derivatives, in order that they might be tested for their analgesic activity.

Since the 2,2-dimethyl-dihydro benzoxazone had been reported, the author decided to try to extend the series using higher ketones in the reaction with salicylamide. From the large number of substituted benzaldehydes available, substituted 2-phenyl derivatives could be prepared. With the long-chain aliphatic aldehydes, the preparation of an homologous series could be attempted. Halogen derivatives of salicylamide could also be used as intermediates, to determine the influence of the halogen atom on the analgesic

action of these derivatives.

In the preparation of derivatives of carbonyl salicylamide, the author made use of numerous halogen derivatives; primary and secondary alkyl halides, aralkyl halides, and acyl halides. Many of these were purchased from supply houses, while others were prepared by the author during an earlier investigation.

# PART III EXPERIMENTAL DETAILS

## Preparation of Salicylamide

Since large quantities of salicylamide would be required in the preparation of a number of derivatives, it was decided to investigate the method proposed by Kline (31) in which methyl salicylate was reacted with a large excess of concentrated $NH_4OH$ in the presence of a wetting agent (Dreft). In this method, 1-volume of methyl salicylate was added to 10-volumes of conc. $NH_4OH$ containing about 0.5% of Dreft. The mixture was allowed to stand for a week (the disappearance of the oily layer showed the reaction to be complete), diluted with water, neutralized with HCl, and the resulting precipitate washed with water and dried. Without further purification the product melted at 136-137°, and was considered pure enough for most purposes. The yield was 70% of the theoretical amount.

This preparation was repeated using 354 gm. of methyl salicylate (C.P.), 1-liter of conc. $NH_4OH$ and 2 gm. of Dreft. The mixture was placed in a 2-liter bottle and shaken occasionally until the oil layer had disappeared -- time 60 hours. The yield was 280 gm. or 88%.

In the second preparation, 456 gm. of methyl salicylate, 1300 cc. of conc. $NH_4OH$ and 5 gm. of Dreft were stirred occasionally in a 3-l. round-bottomed flask until the oily layer had disappeared -- time 40 hours. The yield was 91%, or 373 gm.

It was thus apparent that the degree of subdivision of the oil particles determined the speed of the reaction. Obviously rapid stirring would ensure a thorough emulsification of the oil, but the effect of varying concentrations of different wetting agents on the speed of the reaction was not so obvious. It was therefore decided to test this relationship.

The reactions were carried out in a 3-l. round-bottomed flask fitted with a wire stirrer of the Hershberg type (38) which could be turned at the rate of 1000 r.p.m. The author found that blocks of 1/2 inch Formica through which suitable sized holes had been bored, would serve quite well as bearings for the shaft. Glycerine was used as a lubricant. During the stirring, a 5-10°rise in temperature of the mixture was noted. The results are as follows:

| Wt. of Me-salicylate | Vol. $NH_4OH$ | Type wetting agent | Conc. wetting agent | Time of reaction |
|---|---|---|---|---|
| 924gm. | 2600 cc | Dreft | 15 gm.(0.5%) | 7 hrs. |
| 456 | 1100 | Dreft | 5 gm.(0.33%) | 9 |
| 456 | 1600 | Triton 720 (Röhm & Hass) | 1.9 gm.(0.1%) | 9-1/2 |
| 456 | 1600 | Triton 720 | 5.7 gm.(0.3%) | 6-3/4 |
| 456 | 1600 | Triton 720 | 9.5 gm.(0.5%) | 8-1/2 |
| 456 | 1600 | No wetting agent | | 7 |

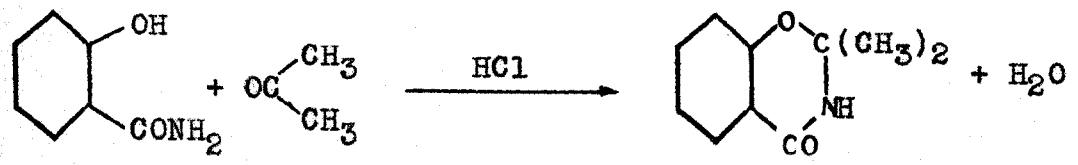
(The yield in each case was 96%)

There thus seems to be no relationship between the concentration of the wetting agent and the speed of the

reaction. The reaction proceeds roughly at the same rate (stirring constant) with or without the wetting agent. It may best be left out under these circumstances since it is rather difficult to wash out of the crude product.

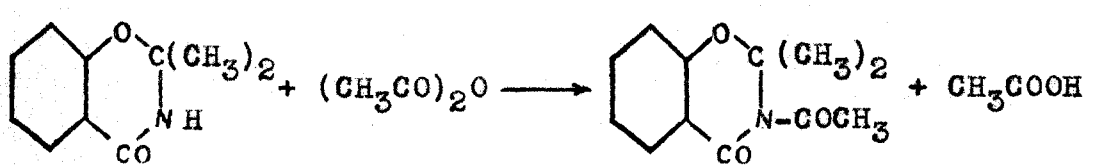
After the reaction was completed, the straw-colored reaction mixture was usually poured into a crock which was fitted with a mechanical stirrer, and the excess base neutralized with dilute sulfuric acid (1:2). Cracked ice was usually added simultaneously in order to keep the temperature down. The solid which precipitated was usually filtered off onto a 20 cm. Buchner funnel and washed with cold water until the washings were no longer soapy and the solid more or less free of the odor of methyl salicylate. If the quantity of salicylamide prepared was too large to allow convenient washing on the funnel available, the solid was washed by decantation in the crock; the supernatent liquid being drawn off with an inverted funnel which could be lowered into the mixture. After the solid had been washed thoroughly, it was either sprea out on brown wrapping paper to air-dry, or was dried on a steam-heated hot plate. Without further purification, the product melted at 136-137°, and was used as such. This melting point and the others reported in this thesis were taken with the aid of the Hershberg Melting Point Apparatus (32), which is an electrically-heated Thiele tube (fitted with a mechanical stirrer) designed to accomodate total immersion (Anschütz) thermometers.

Preparation of 2,2-Dimethyl-3,4-dihydro-1,3-benzoxazin-4-one



Twenty grams of salicylamide were dissolved in 200 cc. of dry acetone and 2 gm. of dry HCl gas were passed into the solution. The flask was then stoppered and allowed to stand at room temperature for 24 hours. The solution was then neutralized with $PbCO_3$, filtered, and the solution evaporated to dryness under reduced pressure. The solid residue was then ground up in a morter with 60 cc of 15% NaOH solution, filtered and washed with water. The residue was recrystallized from 95% alcohol. The compound separated in shining prisms. The filtrate was heated to boiling and water was added until the solution became turbid. On cooling, an additional crop of crystals separated. The total yield was 13 gm. or 50% of the theoretical amount. The compound melted at 137°, which agreed with that reported by H. O. L. Fischer (33).

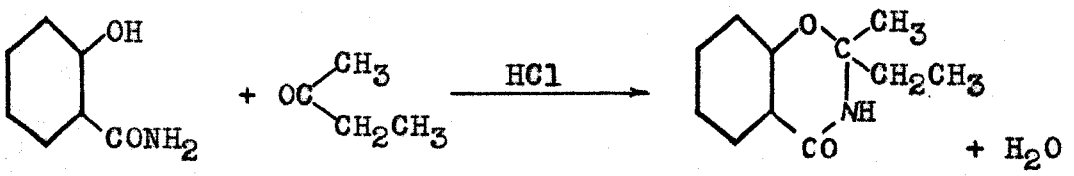
Acetylation of 2,2-Dimethyl-3,4-dihydro-1-3-benzoxazin-4-one



I

Six grams of (I) were dissolved in 40 cc. of acetic anhydride, and the solution refluxed for 6 hours in a round-bottomed flask fitted with a ground-jointed neck and condenser. The solution was then cooled somewhat and poured into 150 cc. of water in a 400 cc. beaker. After all of the acetic anhydride had hydrolysed, an oily layer remained which resisted repeated efforts to cause it to crystallize, such as chilling and scratching of the bottom of the beaker with a glass rod. Finally, the mixture was heated nearly to boiling and the beaker plunged into an ice bath, and the mixture stirred vigorously while it cooled. Soon a solid separated, which was filtered off, washed with water and recrystallized from dilute alcohol. The compound separated in long needles which melted at 57.5-58°(Fischer reported 30-32°). The yield was 5 gm. or 66%.

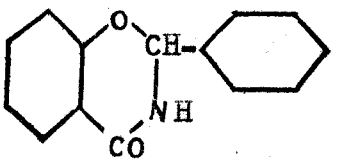
Attempted Preparation of 2-Methyl-2-ethyl-3,4-dihydro-1,3-benzoxazin-4-one




The reaction was carried out exactly as was the preceeding reaction, methyl-ethyl ketone being used instead of acetone. The solid residue however, proved to be soluble in sodium hydroxide, and upon acidification and recrystal-

lization, was identified through mixed melting points as salicylamide. The reaction apparently does not proceed at all with methyl-ethyl ketone.

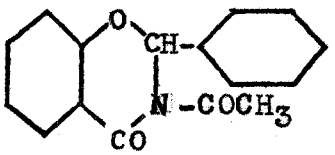
Preparation of 2-Phenyl-3,4-dihydro-1,3-benzoxazin-4-one




A mixture of 200 gm. of salicylamide and 200 cc. of benzaldehyde was suspended in 800 cc. of absolute ether (which had been saturated with dry HCl gas) and heated gently on a water bath under reflux (efficient condenser ! ) with occasional shaking. After about an hour, the solution suddenly solidified, indicating that the reaction was complete. The mixture was then cooled, the solid mass broken, filtered off and washed with a little ice-cold ether to remove the excess aldehyde. The white solid was then transferred to a flask containing 750 cc. of 10% NaOH solution and stirred rapidly for 1/2 hour. The mixture was then diluted with water, and the solid filtered off on a Buchner funnel and washed repeatedly with water. After partially removing the water by suction, the solid was recrystallized from 95% alcohol, from which it separated in long needles. Dilution of the filtrate with a little water yielded a second crop of crystals. The yield was 155 gm. or 47.3% of the theoretical amount. The compound melted at 168.5-169.5° which agreed with that

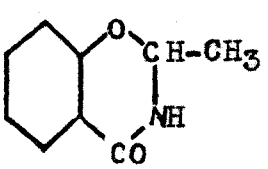
reported by Titherley (10).

Acetylation of 2-Phenyl-3,4-dihydro-1,3-benzoxazin-4-one



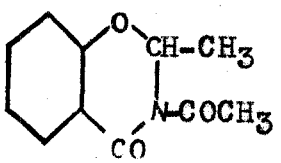
A solution of 4.5 gm. of the 2-phenyl derivative in 40 cc. of acetic anhydride was refluxed gently for 4 hours in a flask fitted with a ground-jointed neck and water-cooled condenser. The solution was then cooled somewhat and poured into 200 cc. of water and allowed to stand with occasional stirring until the anhydride had all hydrolyzed. After about 1/2 hour of scratching and stirring, the oil which had remained began to solidify. The solid was then filtered off, washed with water and dissolved in a small quantity of hot alcohol. On cooling, long needles of the acetyl compound separated. A further quantity of the product was obtained by diluting the alcoholic filtrate with a little water. The total yield was 4.5 gm. melting at 88° which agreed with that reported by Keane (18).

Preparation of 2-Methyl-3,4-dihydro-1,3-benzoxazin-4-one



A mixture of 50 gm. of salicylamide, 50 cc. of paraldehyde and 150 cc. of dry ether (to which 4 cc. of conc. alc. HCl had been added), were heated gently (under an efficient condenser) on a water bath. After about 1/2 hour, all of the solid went into solution. Heating was continued for 2 hours longer, then the reaction mixture was allowed to cool and stand overnight. The reaction mixture had by this time set to a solid mass. This was broken up and filtered off, washed with cold ether, and then stirred for 1/2 hour with 150 cc. of cold 10% NaOH solution. The residue was then filtered off, washed with water and recrystallized from 80% alcohol. Yield 33 gm. or 55.5% of the theoretical amount. The compound crystallized in long white needles which melted at 146-146.5°, which agreed with that reported by Hicks (16).

Acetylation of 2-Methyl-3,4-dihydro-1,3-benzoxazin-4-one




A solution of 5 gm. of the 2-methyl derivative in 40 cc. of acetic anhydride was refluxed gently (in ground-jointed apparatus) for 4 hours, then poured into 200 cc. of water. After all of the acetic anhydride was hydrolysed, a clear oily layer remained on the bottom of the beaker. This was

scratched and chilled for a long period of time, but did not solidify. Finally however, after standing for six days, the oil solidified when scratching was resumed. The solid was filtered off, washed with water, and recrystallized from dilute alcohol. The compound separated in long needles which melted at 54-55°. The yield was 2 gm. It was analyzed for nitrogen by the method of Ma and Zuazaga (34).

Anal. Calcd. for $C_{11}H_{11}O_3N$: N, 6.83 Found: 6.65

Semi-micro Kjeldahl Determination of Nitrogen

The method used by the author consisted assentially in digesting a 20-40 mgm. sample with sulfuric acid in the presence of copper sulfate and potassium sulfate. The ammonia produced was liberated with caustic and distilled into 2% boric acid solution. It was then titrated directly with standard 0.02 N hydrochloric acid, using a mixed indicator which consisted of 1-part of methyl red and 5-parts of bromocresol green.

Apparatus:

a) Digestion Flasks: These were purchased from a chemical supply house. The bulbs were of 10 cc. capacity while the necks were approximately 15 cm. long by 14 mm. in diameter, and were made from Pyrex glass.

b) The Digestion Stand used by the author was patterned after the one described by Niederl and Niederl (35). It consisted of a metal stand having a Transite plate 10 x 35 cm.

with six holes of 25 mm. diameter drilled in it. Centered below the openings and attached to the gas pipe of the stand were six microburners. The fume duct was approximately 40 cm. long and 32 mm. in diameter with six-20 mm. holes blown in it to accomodate the necks of the digestion flasks. It was attached to the stand by two arms extending upward at such an angle that the flasks rested about 50 from the horizontal. It was connected to a good water pump which served to remove the decomposition vapors generated during the digestion. If neither digestion stand nor micro-Kjeldahl digestion flasks are available, the author found 50 cc. round bottomed flasks clamped over improvised micro-burners to be satisfactory. In this event, the digestion must be carried out in the hood.

c) Distillation Apparatus: This apparatus is a modification of the one-piece apparatus of Kirk (36), and was constructed by the author of Pyrex glass. Details of its construction as well as a description of its operation are to be found in the Appendix.

Reagents:

Mixed Indicator: A 0.1% bromocresol green and a 0.1% methyl red solution in 95% alcohol were prepared separately, and 5 parts of bromocresol green solution and 1 part of methyl red solution were mixed in a bottle provided with a dropper. This indicator gives a bluish-purple color in 2% boric acid solution, which changes to bluish green in the presence of a trace of ammonia, and to pink with a trace of mineral acid;

the transition point being very sharp and distinct.

Boric Acid Solution: About 10 gm. of crystal boric acid were dissolved in 500 cc. of boiling distilled water. After cooling, this solution was transferred to a glass-stoppered bottle.

Hydrochloric Acid: 0.02 N. This was prepared by diluting 12 N HCl from the stock-bottle, and standardized against pure sodium carbonate. It was stored in a bottle connected with an automatic-filling borette, into which it could be syphoned as needed.

Catalyst: A pulverized mixture of 3-parts of copper sulfate pentahydrate and 1-part of potassium sulfate.

Procedure:

a) Digestion: A sample of about 30-40 mgm. containing 5-6% of nitrogen is weighed out in a long-handled charging tube (which could be used with solids as well as viscous liquids), and transferred to the bottom of the digestion flask. About 0.8 gm. of the catalyst and 5 cc. of concentrated sulfuric acid (which had been protected from ammonia fumes) were then added. The flask was then placed on the digestion stand, the suction pump turned on, and the flask heated carefully with a small flame. After the initial vigorous decomposition had taken place, the size of the flame could be increased and the contents of the flask boiled vigorously until straw yellow or light green. The digestion time varied with the size of the sample and the nature of the compound.

Some digestions were completed in an hour, while others required as long as 7 hours.

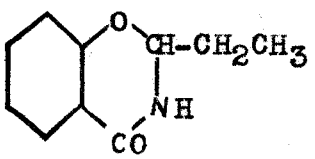
b) Distillation and Titration: The apparatus was steamed and rinsed thoroughly before use. With cold water running in the condenser, and the stopcock on the addition funnel and pinch clamp on the steam jacket closed, the water in the steam generator is boiled at such a rate that 5 cc. of distillate come over per minute. After about 10 minutes of this steaming, the flame is removed from the generator, whereupon the condensate in the distilling flask is sucked out into the steam jacket. After draining this out by opening the pinch clamp, the addition funnel is filled with distilled water which is run into the distilling. The burner is then replaced for a few seconds and removed again. The condensing steam again empties the distilling flask. The apparatus is now ready for use. A 125 cc. Erlenmeyer flask is rinsed with distilled water, and 10 cc. of 2% boric acid and 5 drops of mixed indicator added. The flask is then supported under the condenser with the tip just under the surface of the liquid. The digested sample is cooled and diluted with 5cc. of distilled water and cooled again under the tap. With the water in the steam generator boiling gently (fresh chips of porcelain or corburundum should be added each time the boiling is stopped in order to prevent bumping), and the pinch clamp on the steam trap open, the contents of the digestion flask are quantitatively transferred to the distil-

lation flask. After adding the rinsings, the funnel is washed down with a stream of water from the wash bottle. The stopcock on the funnel is closed, and a solution of 8 gm. of NaOH in 15 cc. of water is added in 2-3 cc. portions, the contents of the distilling flask being mixed after each addition. This is done by momentarily closing the pinch clamp on the steam jacket and allowing a buble of steam to stir up the two layers. This mixing in portions is necessary since sudden mixing of the entire amount of the NaOH solution may cause some of the caustic to be sprayed over into the receiver. If an excess of NaOH has been added, a brown precipitate of CuO will precipitate. The flame under the steam generator is turned up, the pinch clamp on the steam jacket closed, and distillation continued for about 5 minutes. After about 2 minutes, the receiver may be lowered until the tip of the condenser is 1 cm. above the liquid. After about 25 cc. of distillate has been collected, the tip of the condenser is rinsed down, the receiver removed, and the flame turned out. The contents of the distilling flask are then sucked out into the steam jacket and upon opening the pinch clamp, are run into the drain. The ammonia is then titrated with 0.02 N HCl to the end point. After rinsing out the apparatus in the manner described above, it is ready for the next determination.

In the event that a little alkaline spray is carried over in the initial mixing of the NaOH, the indicator in the receiver will turn orange. The determination still is not

spoiled. The solution in the receiver is made acid with a little HCl, and the distillation carried through as usual. After removing the residue from the distilling chamber, the distillate is run in as before, made alkaline with more NaOH, and the ammonia steam distilled into a fresh batch of boric acid solution. The error introduced depends on the care with which the above operations have been carried out.

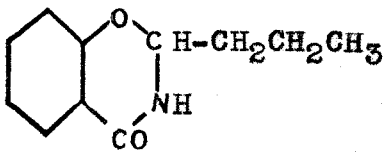
Preparation of 2-Ethyl-3,4-dihydro-1,3-benzoxazin-4-one




A mixture of 50 gm. of salicylamide, 60 cc. of propionaldehyde, 100 cc. of dry ether and 4 cc. of saturated alcoholic HCl was heated gently under reflux on a water bath for 2 hours, then allowed to stand overnight. By that time the mixture had solidified. The lumps were broken up, filtered off, washed with a little cold ether, and stirred for 1/2 hour with 150 cc. of 10% NaOH solution. The solid residue was then filtered off, washed thoroughly with water, and recrystallized from 95% alcohol. The compound separated in long white needles which melted at 116-117.5°. The filtrate was heated to boiling and water added until the solution was turbid. On cooling, an additional crop of crystals separated. Total yield: 36.5 gm. or 57% of the theoretical amount.

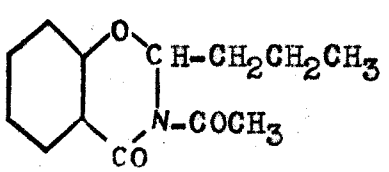
Anal: Calcd. for $C_{10}H_{11}O_2N$: N, 7.91 Found: 7.93

Preparation of 2-n-Propyl-3,4-dihydro-1,3-benzoxazin-4-one



A mixture of 50 gm. of salicylamide, 60 cc. of n-butyraldehyde (which had been freshly distilled before use), 150 cc. of dry ether, and 4 cc. of alcoholic HCl, was refluxed gently on a water bath. In a short time the solution became clear. After 1 hour, heating was discontinued, and the reaction mixture allowed to stand overnight. The next day, the reaction mixture had set to a solid mass. It was then heated under reflux for 4 hours, cooled, and the solid broken up and filtered off. This was stirred for 1/2 hour with 150 cc. of cold 10% NaOH solution, filtered off and washed thoroughly with water, and recrystallized from 80% alcohol. The compound separated in long needles which melted at 85.5-86.5°. The yield was 51 gm. or 73% of the theoretical amount.
Anal. Calcd. for $C_{11}H_{13}O_2N$: N, 7.33 Found: 7.40, 7.20

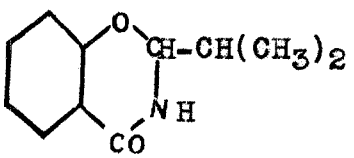
Acetylation of 2-n-Propyl-3,4-dihydro-1,3-benzoxazin-4-one



A solution of 10 gm. of the n-propyl derivative in 40 cc. of acetic anhydride was refluxed (in ground-jointed apparatus) for 6 hours, cooled somewhat and poured into 150 cc. of water. The oil which remained after all of the acetic anhydride had hydrolysed could not be made to solidify, even on cooling, so the excess acetic acid in the mixture was neutralized with 10% NaOH, and the mixture extracted with ether. The ether solution was then dried with calcium chloride, the ether evaporated off under reduced pressure, and the oil which remained distilled under reduced pressure. The yield was 7.6 gm. of a clear viscous oil which boiled at 112-116° under 1 mm. Hg pressure.

Anal. Calcd. for $C_{13}H_{15}O_3N$: N, 6.01 Found: 6.20

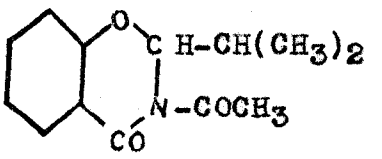
Preparation of 2-i-Propyl-3,4-dihydro-1,3-benzoxazin-4-one




A mixture of 50 gm. of salicylamide, 60 cc. of iso-butyraldehyde, 100 cc. of dry ether and 4 cc. of saturated alcoholic HCl was heated gently on a water bath under reflux for 2 hours and then allowed to stand overnight. The next day the solution remained clear, so it was refluxed for 4 hours longer. The reaction mixture was then chilled in the refrigerator, whereupon the compound crystallized out in

long beautiful needles. These were filtered off and the filtrate concentrated under reduced pressure. An additional quantity of solid separated. This was combined with the first batch and the material purified as before. The yield of the pure product was 34 gm. or 49% of the theoretical amount. The compound melted at 105.5-106.5°, which agreed with the literature (17).

Acetylation of 2-i-Propyl-3,4-dihydro-1,3-benzoxazin-4-one

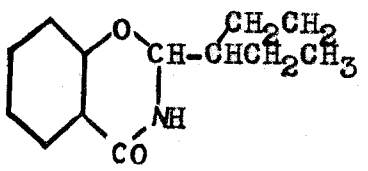



A solution of 10 gm. of the isopropyl derivative in 40 cc. of acetic anhydride was refluxed for 4 hours, and then poured into 300 cc. of water. After all of the acetic anhydride had hydrolysed, an oily layer remained on the bottom of the beaker. On standing overnight, some of the oil held on the surface of the water (probably by surface tension since it was denser than water) solidified. This was pushed down into the oil on the bottom and stirred. In a few minutes the whole mass solidified. This solid was allowed to stand for an hour to allow the mass to solidify completely, and was then filtered off and washed with water. The solid was dissolved in hot alcohol and water added until

the solution became turbid. On cooling, thick crystals separated, which melted at 34.5-35.5°. The yield was 10.5 gm.

Anal. Calcd. for $C_{13}H_{15}O_2N$: N, 6.01 Found: 6.13

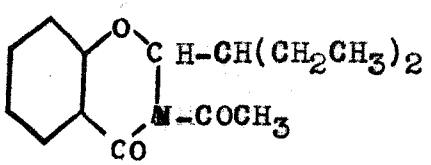
Preparation of 2-(1-ethyl)-n-Propyl-3,4-dihydro-1,3-benzoxazin-4-one



A mixture of 50 gm. of salicylamide, 60 cc. of 2-ethylbutyraldehyde, 150 cc. of dry ether, and 4 cc. of alcoholic HCl, was heated gently under reflux on a water bath for 6 hours, then allowed to stand overnight. Since no solid had separated by that time, the ether was evaporated off under reduced pressure until a thick syrupy oil remained, which did not solidify on chilling. However, on the addition of 2-volumes of ligroin, a solid precipitated out. This was filtered off, extracted with NaOH solution, washed with water, and recrystallized from dilute alcohol. The compound separated in small glassy crystals, which melted at 98-99°. The yield was 39 gm. or 49% of the theoretical amount.

Anal. Calcd. for $C_{13}H_{17}O_2N$: N, 6.39 Found: 6.15, 6.23

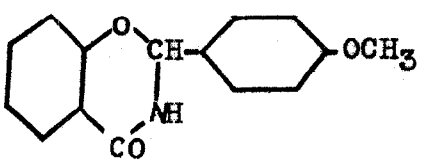
Acetylation of 2-(1-ethyl)-n-Propyl-3,4-dihydro-1,3-benzoxazin-4-one



A solution of 10 gm. of the preceeding benzoxazone in 40 cc. of acetic anhydride was refluxed for 6 hours, poured into water and stirred until the excess acetic anhydride had all hydrolysed. As before, an oil remained. The solution was neutralized with dilute NaOH, cooled, and extracted with ether. The ether extract was then dried over calcium chloride, filtered and evaporated to dryness. In this case, the compound was obtained as a solid residue. This was dissolved in hot alcohol, filtered, and the solution allowed to cool slowly. The compound separated in long needles which melted at 56.5-57.5°. The yield was 10 gm.

Anal. Calcd. for $C_{15}H_{19}O_3N$: N, 5.37 Found: 5.17, 5.16

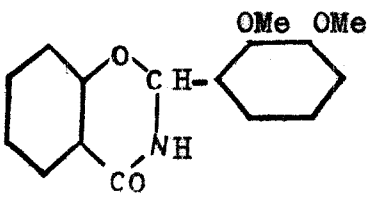
Preparation of 2-p-Methoxyphenyl-3,4-dihydro-1,3-benzoxazin-4-one



A mixture of 50 gm. of salicylamide, 54 cc. of anisaldehyde, 200 cc. of dry ether, and 4 cc. of alcoholic HCl

was heated gently under reflux for 5 hours on a water bath, then allowed to stand overnight. The next day, the solution (containing a few crystals) was transferred to an Erlenmeyer flask, and about 100 cc. of ether removed by reduced-pressure evaporation. About 300 cc. of ligroin were then added to the residue, whereupon a white solid separated. This was filtered off and ground up with 10% NaOH in a morter. Most of the solid dissolved, indicating that the reaction had only preceeded partially. The solid residue was filtered off, washed free of aldehyde with a little cold ether, and recrystallized from alcohol. The compound separated in needles which melted at 166°, in agreement with the value reported by Keane (37). The yield was 7 gm.

Preparation of 2-(2,3-dimethoxy)-Phenyl-3,4-dihydro-1,3-benzoxazin-4-one

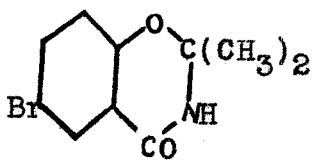



A mixture of 25 gm. of salicylamide and 32 gm. of 2,3-dimethoxy benzaldehyde and 100 cc. of dry benzene was saturated with dry HCl gas, and heated in an Erlenmeyer flask under reflux. The reflux condenser was provided with a calibrated receiving tube (such as is used in the determination of water in petroleum products) so that the water produced during the reaction could be determined, and the

course of the reaction thus followed. In the course of 2 hours of refluxing, 2.2 cc. of water were given off. On cooling the solution, a solid separated out. This was filtered off, extracted with dilute NaOH, washed with water, and recrystallized from alcohol. The compound separated in needles which melted at 150.5-151°. The yield was 19 gm., or 38% of the theoretical amount. An earlier attempt to prepare the same compound, using ether as a solvent with HCl as catalyst and without the removal of water, failed. It thus appears that the above method might be used advantageously in increasing the yields in the preceeding reactions, especially where a high-boiling aldehyde is used.

Anal. Calcd. for $C_{18}H_{15}O_4N$: N, 4.91 Found: 5.08

Preparation of 6-Bromo-2,2-dimethyl-3,4-dihydro-1,3-benzoxazin-4-one

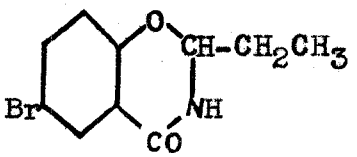



Twelve gm. of 5-bromo-salicylamide (Dow) were dissolved in 350 cc. of dry acetone, and dry HCl gas bubbled in until 4.5 gm. had dissolved. The solution was allowed to stand at room temperature for 24 hours, and was then neutralized with lead carbonate, filtered, and the acetone removed by reduced-pressure evaporation. The solid residue was then extracted

with 10% NaOH, washed with water and dissolved in alcohol. The compound crystallized out in large glassy hexagonal crystals which metled at 180-181°. The filtrate was heated to boiling and water added until the solution became turbid. On cooling, a second crop of crystals was obtained. Total yield, 7 gm., or 50% of the theoretical amount.

Anal. Calcd. for $C_{10}H_{10}O_2NBr$: N, 5.47 Found: 5.68

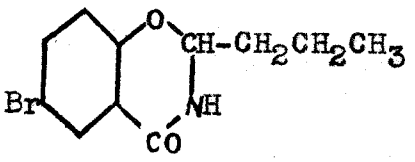
Preparation of 6-Bromo-2-ethyl-3,4-dihydro-1,3-benzoxazin-4-one




A solution of 25 cc. of propionaldehyde in 100 cc. of dry ether was saturated with dry HCl gas. To this solution was added 25 gm. of 5-bromo salicylamide, and the mixture then heated on the water bath under reflux. During the course of 2 hours, the solid went into solution, the solution turned reddish in color and then another separated. The reaction mixture was then cooled, the solid filtered off and extracted with 10% NaOH, and the residue washed with water and recrystallized from 95% alcohol. The compound separated in needles which melted at 149.8-150.5°. The yield was 12 gm., or 40% of the theoretical amount.

Anal. Calcd. for $C_{10}H_{10}O_2NBr$: N, 5.46 Found: 5.77,5.62

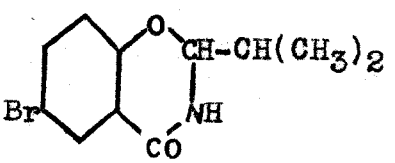
Preparation of 6-Bromo-2-n-propyl-3,4-dihydto-1,3-benzoxazin-4-one



A cooled solution of 25 cc. of n-butyraldehyde in 100 cc. of dry ether was saturated with dry HCl gas, and to this was added 25 gm. of 5-bromo salicylamide. The mixture was gently refluxed on a water bath with occasional stirring. In a short time the solid dissolved, but in an hour another solid appeared. Meanwhile, the liquid turned from water-white to dark red. After standing overnight, the reaction mixture turned black. The solid was filtered off, and the dark adhering solution washed off with a little cold ether. The solid which remained was white. This was extracted with dilute NaOH, washed with water and recrystallized from 95% alcohol. The compound crystallized in needles which melted at 152.5-153.5°. The yield was 18 gm., or 58% of the theoretical amount.

Anal. Calcd. for $C_{11}H_{12}O_2NBr$: N, 5.18 Found: 5.27, 5.29

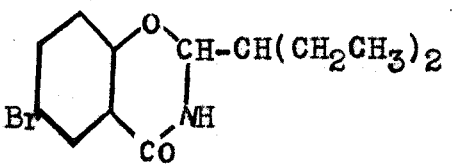
Preparation of 6-Bromo-2-i-propyl-3,4-dihydro-1,3-benzoxazin-4-one



A solution of 25 gm. of isobutyraldehyde in 100 cc. of dry ether was cooled and saturated with dry HCl gas. To this solution was added 25 gm. of 5-bromo salicylamide, and the mixture then heated under reflux on a water-bath for 2 hours. The mixture was then cooled and the solid which had separated was filtered off, washed with a little ether to remove the excess aldehyde, extracted with dilute NaOH, washed with water, and recrystallized from 95% alcohol. The compound melted at 156.5-157°. The yield was 21 gm., or 67%.

Anal. Calcd. for $C_{11}H_{12}O_2NBr$: N, 5.18 Found: 5.18,5.36

Preparation of 6-Bromo-2-(1-ethyl)-n-propyl-3,4-dihydro-1,3-benzoxazin-4-one

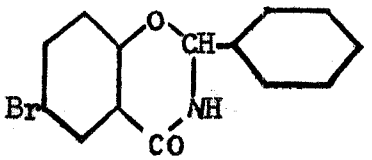



A solution of 25 cc. of 2-ethyl butyraldehyde in 100 cc. of dry ether was saturated with HCl gas. To this was added 25 gm. of 5-bromo salicylamide, and the mixture then heated under reflux on a water bath for 4 hours. There was no discoloration of the solution as before. After standing overnight, a solid separated. This was filtered off, washed with a little cold ether, extracted with 10% NaOH, washed with water and recrystallized from 95% alcohol. The compound crystallized out in white needles which melted at

119-120°. The yield was 20 gm. or 58% of the theoretical amount.

Anal. Calcd. for $C_{13}H_{16}O_2NBr$: N, 4.70 Found: 4.79, 4.68

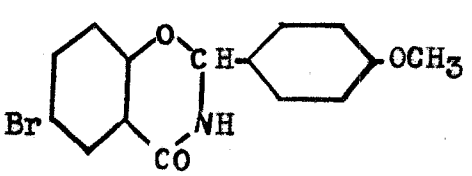
Preparation of 6-Bromo-2-phenyl-3,4-dihydro-1,3-benzoxazin-4-one




A mixture of 25 gm. of 5-bromo salicylamide, 25cc. of benzaldehyde, 100 cc. of dry ether (containing 2 gm. of dry HCl) was heated under reflux on a water-bath for 5 hours. The solid which had separated from the clear solution was filtered off, extracted with dilute NaOH, washed with water, and recrystallized from alcohol. The compound crystallized in needles which melted at 224.5-225.5°, which agreed with the literature (22). The yield was 17.5 gm., or 50% of the theoretical amount.

No reaction was obtained when 2 cc. of alcoholic HCl was used as a catalyst, even after 9 hours of refluxing.

Preparation of 6-Bromo-2-p-methoxyphenyl-3,4-dihydro-1,3-benzoxazin-4-one



A solution of 25 cc. of anisaldehyde in 100 cc. of dry ether was saturated with dry HCl gas, and to this was added 25 gm. of 5-bromo salicylamide. The mixture was heated under reflux on a water bath for 4 hours, cooled, and the solid material filtered off. This was then extracted with alkali, washed with water, and recrystallized from a mixture of alcohol and "Cellosolve" since the compound is rather insoluble in alcohol alone. The compound crystallized in needles which melted at 234-237°. The yield was 8 gm., or 21% of the theoretical amount.

Anal. Calcd. for $C_{15}H_{12}O_2NBr$: N, 4.18 Found: 4.56

Notes on the Preparation of 2-Substituted Benzoxazones

1. While there are numerous literature references to procedures in which salicylamide is reacted with aldehydes to form benzoxazones without the use of a solvent, the author found that almost invariably, resinous by-products were formed during the reaction, and although the yields might be greater in the former case, the final product is harder to isolate in a pure form. Moreover, while an increase in the proportion of HCl used almost invariably increases the reaction rate and the yield, the quantity used must be regulated in individual cases since some aldehydes are more easily polymerized than others under the same conditions.

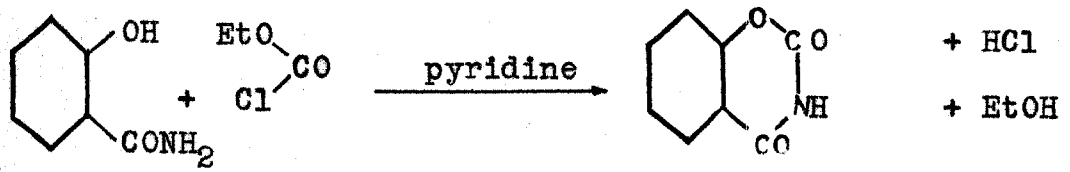
2. If the water produced during the reaction is removed by distillation with an immiscible solvent, condensations may be carried out which would be impossible by other methods. As an example, the author cites the condensation of salicylamide with 2,3-dimethoxy benzaldehyde. There were other reactions of this type which the author has not yet reported.

3. The condensation of salicylamide with long-chain aliphatic aldehydes proceeds slowly, if at all, and the latter are easily polymerized if the concentration of the catalyst is high.

4. The benzoxazones are best acetylated with acetic anhydride. Acetyl chloride causes a hydrolysis of the molecule to salicylamide and the aldehyde. The acetates are usually low-melting solids or viscous liquids.

Preparation of O,N-Carbonyl Salicylamide

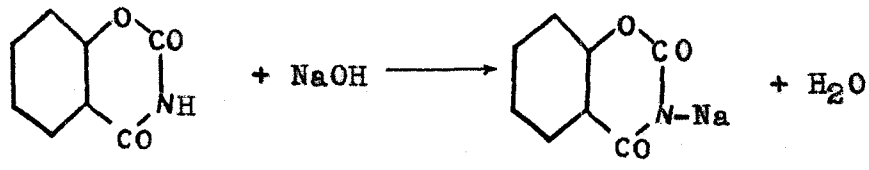
(3,4-Dihydro-1,3-benzoxazin-2,4-dione)




In a 2-liter 3-necked round-bottomed flask fitted with a 500 cc. dropping funnel, thermometer, and a mechanical stirrer of the Hershberg type (38) (which could be rotated rapidly), was placed 300 gm. of powdered salicylamide. Pyridine was added until all of the solid had gone into solution --- about 600 cc. The flask was then immursed in an ice bath and the solution stirred until the temperature had fallen to about 5°. Then 324 gm. of ethyl chloroformate (caution! lacrymatory) were added dropwise at such a rate that the temperature did not rise above 10-12°. This required about 2 hours. By the time the addition of the ethyl chloroformate was completed, the reaction mixture had become quite pasty. The ice bath was then replaced by a hot-water bath, and the mixture heated by this for 2 hours. In a short time, all of the solid had gone into solution, so that stirring could then be stopped. The dropping funnel could also be replaced with a water-cooled condenser, although this is not absolutely necessary since very little of the pyridine vapor escapes at the temperature of the water bath. After heating the reaction mixture for two hours, it was poured with stirring

into 3-liters of a mixture of water and cracked ice. The solid material which precipitated was filtered off and washed with 2-liters of water and allowed to dry over the steam plate. Since the compound proved to be rather insoluble in alcohol (1/2 gm. per 100 cc.) it was recrystallized from "Ethyl Cellosolve" in which it is soluble to the extent of about 20 gm. per 100 cc. at the boiling point. The compound crystallized out in beautiful needles. After filtering off the solid, it was found necessary to wash the material with a little alcohol to remove the last of the Cellosolve. The yield was 299 gm., or 84% of the theoretical amount. The melting point was 230.5-231.5°, which agreed with that in the literature (25).

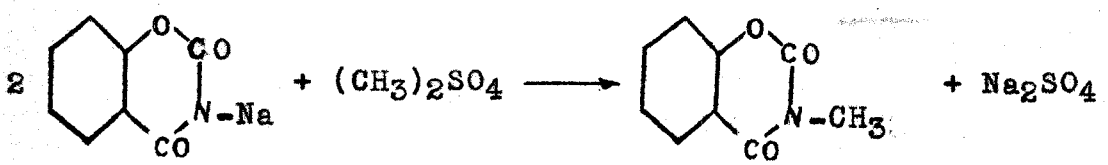
Preparation of the Sodium-salt of O,N-carbonyl salicylamide




Thirty-five gm. of dry carbonyl salicylamide were placed in an 800 cc. beaker and about 40 cc. of 6N NaOH were added in 1-2 cc. portions. As each portion touched the solid, it turned to a yellow paste. This paste was stirred rapidly with a glass rod until the color disappeared, and the mass became white again. As more and more NaOH reacted, the mixture became more and more fluid, until in the end a glycerine-

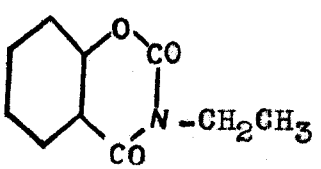
like liquid remained with one or two scattered bits of unreacted solid. An excess of NaOH however, is to be avoided since this will cause an insoluble white solid to precipitate. For some unknown reason, the author found that freshly recrystallized carbonyl salicylamide reacted more readily than that which had stood for some time. After all of the NaOH had been added, 700 cc. of absolute alcohol were added with stirring to precipitate out the sodium salt. Alsolute alcohol is necessary in this procedure since the sodium salt is extremely soluble in water, and the use of 95% alcohol would cause the loss of at least one-third of the yield. The beaker was then allowed to cool in the refrigerator for 1/2 hour before the solid was filtered off on to a Buchner funnel. The filtration may go a little slowly toward the end since the particles are finely divided and the material packs down. After drawing air through the solid to remove as much of the alcohol as possible, the solid was heated over a steam plate, and stored in a vacuum desiccator over anhydrous calcium chloride.

Preparation of N-Methyl-O,N-carbonyl salicylamide



Ten grams of carbonyl salicylamide were dissolved in 6N NaOH, using the same precautions as in the preparation of the sodium salt. The mixture was then cooled in an ice bath while 7.7 gm. (5.7 cc.) of dimethyl sulfate were added dropwise with stirring. This operation was carried out in the hood with extreme care since the vapors of dimethyl sulfate are poisonous and the liquid is corrosive. After almost all of the dimethyl sulfate had been added, the reaction mixture solidified suddenly with the evolution of much heat. The ice bath was then replaced by a water bath, and the reaction mixture heated for 1-half hour, then cooled, and 100 cc. of water added. The solid material was filtered off, and recrystallized from alcohol. The compound crystallized in beautiful needles which melted at 146°, which agreed with that in the literature (25). The yield was 7.7 gm., or 71% of the theoretical amount.

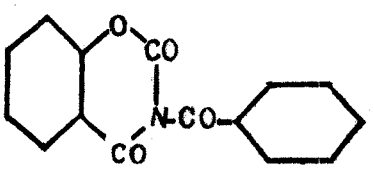
Preparation of N-Ethyl-O,N-carbonyl salicylamide




Ten grams of carbonyl salicylamide were dissolved in 6N NaOH and 9.5 gm. (8.1 cc.) of diethyl sulfate were added dropwise with cooling and stirring. There was very little evidence of a reaction occurring except the appearance of an

oily layer on the bottom of the flask. After all of the diethyl sulfate had been added, the mixture was heated on a water bath for two hours. By this time, a solid had separated out in the mixture. This was filtered off, after cooling the mixture, washed with water, and recrystallized from alcohol. Since the compound was rather solutle in alcohol, the alcohol solution was heated to boiling, and water added until it became turbid and allowed to cool. The compound crystallized in needles which melted at 107°, which agreed with that in the literature (25). The yield was 2.5 gm., or 21% of the theoretical amount.

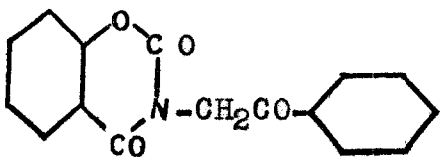
Preparation of N-Benzoyl-O,N-carbonyl salicylamide




Ten grams of carbonyl salicylamide were partially dissolved and suspended in 35 cc. of pyridine, and 9.7 gm. of benzoyl chloride added dropwise with stirring and cooling (when necessary). By the time all of the benzoyl chloride had been added, the mixture had become pasty. The flask was stoppered and the reaction mixture was then allowed to stand for 24 hours. On the addition of 200 cc. of ligroin, a white solid separated. This was filtered off and washed with water, partially dried by drawing air through the solid

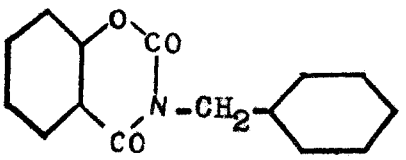
on the filter, and recrystallized from alcohol. The compound crystallized in long needles which melted at 171-172°, which agreed with the literature (25). The yield was 8.5 gm., or 52% of the theoretical amount.

Preparation of N-Phenacyl-O,N-carbonyl salicylamide



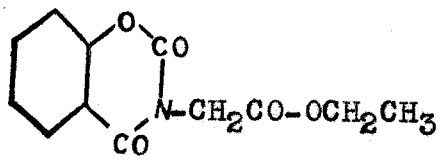

A suspension of 9.2 gm. of the sodium salt of carbonyl salicylamide (dried and powdered), and 7.7 gm. of phenacyl chloride (caution! lacrymatory), in 100 cc. of absolute alcohol, was heated under reflux for 24 hours. The mixture by this time had turned reddish, and there was a small quantity of solid on the bottom of the flask. To this mixture was added 100cc. of ligroin, but no additional solid separated, so the mixture was allowed to stand overnight in the refrigerator. The next day the greenish-brown solid was filtered off, ground up in a morter with water to remove unreacted sodium salt, and recrystallized from alcohol. The compound crystallized out in small cubes (1 mm. on edge) which melted at 186-187°, which agreed with that in the literature (25). The yield was 5.5 gm. of 40% of the theoretical amount.

Preparation of N-Benzyl-O,N-carbonyl salicylamide



Ten grams of the sodium salt of carbonyl salicylamide were thoroughly dried, powdered, and mixed with 20 cc. of benzyl chloride in a 125 cc. Erlenmeyer flask. The flask was then fitted with an air-cooled condenser closed with a calcium chloride tube. This condenser was 60-70 cm. long and was made from a piece of 8 mm. melting-point tubing, which had walls about 0.5 mm. thick. The flask was heated over a free flame which had been adjusted to such a height that the reaction mixture refluxed gently. The flask was shaken occasionally to keep the pasty mixture from caking. After about 3 hours, most of the solid had gone into solution. The contents of the flask were then poured into water in order to remove as far as possible the NaCl and the unreacted Na-salt. The pasty mixture on the bottom of the beaker then consisted of the benzyl-derivative and excess benzyl chloride. This was filtered off on a Buchner funnel, and the solid material pressed under water in order to force most of the benzyl chloride through. The solid residue was then washed with a little dilute alcohol, and recrystallized from 95% alcohol. The compound crystallized in fine needles which melted at 135°, which agreed with the literature (39). The yield was 7.5 gm., or 51% of the theoretical amount.

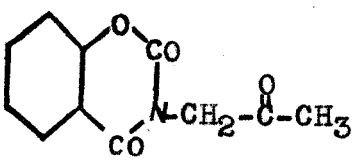
Preparation of the Ethyl Ester of α-N-carbonyl salicylamido-Acetic Acid



A mixture of 10 gm. of sodio-carbonyl salicylamide and 30 cc. of ethyl-α-chloroacetate was refluxed for 3 hours in a 125 cc. Erlenmeyer flask fitted with an air-cooled condenser closed with a calcium chloride tube. Occasional shaking served to keep the pasty mass well mixed. At the end of 3 hours a bit of the solid material was withdrawn, placed on a piece of pink litmus paper, and moistened with distilled water. If any unreacted Na-salt had been present, it would have given a basic reaction. Since the material tested was neutral, the reaction was considered to be over. The reaction mixture was then cooled and ligroin added to precipitate any of the compound which might have beed dissolved in the excess halide. After cooling the mixture for an hour in the refrigerator, the solid material was filtered off, washed with a little ligroin, sucked almost dry by drawing air through the mass on the filter, then washed free of the unreacted sodio-carbonyl salicylamide by adding a layer of water above the solid on the filter and drawing it slowly through the mass while at the same time keeping it tightly packed with the flattened end of a thick glass rod. The residue was then

recrystallized from alcohol. Since the crude solid was slightly brown, a little Darco charcoal was used to remove this discoloration. The compound crystallized in needles which melted at 126.5-127.5°, which agreed with that in the literature (39). The yield was 11 gm., or 82% of the theoretical amount.

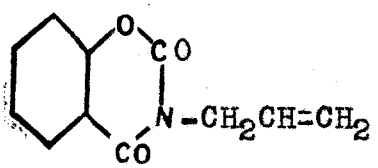
Preparation of N-Acetonyl-O,N-carbonyl salicylamide



A mixture of 10 gm. of sodio-carbonyl salicylamide and 30 cc. of bromoacetone (lacrymatory) was heated in a 125cc. Erlenmeyer flask fitted with a small water-cooled condenser closed with a calcium chloride tube, for a period of 7 hours, cooled and the reaction mixture treated with ligroin. A viscous oil separated which, after scratching and seeding, was set aside to cool in the refrigerator. After several hours, the oil set to a semi-solid mass which was filtered off, pressed free of liquid, washed successively with ligroin, then water, and recrystallized from alcohol. The compound separated in fine needles which melted at 99.5-100°. The yield was 2 gm., or 17% of the theoretical amount.

Anal. Calcd. for $C_{11}H_9O_4N$: N, 6.40 Found: 6.59

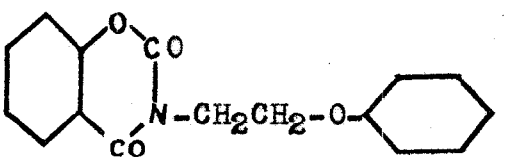
Preparation of N-Allyl-O,N-carbonyl salicylamide



A mixture of 12 gm. of sodio-carbonyl salicylamide and 30 cc. of allyl bromide was refluxed for 36 hours in a 100 cc. round-bottomed flask fitted with a ground joint and water-cooled condenser. The mixture was then cooled, the solid mass broken up, and made into a paste with a little acetone, and then re-precipitated with ligroin. After cooling the mixture for several hours, the solid was filtered off, washed thoroughly with water and recrystallized from alcohol. The compound crystallized in small white needles which melted at 101.5-102.5°. The yield was 10 gm. or 76% of the theoretical amount.

Anal. Calcd. for $C_{11}H_9O_3N$: N, 6.90 Found: 7.05

Preparation of N-(β-Phenoxyethyl)-O,N-carbonyl salicylamide

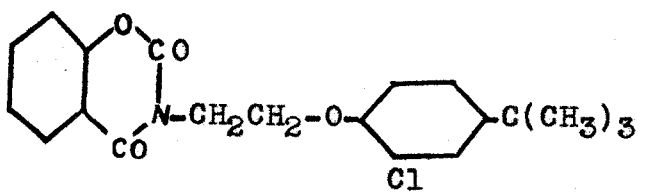


A mixture of 7 gm. of sodio-carbonyl salicylamide and 20 cc. of β-chloroethyl-phenyl ether was heated under reflux in a 125 cc. Erlenmeyer flask fitted with an air-cooled

condenser closed with a calcium chloride tube. After 9 hours most of the solid had gone into solution, so the contents of the flask were transferred to a beaker, cooled, and ground up thoroughly with ligroin. The solid was then filtered off, dried, and washed thoroughly with water, and recrystallized from alcohol. The compound crystallized in small needles which melted at 137-137.5°. The yield was 6.5 gm., or 65% of the theoretical amount.

Anal. Calcd. for $C_{16}H_{13}O_4N$: N, 5.24 Found: 5.22

Preparation of N-(4-tert-butyl-2-chloro-phenoxy)-Ethyl-O, N-carbonyl salicylamide

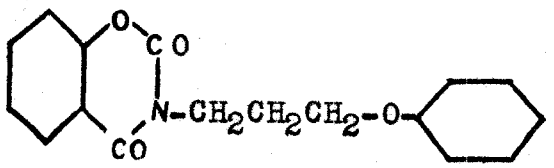



A mixture of 12 gm. of sodio-carbonyl salicylamide and 25 cc. of (4-tert-butyl-2-chlorophenyl)-2-chloroethyl ether, was heated on a hot-plate to 175° for 36 hours in a 125 cc. Erlenmeyer flask fitted with an air condenser closed with a calcium chloride tube. The solid was made into a paste with a little acetone and then reprecipitated with ligroin, cooled for several hours, filtered, dried, and washed thoroughly with water. The residue was recrystallized from alcohol. The compound separated in small white needles which melted

at 130-131°. The yield was 11 gm., or 49% of the theoretical amount.

Anal. Calcd. for $C_{20}H_{21}O_4ClN$: N, 3.75 Found: 3.87

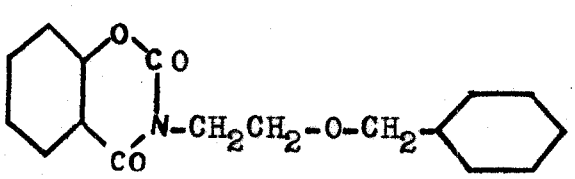
Preparation of N-(γ-phenoxy)-Propyl-O,N-carbonyl salicylamide



A mixture of 12 gm. of sodio-carbonyl salicylamide and 30 cc. of γ-phenoxypropyl bromide was heated to 185°, in an oil bath for 17 hours, in a 125 cc. Erlenmeyer flask fitted with an air-cooled condenser closed with a calcium chloride tube. The mixture was then cooled, ligroin added, and the flask set aside to cool for several hours in the refrigerator. The solid was then filtered off, washed with a little ether to remove excess bromide, then with water, and recrystallized from alcohol. The compound separated in small needles which melted at 108-108.5°. The yield was 11 gm., or 61% of the theoretical amount.

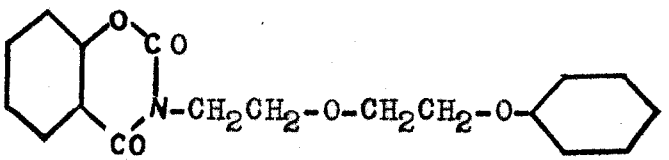
Anal. Calcd. for $C_{17}H_{15}O_4N$: N, 4.72 Found: 4.96

Preparation of N-( -benzyloxy)-Ethyl-O,N-carbonyl salicylamide



A mixture of 12 gm. of sodio-carbonyl salicylamide and 30 cc. of -chloroethyl-benzyl ether was heated to 185° in an oil bath for 17 hours, in a 125 cc. Erlenmeyer flask fitted with an air condenser. The reaction mixture was then treated as in the above procedure. The compound after isolation and recrystallization from alcohol melted at 96.5-97.5°. The yield was 11 gm., or 61% of the theoretical amount.
Anal. Calcd. for $C_{17}H_{15}O_4N$: N, 4.72 Found: 5.07

Preparation of β-Phenoxy-β'-N-carbonylsalicylamido-diethyl ether

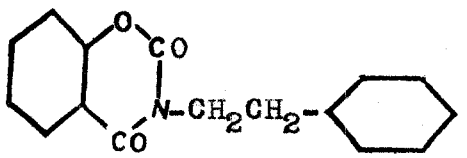


A mixture of 10 gm. of sodio-carbonyl salicylamide and 30 cc. of β-phenoxy-β'-chloroethyl ether was refluxed under an air-cooled condenser in a 125 cc. Erlenmeyer flask for 2 hours. The reaction mixture (which by this time had turned black) was allowed to cool, then ligroin was added and stirred well into the pasty mass. After standing in the refrigerator, most of the solid which had been in solution had precipitated, and it was filtered off, washed with water, and recrystallized from alcohol -- Darco being used to decolorize the material. The compound separated in small needles which melted at 86-87°. The yield was 7 gm., or 40% of the theo-

retical amount.

Anal. Calcd. for $C_{16}H_{17}O_3N$: N, 4.28 Found: 4.37

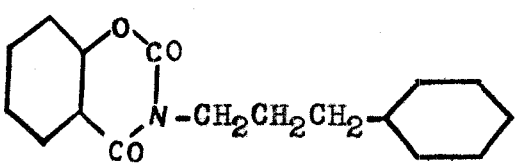
Preparation of N-(β-phenyl)-Ethyl-O,N-carbonyl salicylamide



A mixture of 12 gm. of sodio-carbonyl salicylamide and 25 cc. of phenylethyl bromide was heated in a 125 cc. Erlenmeyer flask fitted with an air-cooled condenser closed with a calcium chloride tube, for 36 hours on a hot-plate at a temperature of 175°. The reaction mixture was then cooled, the solid broken up and made into a paste with a little acetone, and precipitated with ligroin. After standing in the refrigerator for several hours, the brownish solid material was filtered off, washed with water, dissolved in 95% alcohol (14 gm./700 cc.), treated with Darco charcoal, and allowed to cool. The compound after two recrystallizations melted at 163.5-165°. The yield was 11.5 gm., or 67% of the theoretical amount.

Anal. Calcd. for $C_{16}H_{13}O_3N$: N, 5.25 Found: 5.39

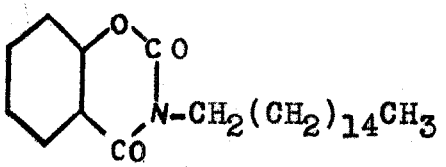
Preparation of N-(γ-phenyl)-Propyl-O,N-carbonyl salicylamide



A mixture of 12 gm. of sodio-carbonyl salicylamide and 25 cc. of phenylpropyl bromide was heated in a 125 cc. Erlenmeyer flask fitted with an air-cooled condenser closed with a calcium chloride tube, for 36 hours on a hot-plate at a temperature of 175°. The reaction mixture was purified as in the preceeding preparation. The compound which was more soluble than the phenyl-ethyl derivative, crystallized in prisms which melted at 71-72°. The yield was 8 gm., or 44% of the theoretical amount.

Anal. Calcd. for $C_{17}H_{15}O_3N$: N, 4.98 Found: 5.10

Preparation of N-Cetyl-O,N-carbonyl calicylamide

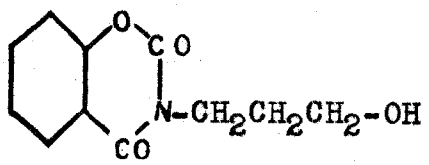



A mixture of 12 gm. of sodio-carbonyl salicylamide and 25 cc. of cetyl bromide was heated in a 125 cc. Erlenmeyer flask fitted with an air condenser closed with a calcium chloride tube, for 23 hours on a hot-plate at a temperature of 175°. On cooling, the reaction mixture set to a white wax-like solid. This was made into a paste with a little acetone, then treated with an excess of ligroin. The solid was then filtered off, and washed with water. The residue was dissolved in hot alcohol, but as soon as the solution had cooled slightly, it set to a solid mass. Even the use

of a hot-water funnel could not prevent this long enough for it to be filtered. The solid was then filtered off and recrystallized from ethyl acetate, from which it separated as a powdery white solid. The compound melted at 94-95.5°. The yield was 16 gm., or 64% of the theoretical amount.

Anal. Calcd. for $C_{24}H_{37}O_2N$: N, 3.62 Found: 3.73

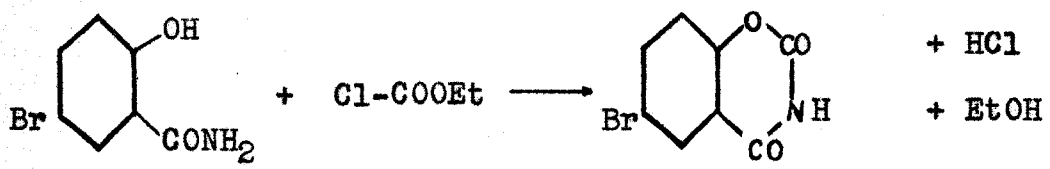
Preparation of N-(γ-hydroxy)-Propyl-O,N-carbonyl salicylamide



A mixture of 12 gm. of sodio-carbonyl salicylamide and 25 cc. of trimethylene chlorohydrin was heated under reflux for 17 hours. The reaction mixture on cooling, solidified. This was broken up, made into a paste with acetone, and precipitated with ligroin. After cooling the mixture in the refrigerator for several hours, the solid was filtered off, washed with water, and recrystallized from alcohol. The compound separated out as a finely divided solid, which melted at 99-101°. The yield was 6.5 gm., or 46% of the theoretical amount.

Anal. Calcd. for $C_{11}H_{11}O_4N$: N, 6.33 Found: 6.07

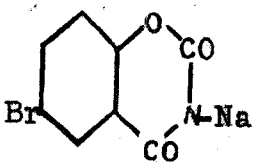
Preparation of 6-Bromo-O,N-carbonyl salicylamide




In a 3-necked 500 cc. round-bottomed flask fitted with a Hershberg wire stirrer, thermometer, and 60 cc. dropping funnel, was placed a solution of 39 gm. of 5-bromo salicylamide in 150 cc. of pyridine. An ice-bath was placed around the flask and the contents were stirred until the temperature had fallen below 10°. Then, 27 gm. of ethyl chloroformate were added dropwise at such a rate that the temperature did not rise above 10°. The ice-bath was then replaced by a hot-water bath. After heating the mixture for 2 hours, the contents of the flask were poured with stirring into a mixture of ice and water. The solid which precipitated was filtered off and washed with water, and recrystallized from "Butyl Cellosolve". The compound crystallized in plates which melted at 287-288°. The yield was 32 gm., or 73% of the theoretical amount.

Anal. Calcd. for $C_8H_4O_3NBr$: N, 6.19 Found: 6.09, 6.34

Preparation of the Sodium Salt of 6-Bromo-carbonyl salicylamide




In an 800 cc. beaker was placed 8 gm. of 6-bromo-carbonyl salicylamide, and 15 cc. of 6N NaOH were added with stirring in 1-2 cc. portions; each portion being allowed to react before the next was added. To the resulting past mass was added 500 cc. of absolute alcohol to precipitate out the sodium salt. The solid was then filtered off and dried over a steam table at 105°. The yield was 7.5 gm. or 75% of the theoretical amount.

Anal. Calcd. for $C_8H_3O_3NBrNa$: N, 5.30 Found: 5.52, 5.44

## Notes on the preparation of Derivatives of O,N-carbonyl Salicylamide

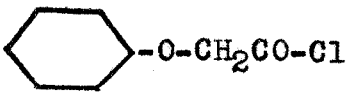
1. For some unknown reason, the reaction between aqueous sodium hydroxide and carbonyl salicylamide to form the sodium salt, seems to go more smoothly with freshly recrystallized carbonyl salicylamide. With samples which have been prepared for some time, the sodium salt may precipitate out while the NaOH is being added. This will also happen if an excess of NaOH is added at one time.

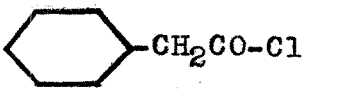
2. Unless the halide is very active, the reaction temperature must be rather high in order to obtain an appreciable reaction rate. This is most conveniently obtained by using an excess of the high-boiling alkyl (or aralkyl) halide as a solvent, since a high concentration of reactant is essential. Moreover, the reaction temperature must be high enough for the product to melt and be dissolved in the solvent, not only to prevent its coating over the unreacted sodium-salt, but also to prevent its being coated over by the sodium halide formed in the reaction. It was found that mechanical stirring of the reaction mixture did not appreciably alter either the reaction rate or the yield, and due to the long periods of time usually required, it might be dispensed with in the interest of economy.

3. Satisfactory yields in the reactions between carbonyl salicylamide and acid halides (other than benzoyl) could not be obtained under the same conditions. The following acid

halides were used:

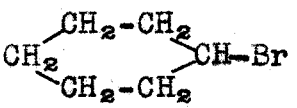
$CH_3CO\text{-}Cl$ Acetyl Chloride

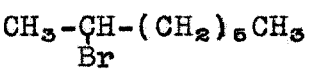
 Phenoxy-acetyl chloride

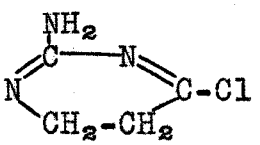
 Phenyl-acetyl chloride

The carbonyl salicylamide could usually be recovered unchanged at the end of the reaction. Even the reaction between the acid halide and sodio-carbonyl salicylamide in an inert solvent usually resulted in the production of carbonyl salicylamide.

4. Secondary halides do not react at all with sodio-carbonyl salicylamide under the usual conditions. The following secondarey halides were tried:

 Cyclohexyl bromide
Cyclohexyl bromide

 sec-Octyl bromide

 2-Amino-4-chloro pyrimidine

Their unreactivity might be due in part to stearic hindrance, but since in most cases some carbonyl salicylamide is regenerated (amounting in one instance to a quantitative recovery), it may be that the basic sodio-carbonyl salicylamide is able to split out HX from the compound (like NaOEt), and

this acid caused the release of the carbonyl salicylamide.

5. Very low yields were usually obtained with the hydroxyalkyl halides (especially halohydrins) -- usually less than a 10% yield of the desired product. The following compounds were reacted with sodio-carbonyl salicylamide with low yields:

| | |
|---|---|
| $Cl\text{-}CH_2CH_2\text{-}OH$ | Ethylene chlorohydrin |
| $Cl\text{-}CH_2CH_2CH_2\text{-}OH$ | Trimethylene chlorohydrin |
| $Cl\text{-}CH_2CH_2\text{-}O\text{-}CH_2CH_2\text{-}OH$ | $\beta$-Hydroxy-$\beta'$-chloroethyl ether |

# PART IV

## PHYSIOLOGICAL ACTION OF THE DIHYDRO-BENZOXAZONES AND OF THE CARBONYL SALICYLAMIDE DERIVATIVES

These compounds were tested for their analgesic activity in the laboratories of Parke, Davis and Co., Detroit, Michigan. This analgesic activity was evaluated by measuring the rise in pain threshold produced after their administration to guinea pigs. The exact experimental procedure used cannot be published at this time, but it is understood that it is a variation of the procedure employed by Hardy, Wolff, and Goodell (40) for measuring the pain threshold in humans.

In the Wolff, Hardy, Goodell method, light from a 1000 watt lamp is focussed by a condensing lens through a fixed aperture onto the blackened forehead of the subject. The intensity of the radiation was controlled by means of a rheostat. Immediately in front of the lamp was an automatic shutter which was arranged to allow radiation to pass to the subject for exactly three seconds. This exact timing of the exposure was important since the authors found that the pain threshold depended upon the length of the radiation. The stimulus felt was considered to be purely thermal. After the subject had been irradiated, he reported the sensation. If there had been no pain, the exposure was repeated with a more intense light after thirty to sixty seconds. They reported that the threshold was easily observed even by an

untrained subject. The subject was then removed and the radiation measured by a radiometer in gram-calories per square centimeters per second. The measurements were considered to be reproducable within ± 5% of the average value. After the required period after the administration of an analgesic drug, the procedure was repeated. The difference in intensity of light required to cause pain was considered to be the rise in pain threshold.

In adapting such a method to test animals, use can be made of the tendency of such animals to move almost any part of their bodies which might be strongly stimulated. For example, Smith, D'Amour and D'Amour (41), in a variation of this method, used the tendency of rats to flick their tails aside when they were strongly irradiated; the movement indicating the pain threshold.

All of the compounds described in the experimental section were tested for their analgesic action on guinea pigs. While it is impossible at the present time to publish the exact results, a qualitative description of their physiological actions might perhaps be in order. From a survey of the results, several trands are apparent:

1. The acute toxicity of these compounds varies with the type of compound and with the method of administration. For the dihydro benzoxazones, the MLD-50 in guinea pigs was approximately 400mg./kg. subcutaneously, and 600 mg./kg. when administered orally. For the carbonyl salicylamide derivatives, the acute toxicity under oral administration varied between

700 and 1000 mg/kg. As a comparison, Aspirin when orally administered, has an acute toxicity of about 600 mg/kg.

2. Concerning the analgesic activity of these compounds; the dihydro benzoxazones proved to be the more promising. Of these, 2-phenyl-dihydro benzoxazone was by far the most active. The rise in pain threshold after the administration of this drug proved to be about twice that of aspirin. This may have been due to several factors. It might be a case of synergism between the analgesic action of the salicylamide and the hypnotic action of the benzaldehyde produced on hydrolysis. Observers have noted a slight increase in the activity of analgesics when administered along with hypnotics such as the barbiturates. On the other hand, the action may have been due to the 2-phenyl derivative itself. It was noted that when methoxy groups were substituted in the benzene ring, as in the p-methoxyphenyl derivative, and in the 2,3-dimethoxyphenyl derivative, the activity was greatly reduced. The other dihydro benzoxazones showed activity equal to, and in some cases greater than Aspirin.

3. Acetylation of the dihydro benzoxazones cut down the analgesic activity considerably. This might be due to the fact that the N-acetyl salicylamide formed from the decomposition of these compounds, is less active than salicylamide itself.

4. The 6-bromo-dihydro benzoxazones in general showed little analgesic action, as compared with the unhalogenated derivatives.

5. Of the carbonyl salicylamide derivatives, the sodium salt was without analgesic action, probably because of its extreme solubility. N-benzoyl carbonyl salicylamide showed promising analgesic activity, but chronic toxicity studies showed that it caused some damage to the internal organs. None of the other derivatives showed any greater analgesic activity than Aspirin.

6. N-allyl carbonyl salicylamide was found to possess some hypnotic activity on mice, but not on rats.

## Use of the Benzoxazones as Sun Screens

It has been found that of the solar spectrum which reached the earth, a certain part of the ultraviolet radiations is capable of causing tanning and burning of the human skin, when exposed to these rays for a certain length of time. If the wavelength of light is plotted against the relative spectral effectiveness of radiant energy in the production of sunburn and of suntan, two curves will be obtained which more less coincide at a mixiмum point at a wavelength of 2950-3000 Å. It has been found that for light of wavelength shorter than 2700 Å, only superficial effects are produced, while light of wavelength 2950-3150 Å produced sunburn followed by tanning, and energy of wavelength longer than 3150 Å produced direct tanning with little or no burning.

Cosmetics manufacturers have introduced substances called

"sun screens" which have the power of absorbing ultraviolet light of the wavelength which causes burning. These are spread in a thin layer on the skin, and allow it to be tanned by the energy of higher wave length which is allowed to pass. Among the hundreds of compounds which have been tested for this property are a number of salicylates:

| | |
|---|---|
| Benzyl salicylate | Bornyl salicylate |
| Triethanolamine sylicylate | Salicylate of diethylene-glycol nonoethyl ether |
| Phenyl salicylate | Sodium salicylate |
| Phenylphenyl salicylate | Amyl salicylate |

Several of the dihydro benzoxazones and carbonyl salicylamide derivatives were therefore tested for their sun-screen activity. It was found that the absorption curves of each member of a given type were almost identical. The maximum for the dihydro benzoxazones occurred at about 2900-3000 Å, while that of the carbonyl salicylamide derivatives had shifted to about 3100 Å. The dihydro benzoxazones therefore seemed more promising in that respect. Tests were also made on these compounds to determine the changes, if any, which occurred on prolonged exposure. Since chemical sun-screens absorb the ultraviolet energy they come in contact with, chemical change of the screen often takes place which often destroys the activity of the compound, or in some cases the opposite happens, the screening action may be enhanced. It was found that on continued exposure of the dihydro benzoxazones to ultraviolet light, the absorption maximum in-

creases, indicating that the screening power of these compounds is enhanced on exposure.

One of these compounds, 2,2-dimethyl-dihydro benzoxazone was given a practical test. A 5% solution of it in 95% ethyl alcohol was made up, and to this was added some butyl stearate to serve as a film-forming substance. This solution was painted in strips onto the skin, which was then exposed to the sun for several hours. After about 20 hours, the untreated areas showed a definite reddening, but the portions which ha been treated with the sun-screen were unaffected.

# PART V

## SUMMARY

1. A convenient method for the preparation of large quantities of salicylamide is described.

2. Salicylamide condenses in the presence of HCl with certain aldehydes and with acetone, to form dihydro benzoxazones. It does not react, under the same conditions, with higher ketones. A list of the compounds prepared, as well as some of their derivatives, is to be found in Appendix 1.

3. In the presence of pyridine, salicylamide condenses with ethyl chloroformate to form O,N-carbonyl salicylamide. The imido hydrogen of this compound is acidic enough to be replaced by metals, and these metal salts will react with alkyl halides to form N-substituted derivatives. A list of the compounds prepared is to be found in Appendix 1.

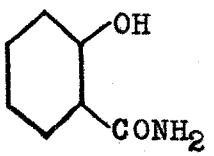
4. On Guinea Pigs, the dihydro benzoxazones showed marked analgesic activity, greater than that shown by the carbonyl salicylamide derivatives. Acetylation of the imido hydrogen or the substitution of bromine in the nucleus was found to reduce this activity greatly.

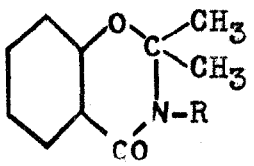
5. A simplified steam-distillation apparatus for use in the semi-micro Kjeldahl determination of nitrogen has been described (Appendix 2.).

PART VI

APPENDIX 1

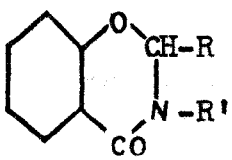
TABLE OF COMPOUNDS PREPARED

| No. | Formula | Name | New * |
|---|---|---|---|
| 1. |  | Salicylamide | |

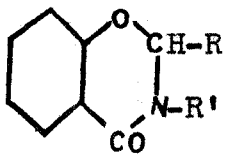
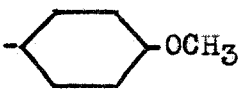
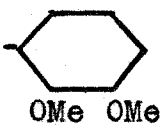
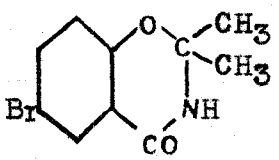
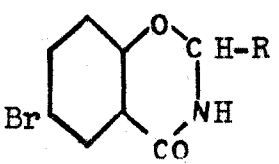


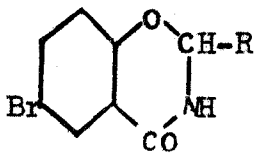
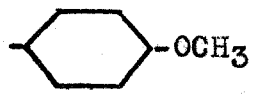
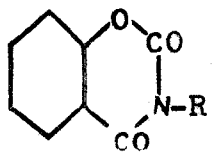
Value of R

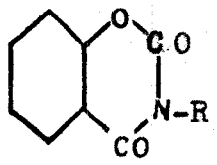
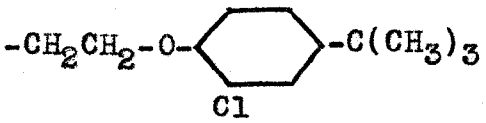
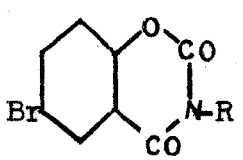
| | | | |
|---|---|---|---|
| 2. | Hydrogen | 2,2-dimethyl-3,4-dihydro-1,3-benzoxazin-4-one | |
| 3. | $-CO-CH_3$ | N-acetyl-2,2-dimethyl-3,4-dihydro-1,3-benzoxazin-4-one | |



| | Value of R | Value of R' | | |
|---|---|---|---|---|
| 4. | Phenyl | Hydrogen | 2-phenyl-3,4-dihydro-1,3-benzoxazin-4-one | |
| 5. | Phenyl | $-CO-CH_3$ | N-acetyl-2-phenyl-3,4-dihydro-1,3-benzoxazin-4-one | |
| 6. | $-CH_3$ | Hydrogen | 2-methyl-3,4-dihydro-1,3-benzoxazin-4-one | |
| 7. | $-CH_3$ | $-CO-CH_3$ | N-acetyl-2-methyl-3,4-dihydro-1,3-benzoxazin-4-one | * |
| 8. | $-CH_2CH_3$ | Hydrogen | 2-ethyl-4,3-dihydro-1,3-benzoxazin-4-one | * |

| No. | Formula | Name | New * |
|---|---|---|---|
| |  | | |
| | Value of R Value of R' | | |
| 9. | $-CH_2CH_2CH_3$ Hydrogen | 2-n-propyl-3,4-dihydro-1,3-benzoxazin-4-one | * |
| 10. | $-CH_2CH_2CH_3$ $-CO-CH_3$ | N-acetyl-2-n-propyl-3,4-dihydro-1,3-benzoxazin-4-one | * |
| 11. | $-CH(CH_3)_2$ Hydrogen | 2-i-propyl-3,4-dihydro-1,3-benzoxazin-4-one | |
| 12. | $-CH(CH_3)_2$ $-CO-CH_3$ | N-acetyl-2-i-propyl-3,4-dihydro-1,3-benzoxazin-4-one | * |
| 13. | $-CH(CH_2CH_3)_2$ Hydrogen | 2-(1-ethyl)-n-propyl-3,4-dihydro-1,3-benzoxazin-4-one | * |
| 14. | $-CH(CH_2CH_3)_2$ $-CO-CH_3$ | N-acetyl-2-(ethyl)-n-propyl-3,4-dihydro-1,3-benzoxazin-4-one | * |
| 15. |  Hydrogen | 2-p-methoxyphenyl-3,4-dihydro-1,3-benzoxazin-4-one | |
| 16. |  Hydrogen | 2-(2,3-dimethoxy)-phenyl-3,4-dihydro-1,3-benzoxazin-4-one | * |
| 17. |  | 6-bromo-2,2-dimethyl-3,4-dihydro-1,3-banzoxazin-4-one | * |
| |  | | |
| | Value of R | | |
| 18. | $-CH_2CH_3$ | 6-bromo-2-ethyl-3,4-dihydro-1,3-benzoxazin-4-one | * |

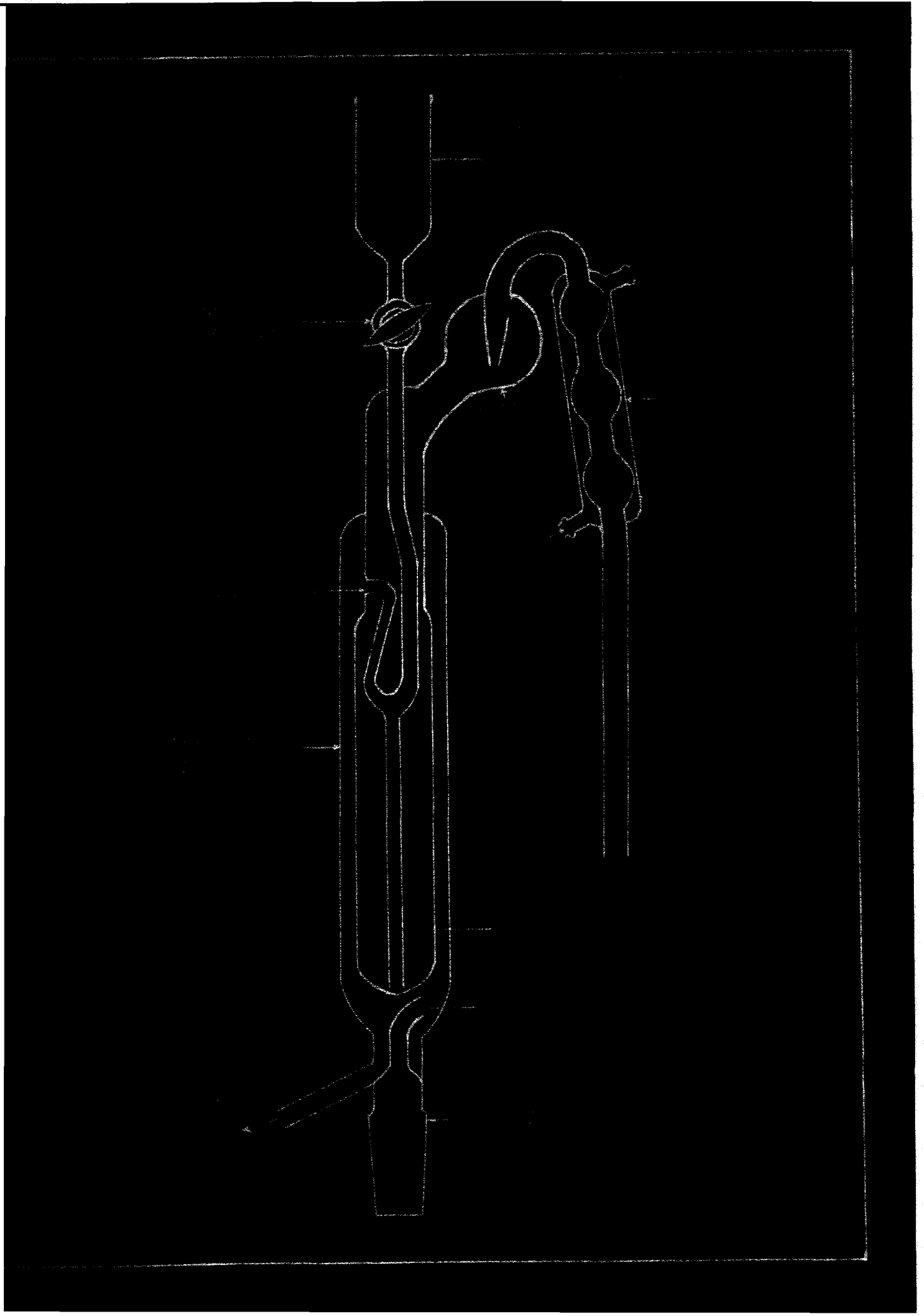
| No. | Formula | Name | New * |
|---|---|---|---|
| |  | | |
| | Value of R | | |
| 19. | $-CH_2CH_2CH_3$ | 6-bromo-2-n-propyl-3,4-dihydro-1,3-benzoxazin-4-one | * |
| 20. | $-CH(CH_3)_2$ | 6-bromo-2-i-propyl-3,4-dihydro-1,3-banzoxazin-4-one | * |
| 21. | $-CH(CH_2CH_3)_2$ | 6-bromo-2-(1-ethyl)-n-propyl-3,4-dihydro-1,3-benzoxazin-4-one | * |
| 22. |  | 6-bromo-2-phenyl-3,4-dihydro-1,3-benzoxazin-4-one | |
| 23. |  | 6-bromo-2-p-methoxyphenyl-3,4-dihydro-1,3-benzoxazin-4-one | * |
| |  | | |
| | Value of R | | |
| 24. | Hydrogen | O,N-carbonyl salicylamide | |
| 25. | Sodium | N-sodio-O,N-carbonyl salicylamide | |
| 26. | $-CH_3$ | N-methyl-O,N-carbonyl salicylamide | |
| 27. | $-CH_2CH_3$ | N-ethyl-O,N-carbonyl salicylamide | |
| 28. | $-CO-C_6H_5$ | N-benzoyl-O,N-carbonyl-salicylamide | |
| 29. | $-CH_2CO-C_6H_5$ | N-phenacyl-O,N-carbonyl-salicylamide | |
| 30. | $-CH_2-C_6H_5$ | N-benzyl-O,N-carbonyl-salicylamide | |
| 31. | $-CH_2CO-OC_6H_5$ | ethyl-α-(N-carbonylsalicylamido)-acetate | |

| No. | Formula | Name | New * |
|---|---|---|---|
| |  | | |
| | Value of R | | |
| 32. | $-CH_2-CO-CH_3$ | N-acetonyl-O,N-carbonyl-salicylamide | * |
| 33. | $-CH_2CHCH_2$ | N-allyl-O,N-carbonyl-salicylamide | * |
| 34. | $-CH_2CH_2-O-C_6H_5$ | N-(β-phenoxy)-ethyl-O,N-carbonyl salicylamide | * |
| 35. |  | N-(4-tert-butyl-2-chloro-phenoxy)-ethyl-O,N-carbonyl salicylamide | * |
| 36. | $-CH_2CH_2CH_2-O-C_6H_5$ | N-(γ-phenoxy)-propyl-O,N-carbonyl salicylamide | * |
| 37. | $-CH_2CH_2-O-CH_2-C_6H_5$ | N-(β-benzyloxy)-ethyl-O,N-carbonyl salicylamide | * |
| 38. | $-CH_2CH_2-O-CH_2CH_2-O-C_6H_5$ | β-phenoxy-β'-(N-carbonylsalicylamido)-diethyl ether | * |
| 39. | $-CH_2CH_2-C_6H_5$ | N-(β-phenyl)-ethyl-O,N-carbonyl salicylamide | * |
| 40. | $-CH_2CH_2CH_2-C_6H_5$ | N-(γ-phenyl)-propyl-O,N-carbonyl salicylamide | * |
| 41. | $-CH_2(CH_2)_{14}CH_3$ | N-cetyl-O,N-carbonyl salicylamide | * |
| 42. | $-CH_2CH_2CH_2-OH$ | N-(γ-hydroxy)-propyl carbonyl salicylamide | * |
| |  | | |
| | Value of R | | |
| 43. | Hydrogen | 6-bromo-O,N-carbonyl salicylamide | * |
| 44. | Sodium | 6-bromo-N-sodio-O,N-carbonyl salicylamide | * |

## DATA ON COMPOUNDS PREPARED

| No. | Formula | Mol. Wt. | Melting Point | Analysis, %N Calcd. | Found | Yield,% |
|---|---|---|---|---|---|---|
| 1. | $C_7H_7O_2N$ | 137 | 136-137° | | | 96 |
| 2. | $C_{10}H_{11}O_2N$ | 177 | 136-137° | | | 50 |
| 3. | $C_{12}H_{13}O_3N$ | 223 | 57.5-58° | | | 66 |
| 4. | $C_{14}H_{11}O_2N$ | 225 | 168.5-169.5° | | | 47.3 |
| 5. | $C_{16}H_{13}O_3N$ | 267 | 88° | | | 84 |
| 6. | $C_9H_9O_2N$ | 163 | 146-146.5° | | | 55.5 |
| 7. | $C_{11}H_{11}O_2N$ | 203 | 54-55° | 6.83 | 6.65 | 32 |
| 8. | $C_{10}H_{11}O_2N$ | 177 | 116-117.5° | 7.91 | 7.93 | 57 |
| 9. | $C_{11}H_{13}O_2N$ | 191 | 85.5-86.5° | 7.33 | 7.40, 7.20 | 73 |
| 10. | $C_{13}H_{15}O_3N$ | 233 | 112-116° (b.p.) 1 mm. Hg | 6.01 | 6.20 | 62 |
| 11. | $C_{11}H_{13}O_2N$ | 191 | 105.5-106.5° | | | 49 |
| 12. | $C_{13}H_{15}O_3N$ | 233 | 34.5-35.5° | 6.02 | 6.13 | 86 |
| 13. | $C_{13}H_{17}O_2N$ | 219 | 98-99° | 6.39 | 6.15, 6.23 | 49 |
| 14. | $C_{15}H_{19}O_3N$ | 261 | 56.5-57.5° | 5.37 | 5.17, 5.16 | 84 |
| 15. | $C_{15}H_{13}O_3N$ | 255 | 166° | | | 7.5 |
| 16. | $C_{15}H_{15}O_4N$ | 285 | 150.5-151° | 4.91 | 5.08 | 37 |
| 17. | $C_{10}H_{10}O_2NBr$ | 256 | 180-181° | 5.47 | 5.68 | 50 |
| 18. | $C_{10}H_{10}O_2NBr$ | 256 | 149.8-150.5° | 5.47 | 5.77,5.62 | 40 |
| 19. | $C_{11}H_{12}O_2NBr$ | 270 | 152.5-153.5° | 5.18 | 5.27,5.29 | 58 |
| 20. | $C_{11}H_{12}O_2NBr$ | 270 | 156.5-157° | 5.18 | 5.18,5.36 | 67 |
| 21. | $C_{13}H_{16}O_2NBr$ | 298 | 119-120° | 4.70 | 4.79,4.68 | 58 |
| 22. | $C_{14}H_{10}O_2NBr$ | 304 | 224.5-225.5° | | | 50 |
| 23. | $C_{15}H_{12}O_3NBr$ | 334 | 234-237° | 4.18 | 4.56 | 21 |

| No. | Formula | Mol. Wt. | Melting Point | Analysis, % N Calcd. | Found | Yield, % |
|---|---|---|---|---|---|---|
| 24. | $C_8H_5O_3N$ | 163 | 230.5-231.5° | | | 84 |
| 25. | $C_8H_4O_3NNa$ | 185 | | | | 99 |
| 26. | $C_9H_7O_3N$ | 177 | 146° | | | 71 |
| 27. | $C_{10}H_9O_3N$ | 191 | 107° | | | 21 |
| 28. | $C_{15}H_9O_4N$ | 267 | 171-172° | | | 52 |
| 29. | $C_{16}H_{11}O_3N$ | 281 | 186-187° | | | 40 |
| 30. | $C_{15}H_{11}O_3N$ | 253 | 135° | | | 51 |
| 31. | $C_{12}H_{11}O_6N$ | 249 | 126.5-127.5° | | | 82 |
| 32. | $C_{11}H_9O_4N$ | 219 | 99.5-100° | 6.40 | 6.59 | 17 |
| 33. | $C_{11}H_9O_3N$ | 203 | 101.5-102.5° | 6.90 | 7.05 | 76 |
| 34. | $C_{16}H_{13}O_4N$ | 267 | 137-137.5° | 5.24 | 5.22 | 65 |
| 35. | $C_{20}H_{21}O_4NCl$ | 374.5 | 130-131° | 3.75 | 3.87 | 49 |
| 36. | $C_{17}H_{15}O_4N$ | 297 | 108-108.5° | 4.72 | 4.96 | 61 |
| 37. | $C_{17}H_{15}O_4N$ | 297 | 96.5-97.5° | 4.72 | 5.07 | 61 |
| 38. | $C_{18}H_{17}O_3N$ | 327 | 86-87° | 4.28 | 4.37 | 40 |
| 39. | $C_{16}H_{13}O_3N$ | 267 | 163.5-165° | 5.25 | 5.39 | 67 |
| 40. | $C_{17}H_{15}O_3N$ | 281 | 71-72° | 4.98 | 5.10 | 44 |
| 41. | $C_{24}H_{37}O_3N$ | 387 | 94-95.5° | 3.62 | 3.73 | 64 |
| 42. | $C_{11}H_{11}O_4N$ | 221 | 99-101° | 6.33 | 6.07 | 46 |
| 43. | $C_8H_4O_3NBr$ | 242 | 287-288° | 6.19 | 6.09, 6.34 | 73 |
| 44. | $C_8H_3O_3NBrNa$ | 264 | | 5.30 | 5.52, 5.44 | 75 |



# APPENDIX 2

## SEMI-MICRO DISTILLATION APPARATUS

From the preceeding illustration of this apparatus, several advantages of this design are apparant. All rubber connections are eliminated from the distillation train. The danger of breakage is reduced by its strong compact construction. It takes up little desk space because of its compact, upright design. Since the distilling flask is surrounded by the steam jacket, very little condensation occurs in the flask. Only one precaution is necessary in its successful operation, i.e., the prevention of sucking back of the sample.

The apparatus consists of a distilling flask (32 mm. in diameter by 15 cm. in length, with a volume of approximately 100 cc.), enclosed in a 45 mm. glass jacket which serves as a steam jacket and trap. The steam generator consists of a 500 cc. two-necked flask; one neck of which is fitted with a 24/40 ♀ joint for fitting to the apparatus, while the other is a 14/35 ♀ joint fitted with a cap, through which water and fresh boiling stones (porcelain or silicon carbide) may be added. A larger sized flask for use as a steam generator is not recommended due to the loss of smoothness of control of the distillation.

A tube is sealed into the flask and an opening into the steam jacket leads steam through the solution being distilled. The arm of a Y in this tube is sealed through

the top of the flask to the filling funnel. Leading from the top of the flask is a trap (made from a 50 cc. bulb) and a tube leading to the bulb condenser which drains through a vertical delivery tube into the receiver. The use of Pyrex glass in the condenser is not objectionable since it has been shown (42) that it causes no more errors in operation than would a silver-tubed condenser.

The apparatus is shielded from drafts by cardboard screens to prevent sudden cooling. A few chips of porcelain or silicon carbide are used in the generator to prevent irregular boiling.

The apparatus is used in a manner similar to the usual micro-Kjeldahl distillation. The digested sample is rinsed in through the filling funnel, followed by caustic. It is inadvisable to mix the two layers all at once, since the resulting foaming may splash over into the receiver. It is mixed a little at a time until the solution is almost basic, by momentarily closing the drain tube and letting a bubble of steam stir up the contents, or the operator may stir up the mixture himself by gently puffing through a mouthpiece attached to the drain tube, before the water in the generator has started to boil. The last of the caustic is added to make the solution basic, the cock on the addition funnel and the clamp on the drain are closed, and the steam then allowed to run into the now basic solution. After the distillation has once started, no more cold liquid may be

added through the funnel since the resulting condensation of steam would suck the contents of the flask into the stream jacket. This also happens on removing the flame from the generator, and since it is quite rapid, it is necessary to make certain that the flame is well shielded during the distillation. After the distillation is over and the residue in the flask sucked into the steam trap and drained out, the flask is rinsed with a little cold water, which is also promptly sucked into the trap. The apparatus is then ready for the next sample. It is advisable to add a small chip to the generator before it is reheated in order to insure smooth boiling from the beginning.

# REFERENCES

The following books were used as basic material for the survey of antipyretics and analgesics:

Goodman, L., and Gilman, A., "The Pharmacological Basis of Therapeutics", The Macmillan Co., New York, (1940).

Hanzlik, P. L., "Actions and Uses of the Salicylates and Cinchophen in Medicine", Williams & Wilkins Co., Baltimore, (1927).

Jenkens, G. L., and Hartung, W. H., "The Chemistry of Organic Medicinal Products", John S. Swift Co., St. Louis, (1941).

Karrer, Paul, "Organic Chemistry", Eng. trans. from 5th German by A. J. McKee, Nordeman Publ. Co., New York, (1938).

May, P., and Dyson, G. M., "The Chemistry of Synthetic Drugs", 4th Ed., Longmans, Green and Co., New York, (1939).

Sollmann, T. A., "A Manual of Pharmacology", 5th Ed., W. B. Saunders Co., Philadelphia, (1936).

1. Knorr, Annalen, 238, 137 (1887).
2. D. R. P., 26,429, 33,536, 40,337, 42,726; Winther, "Patente der organischen Chemie", Vol. I, pp. 1135-58.
3. Doebner and Giesecke, Annalen, 242, 291 (1887).
4. D. R. P., 287,302 (1915).
5. Kolbe and Lautemann, Annalen, 113, 115 (1860).
6. Titherley and Hicks, J. Chem. Soc., 87, 1207 (1905).
7. Gerhardt and Chiozza, Ann. Chim. Phys., 46, 169 (1856).

8. Auwers, Ber., 38, 3256 (1905).
9. McConnan and Titherley, J. Chem. Soc., 89, 1321 (1905).
10. Titherley, J. Chem. Soc., 91, 1420 (1907).
11. Roth, Annalen, 154, 72 (1870).
12. Schuster, Annalen, 154, 80 (1870).
13. Hoffmann and Meyer, Ber., 25, 311 (1892).
14. Einhorn, Annalen, 343, 207 (1905).
15. Cebrian, Ber., 31, 1592 (1898).
16. Hicks, J. Chem. Soc., 97, 1032 (1910).
17. Moucka and Rögl, Ber., 59B, 756 (1926).
18. Keane and Nicholls, Pro. Chem. Soc., 23, 36 (1907).
19. Auwers, Ber., 40, 3506 (1907).
20. Titherley, J. Chem. Soc., 97, 200 (1910).
21. Titherley, and Hughes, J. Chem. Soc., 97, 1368 (1910).
22. Hughes and Titherley, J. Chem. Soc., 99, 23 (1912).
23. Bogisch, Chemik. Ztg., 13, 1078 (1889).
24. Schmidt, Journ. für prakt. Chem., (2) 5, 58 (1872).
25. Einhorn and Mettler, Ber., 35, 3647 (1902).
26. D. R. P., 117,346 (Winther, Vol. I, p208).
27. Wallach, Annalen, 184, 19 (1977).
28. Schiff, Annalen, 101, 93 (1857).
29. Einhorn and Schmidlin, Ber., 35, 3653 (1902).
30. Limpricht, Annalen, 98, 261 (1856).
31. Kline, J. Chem. Ed., 19, 332 (1942).
32. Hershberg, Ind. Eng. Chem., Anal. Ed., 8, 312 (1936).
33. Fischer, Ber., 65, 1032 (1932).

34. Ma and Zuazaga, Ind. Eng. Chem., Anal. Ed., 14, 280 (1942).

35. Niederl and Niederl, "Micromethods of Quantitative Organic Elementary Analysis", 2nd Ed., p71, John Wiley & Sons, New York, (1942).

36. Kirk, Ind. Eng. Chem., Anal. Ed., 8, 223 (1936).

37. Keane, J. Chem. Soc., 91, 264 (1907).

38. Fieser, "Experiments in Organic Chemistry ", 2nd Ed., p308, D. C. Heath and Co., New York, (1941).

39. Bogisch, Dissert. Rostock (1889), Beil. XXVII p263.

40. Hardy, Wolff, and Goodell, J. Clin. Investigation, 19, 649 (1940).

41. Smith, D'Amour and D'Amour, J. Pharm. & Exper. Therap., 77, 184 (1943).

42. Kammerer and Hallett, Ind. Eng. Chem., 19, 1295 (1927).