CXXII.—*Labile Isomerism among Benzoyl Derivatives of Salicylamide.*

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SALICYLAMIDE may be expected to give rise to two benzoyl derivatives :

- (a) $\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{CO}\cdot\text{NH}\cdot\text{CO}\cdot\text{C}_6\text{H}_5$, *N*-benzoylsalicylamide.
- (b) $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{O}\cdot\text{C}_6\text{H}_4\cdot\text{CO}\cdot\text{NH}_2$, *O*-benzoylsalicylamide.

By the action of methyl salicylate on sodium benzamide, one of the authors (Trans., 1902, 81, 1533) obtained a product (m. p. 122°) which was described as salicylbenzamide, $\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{CO}\cdot\text{NH}\cdot\text{CO}\cdot\text{C}_6\text{H}_5$, that is, (a) the *N*-benzoyl derivative. The assumption that the compound, which on analysis gave 5.67 per cent. of nitrogen (theory requires $\text{N}=5.80$ per cent.), possessed this structural formula was based on the following considerations: (1) its synthesis, a general reaction having been established between esters and sodium acylamides whereby sodium secondary amides are formed; (2) its properties, notably its easy decomposition with aqueous alkalis into salicylic acid and benzamide, and the fact that it gives an intense violet coloration with ferric chloride; (3) its non-identity with the *O*-benzoyl derivative, (b) $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{O}\cdot\text{C}_6\text{H}_4\cdot\text{CO}\cdot\text{NH}_2$ (m. p. 200°), described previously.

Further experiments recently carried out by the authors show that this assumption was wrong, and that the substance is a peculiar double compound of benzamide and salicylic acid ($\text{N}=5.4$ per cent.) which shows the above properties, and whilst attempts to prepare

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N-benzoylsalicylamide have failed, other benzoyl derivatives of salicylamide have been isolated during the investigation which are of considerable interest.

Excluding the substance melting at 122°, the only benzoyl derivative of salicylamide hitherto described is the compound melting at 200°, which was obtained by Gerhardt and Chiozza (*Ann. Chim. Phys.*, 1856, **46**, 139; *Jahresber.*, 1856, 502) by heating salicylamide and benzoyl chloride at 180°, and was described by them as "benzoylsalicylamide,"*

Limpricht (*Annalen*, 1856, **99**, 249), who subsequently investigated the same compound and prepared several metallic derivatives, called it "benzoylsalicylaminssäure," since he assumed that salicylamide was an acid ("salicylaminssäure"), and gave Gerhardt's compound the formula $\text{NH}(\text{C}_{14}\text{H}_5\text{O}_2)(\text{C}_{14}\text{H}_4\text{O}_2) \left\{ \begin{smallmatrix} \text{O}_2 \\ \text{H} \end{smallmatrix} \right\}$. It is quite evident that Gerhardt and Chiozza, as well as Limpricht, considered the compound to be an *N*-benzoyl derivative, and their formulæ interpreted into the modern system become $\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{CO}\cdot\text{NH}\cdot\text{CO}\cdot\text{C}_6\text{H}_5$. In spite of this, and although no further work appears to have been done on the substance, it is quoted in Beilstein's *Handbuch* (vol. ii, p. 1500) as the *O*-benzoyl derivative, $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{O}\cdot\text{C}_6\text{H}_4\cdot\text{CO}\cdot\text{NH}_2$.

Einhorn (in a private communication to one of the authors) mentions that the same compound is produced by the benzylation of salicylamide by the pyridine method, but doubts whether it is the *O*-benzoyl derivative.

From what is described below, it will be seen that the constitution of this compound is of considerable importance. A close investigation of its properties, and especially the fact that it does not under any conditions give a coloration with ferric chloride, establishes clearly the fact that the benzoyl group is attached to the phenolic oxygen atom, and not to nitrogen, but it is also evident, as will be shown, that the compound is not the simple amide, $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{O}\cdot\text{C}_6\text{H}_4\cdot\text{CO}\cdot\text{NH}_2$.

Originally with the object of clearing up the relation between Gerhardt's compound and the product melting at 122°, the authors have investigated

- (a) The interaction of methyl salicylate and sodium benzamide.
- (b) The interaction of benzoyl chloride and salicylamide in presence of aqueous alkali.
- (a) The object in repeating this work was to obtain the compound

* When pure, the substance melts at 208°. To simplify the description in the text, where the substance is frequently mentioned, it is referred to as Gerhardt's compound.

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described as *N*-benzoylsalicylamide and investigate it more completely. It was found that under suitable conditions both the substance melting at 122° and Gerhardt's compound were formed, but the expected *N*-benzoylsalicylamide was not obtained.

(b) The object in benzoylating salicylamide in the cold by a wet method was to ascertain whether the product of benzoylation was identical with Gerhardt's compound, the simple reaction being expected:

It was found that although under suitable conditions this normal change takes place, the process is complicated by secondary reactions. The normal benzoylation leads to the production of the simple *O*-benzoylsalicylamide which is *not identical* with Gerhardt's compound; it was isolated with difficulty as an unstable crystalline substance, melting when pure at 144°, but it passes with remarkable ease into Gerhardt's isomeride (m. p. 208°).

Benzoil chloride and salicylamide, by the Schotten-Baumann process, using cold aqueous sodium carbonate instead of caustic soda, yield three substances in varying proportion according to circumstances, namely: (1) monobenzoylsalicylamide (m. p. 144°); (2) monobenzoylsalicylamide (m. p. 208°, identical with Gerhardt's compound); (3) dibenzoylsalicylamide (m. p. 129°).

In some cases (2), which is usually produced only in small quantity, is not formed at all, and in any case it has been shown that it is formed not directly but as a result of rearrangement of (1). The compound (3) is also formed not directly but from (2), and it has been shown by a separate experiment that Gerhardt's compound is readily converted into dibenzoylsalicylamide (m. p. 129°) by benzoylation in presence of aqueous sodium carbonate.

Isomerism of the Two Monobenzoylsalicylamides.

There can be no question that the primary action in the benzoylation of salicylamide in presence of sodium carbonate leads to the formation of the less stable derivative (1) melting at 144°, which readily undergoes transposition to the more stable derivative (2) melting at 208°. These two substances, which are isomeric and have the same molecular weight, are of exceptional interest. Their isomerism cannot be accounted for by assuming that the benzoil groups are differently situated, that is, that one is *O*-benzoil- and the other *N*-benzoil-salicylamide, since there are reasons for believing that both are *O*-benzoil derivatives. The main reasons are: (1) neither gives any coloration with ferric chloride in any solvent, but both after

hydrolysis even with cold alkali develop an intense violet coloration owing to the formation of salicylamide; (2) neither is decomposed by heating with aqueous ammonia, whereas an *N*-benzoyl derivative would be easily broken up like dibenzamide; (3) on heating, both yield a polymeric form of *O*-benzoylsalicylonitrile; (4) their mode of formation by wet benzoxylation is intelligible on the assumption that they are *O*-benzoyl derivatives.

Reviewing the various possible monobenzoyl derivatives that might be produced in the benzoxylation of salicylamide by the Schotten-Baumann process, it is necessary to take into account the possibility of salicylamide undergoing tautomeric or (which is very unlikely) isomeric change, so that conceivably it might give rise to derivatives of the forms:

Isomeric change leading to oxime forms (γ) and (δ) is very improbable, but might be considered, since the reverse change (from oxime to amide) is always possible. The possible monobenzoyl derivatives of the above forms are:

Since the two benzoyl derivatives under discussion give no ferric chloride reaction, and behave generally as *O*-benzoyl derivatives, *c*, *d*, *e*, and *g* are excluded; *f* (*O*-benzoylsalicylaldoxime) is also excluded since it is known and melts at 130° (Beckmann, *Ber.*, 1893, 26, 2625). Of the three remaining alternatives, *b* must represent the constitution of the more stable monobenzoyl derivative melting at 208° since it is readily soluble in alkalis, whilst the less stable compound (m. p. 144°) may have either of the formulæ *a* and *h*. The latter formula *h* is improbable because compounds containing the grouping $\text{CH} \cdot \text{NH}$ are known only in the form of *N*-alkyl or aryl derivatives,

and because the formation of such a substance would involve the rearrangement of salicylamide, for which there is no evidence. Moreover, the properties of the derivative in question (m. p. 144°) are

inconsistent with formula *h*, since a compound of this constitution would be immediately acted on by benzoyl chloride, or at least be unstable in the presence of this reagent. Thus Beckmann (*Ber.*, 1893, 26, 2627) has shown that both $\text{C}_6\text{H}_5 \cdot \text{CH} - \text{N} \cdot \text{CH}_2 \cdot \text{C}_6\text{H}_5$ and

$\text{OH} \cdot \text{C}_6\text{H}_4 \cdot \text{CH} - \text{N} \cdot \text{CH}_2 \cdot \text{C}_6\text{H}_5$ rapidly undergo rearrangement, on treat-

ment with benzoyl chloride, to the stable amide forms respectively, $\text{C}_6\text{H}_5 \cdot \text{CO} \cdot \text{NH} \cdot \text{CH}_2 \cdot \text{C}_6\text{H}_5$ and $\text{OH} \cdot \text{C}_6\text{H}_4 \cdot \text{CO} \cdot \text{NH} \cdot \text{CH}_2 \cdot \text{C}_6\text{H}_5$; the compound melting at 144° , on the other hand, is unaffected by heating with benzoyl chloride. There only remains therefore formula *a* for the substance, and this is consistent with its properties and mode of formation from salicylamide.

Since the possibility of stereochemical isomerism is excluded, and the difference between the two monobenzoyl derivatives of salicylamide must be explained on structural grounds, on the above reasoning it would appear that the origin of the difference lies solely within the amide grouping, since otherwise it is necessary to assume for one of the compounds some fundamental structural difference, such as a formula of the

following type: $\begin{array}{c} \text{CO} \cdot \text{NH} \\ | \\ \text{C}_6\text{H}_4 \cdot \text{O} \end{array} > \text{C} < \begin{array}{c} \text{C}_6\text{H}_5 \\ | \\ \text{OH} \end{array}$, for which there is no evidence.

The most intelligible hypothesis is to assume that isomerism is referred to the tautomeric amide group, which appears in two distinct forms, $-\text{CO} \cdot \text{NH}_2$ and $-\text{C}(\text{OH}) \cdot \text{NH}$, producing labile isomerides.

There are as yet no examples known of such labile isomerism among simple amides, and the isolation of such isomerides appears to be only possible when the influence of a neighbouring group is strong and favourable. The possibility of the existence of iminohydroxy-compounds containing the grouping $-\text{C}(\text{OH}) \cdot \text{NH}$, isomeric with amides, has already been suggested by Eschweiler (*Chem. Centr.*, 1898, ii, 527), who has obtained products which he calls "iminohydrins" by the action of water, or water in presence of a metallic base, on the iminoethers obtained from the nitriles of certain hydroxy-acids, such as glycollic and lactic acids. The constitution of these iminohydrins, however, is uncertain, and there appears to be no evidence of labile isomerism, but the substances were described as less fusible than the corresponding amides, and as having both basic and weakly acidic properties.

The authors suggest the name "iminohydroxide" as perhaps the most suitable designation for compounds containing the grouping $-\text{C}(\text{OH}) \cdot \text{NH}$ which are distinct from the isomeric amides. The isolation of two forms of *O*-benzoylsalicylamide, one of which is labile

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throws some light on the tautomerism of amides, and renders it probable that some amides really have the imino-hydroxy-structure and not the ordinary amide formula, and it is possible that salicylamide, for instance, which is soluble in sodium carbonate and ammonia, and behaves as a monobasic acid, is $\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{C}(\text{OH})\cdot\text{NH}$ and not $\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{CONH}_2$. Benzamide is without doubt $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{NH}_2$, but in aqueous solution this form evidently exists in equilibrium with the tautomeric form $\text{C}_6\text{H}_5\cdot\text{C}(\text{OH})\cdot\text{NH}$. Adopting the view in reference to amides that in favourable circumstances tautomerism may merge into actual isomerism, and accepting this explanation of the isomerism of the *O*-benzoylsalicylamides, the latter must be represented:

The view that these two substances owe their difference to different structure in the amide grouping is supported by the properties of the compounds. The labile form, on heating a few degrees above its melting point, rapidly changes to the stable form, which, having a higher melting point, separates out as a solid. The transformation occurs nearly quantitatively, and does not appear to be reversible. The labile form in alcoholic solution at the ordinary temperature slowly changes to the stable form, which, being sparingly soluble in alcohol, crystallises out, and the transformation is complete in a week. The change in alcoholic solution is hastened by a trace of sodium ethoxide, and is practically instantaneous if an excess of sodium ethoxide or sodium hydroxide is added, a yellow solution or a solid mass resulting, which contains the sodium compound of the stable form. The labile form is similarly transformed into the stable modification in pyridine solution, but only slowly at the ordinary temperature, the change being complete in a week. The transformation rapidly takes place in boiling water, in which the labile form is somewhat soluble, and in the course of 60—80 seconds the stable form, which is practically insoluble in boiling water, separates out quantitatively in the form of a flocculent, microcrystalline solid. The labile form, however, appears to be unaffected in benzene solution, and, being sparingly soluble in the cold and readily in the hot solvent, may be purified without loss by crystallisation from this medium. The rate of transformation in alcoholic solution at the ordinary temperature is sufficiently slow to enable alcohol to be used in its purification provided it is quickly precipitated out of solution by the addition of cold water. In general it would appear that the transformation from the labile to the stable form is effected by ionising solvents. The transformation-velocities have not yet been measured.

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The stable form is readily soluble in aqueous sodium hydroxide, forming a yellow solution of the sodium salt; it is also soluble in sodium carbonate, and even in ammonia, and from the resulting yellow solutions it is precipitated unchanged by acids as a white, gelatinous solid. The labile form, on the other hand, is insoluble in aqueous alkalis, but gradually changed by them, and even by ammonia, and on standing passes completely into a yellow solution from which the stable form is precipitated by acids; the change is quantitative. From their respective behaviour with alkali, there can be no doubt that it is the less easily fusible stable form which has the iminohydroxy-structure, and, therefore, the labile form the simple amide configuration. It is particularly the latter circumstance that renders it possible that many supposed amides are really iminohydroxides. Of the two forms of *O*-benzoylsalicylamide, that possessing the amide formula is unquestionably the labile modification, and in no circumstances as yet has it been found that a reverse change from the iminohydroxide to amide takes place. It is of interest to record that the instability of the labile form is not confined merely to the grouping $\text{-CO}\cdot\text{NH}_2$ involved in the change. The stability of the entire molecule is apparently affected. Thus with acetic anhydride, which ordinarily has very little effect on amides, it is transformed partly into the acetyl derivative,

(m. p. 97°), but at the same time partly by loss of water into benzoylsalicylonitrile; similarly, during benzoylation in presence of pyridine it is partly converted into the nitrile. The stable form, on the other hand, gives no benzoylsalicylonitrile with acetic anhydride, and behaves normally during pyridine benzoylation (see p. 1224). Again, although the stable form is soluble in cold concentrated sulphuric acid without change, the labile form is readily hydrolysed, yielding salicylamide and benzoic acid, thus showing greater general instability. Owing to the extreme ease with which the labile form changes into the stable, great difficulty was encountered in isolating the former in workable quantities, since the transformation occurs continually during its formation by wet benzoylation and subsequent purification. Several attempts failed to produce any of the substance, but ultimately, by adopting special precautions, it was found possible to isolate the labile compound perfectly pure and in moderately good yield.

Besides the two monobenzoyl derivatives obtained in the benzoylation of salicylamide, a dibenzoyl derivative (3) was isolated, which melted, when pure, at 129° , and in many cases this substance was formed in the largest proportion. Its production is due to the further action of benzoyl chloride in presence of sodium carbonate on *O*-benzoylsalicyliminohydroxide, which is continually being formed during the reaction by the rearrangement of *O*-benzoylsalicylamide. This

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secondary benzoylation occurs with greater rapidity than the primary process, which leads to the formation of *O*-benzoylsalicylamide; hence there is a great tendency during the benzoylation of salicylamide towards the production of dibenzoylsalicylamide, even when 1 mol. of benzoyl chloride only is used, in which case a large proportion of the salicylamide remains unaffected. Since, however, the dibenzoyl derivative is formed from the *O*-benzoylsalicyliminohydroxide, and not directly from the salicylamide or *O*-benzoylsalicylamide, the extent of production of the dibenzoyl derivative is obviously determined by the rate of transformation of the labile into the stable monobenzoyl derivative. Hence, by limiting the rate of rearrangement, more *O*-benzoylsalicylamide and correspondingly less dibenzoylsalicylamide is formed. This was effected by careful and slow addition of the alkali, which is the chief agent effecting rearrangement, and by offering the maximum surface of contact between the benzoyl chloride and sodium salicylamide in order to hasten the primary benzoylation. Working under these conditions, the largest yield of the labile monobenzoyl derivative was obtained, whilst when the conditions were reversed the largest yield of the dibenzoyl derivative resulted.

Dibenzoylsalicylamide may be either $\text{BzO} \cdot \text{C}_6\text{H}_4 \cdot \text{C}(\text{OBz}) : \text{NH}$ or $\text{BzO} \cdot \text{C}_6\text{H}_4 \cdot \text{CO} \cdot \text{NHBz} \rightleftharpoons \text{BzO} \cdot \text{C}_6\text{H}_4 \cdot \text{C}(\text{OH}) : \text{NBz}$. Although the first of these formulæ might be accepted as consistent with its mode of formation from *O*-benzoylsalicyliminohydroxide by wet benzoylation, the second must be adopted for the following reasons: (1) it is produced by the pyridine benzoylation of *both* *O*-benzoylsalicylamide and *O*-benzoylsalicyliminohydroxide; (2) on benzoylation in presence of pyridine, it yields a tribenzoyl derivative of salicylamide which, from its stability, must be regarded as the tertiary amide,

(3) it behaves normally as a secondary amide, is readily hydrolysed by alkali, even by ammonia, and shows a tautomeric character. The compound is therefore *O-N*-dibenzoylsalicylamide.

A compound isomeric with this substance and having the same melting point (128°) and similar solubilities has been described by Beckmann (*Ber.*, 1893, **26**, 2625), namely, dibenzoylsalicylaldoxime, obtained by the benzoylation of salicylaldoxime by the Schotten-Baumann method. Owing to the close resemblance between these two substances, it was at first thought that they were identical, and that therefore either the oxime or the amide, from which they were respectively derived, had undergone rearrangement during benzoylation. This assumption was, however, disproved by a close comparison of the properties of dibenzoylsalicylamide with the dibenzoyl derivative obtained by repeating Beckmann's work. Beckmann's compound is

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somewhat less soluble in solvents than the authors' compound, and is totally unaffected by aqueous sodium hydroxide; further, on heating above its melting point, it decomposes suddenly into benzoylsalicylonitrile and benzoic acid, and is thus distinguished from its isomeride, which breaks up slowly at a much higher temperature. There is not the slightest doubt as to non-identity of the two substances.

The existence of two forms of monobenzoylsalicylamide, one of which is labile, might be expected to render likely the existence of two corresponding forms of *O-N*-dibenzoylsalicylamide, $\text{BzO} \cdot \text{C}_6\text{H}_4 \cdot \text{CO} \cdot \text{NHBz}$ and $\text{BzO} \cdot \text{C}_6\text{H}_4 \cdot \text{C}(\text{OH}) : \text{NBz}$. As already stated, both monobenzoyl derivatives yield the same dibenzoyl derivative on further benzoylation whether by the wet or the pyridine method. It is evident, therefore, that the labile character becomes sufficiently enhanced by the introduction of a second benzoyl group to render possible the existence of only one, namely, the stable modification of the dibenzoyl derivative, which probably has the benzoylimino-hydroxy-structure, and the phenomenon of labile isomerism has merged into one of actual tautomerism. There is, however, distinct evidence of the existence of a second very labile form of the dibenzoyl derivative which has not yet been isolated, but a mixture of what appears undoubtedly to be the two forms has been obtained (see p. 1226), which has different physical and chemical properties from those of the stable modification, and attempts are being made to isolate the labile substance.

Dibenzoylsalicylamide, on further benzoylation in presence of pyridine, yields tribenzoylsalicylamide, melting at 188° , which from its sparing solubility in solvents, its stability, and general resemblance to tribenzamide must be regarded as the tertiary amide,

The genetic relations of the benzoyl derivatives of salicylamide as elucidated in this investigation may be conveniently set forth in the scheme :

EXPERIMENTAL.

Condensation of Methyl Salicylate and Sodium Benzamide.

In repeating this work, the condensation was effected as described previously (Titherley, Trans., 1902, **81**, 1533). From the product after treatment with iced water and filtering, a discoloured alkaline solution was obtained which, on acidifying, gave an oil quickly solidifying to a brown, granular solid. The latter was drained on a porous plate to remove traces of oily methyl salicylate present. The solid consisted of a mixture of two substances which were separated by treatment with boiling water. The insoluble residue, after purification by crystallising from alcohol, melted at 205° and was found to be identical with Gerhardt's compound. The portion which was soluble in hot water and which showed a tendency to be deposited in an oily form separated out in faintly discoloured needles; after crystallisation from light petroleum, it was obtained in flat, colourless needles melting at 120° . This substance, which was previously mistaken for *N*-benzoylsalicylamide, contained 5.81 per cent. of nitrogen, and proved on investigation to be a *double compound* having the composition

which has already been described by Pinner (*Ber.*, 1890, **23**, 2936), who isolated it as a by-product in the condensation of methyl salicylate and benzamidine in presence of sodium hydroxide. Similar double compounds of benzamide with oxalic and succinic acid have been

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described by one of the authors (Trans., 1904, 85, 1682). That the above substance melting at 120° is a double compound and not the supposed *N*-benzoylsalicylamide is proved by the following circumstances: (1) the larger crystals are rendered opaque by careful treatment with aqueous sodium hydrogen carbonate in the cold, owing to decomposition into benzamide and salicylic acid, which goes into solution: this property is characteristic of the other double compounds of benzamide alluded to; (2) on warming with strong aqueous ammonia, the compound (m. p. 120°) decomposes yielding benzamide (m. p. 128°) and salicylic acid (m. p. 155°). *N*-Benzoylsalicylamide would yield benzamide and salicylamide (m. p. 138°), as dibenzamide with ammonia yields only benzamide and no benzoic acid; (3) a compound identical in every respect with the substance melting at 120° can be prepared by digesting a mixture of salicylic acid and benzamide with an excess of alkali, filtering, acidifying, and recrystallising the precipitate from water.

Although a large number of experiments were carried out on the condensation of sodium benzamide and methyl salicylate under varied conditions, it was never found possible to obtain *N*-benzoylsalicylamide, which is apparently too unstable in presence of alkali to be thus isolated. The method is evidently of no value for the synthesis of this substance, and other methods which have as yet been attempted have been equally unsuccessful. The production of Gerhardt's compound, in which, for reasons already stated, the benzoyl group is without doubt attached to phenolic oxygen, shows, moreover, that the hydroxyl group in methyl salicylate interferes with the normal condensation which would produce the *N*-benzoyl derivative.

Wet Benzoylation of Salicylamide.

Preparation of O-Benzoylsalicylamide, O-Benzoylsalicyliminohydroxide, and O-N-Dibenzoylsalicylamide.

Benzoyl chloride acts fairly rapidly on an aqueous solution of salicylamide in sodium hydroxide (each in the proportion of 1 mol.), giving dibenzoylsalicylamide and *O*-benzoylsalicyliminohydroxide and very small quantities of *O*-benzoylsalicylamide. The action is accompanied by a generation of heat, and if the whole mass is not well cooled the products formed are quickly hydrolysed forming salicylamide and benzoic acid. By working carefully, a 14 per cent. yield of dibenzoylsalicylamide (m. p. 126°) and a 6 per cent. yield of *O*-benzoylsalicyliminohydroxide (m. p. 205°) were obtained, whilst the yield of the labile *O*-benzoylsalicylamide (m. p. 141°) did not exceed 1–2 per cent.

By using aqueous sodium carbonate instead of sodium hydroxide in the benzoylation of salicylamide, the same three compounds are produced, but the process can be better controlled, and under the conditions described below may be used with greater success for the preparation of the labile compound. Even slight variation of conditions, chiefly temperature, concentration, and the order of addition of the materials, greatly affects the proportion of the three substances formed relatively to each other and to the salicylamide originally present. In any case, when molecular proportions of the interacting materials are taken, large quantities of unchanged salicylamide are found at the end of the reaction. This is due partly to the formation of dibenzoylsalicylamide, which cannot be entirely prevented, and partly to continual hydrolysis of the three benzoyl derivatives occurring concurrently with their formation. In the earlier experiments, attempts were made to avoid these difficulties by hastening the benzoylation by violent stirring with a machine, but this mechanical mixing tended to increase rather than diminish the yield of dibenzoylsalicylamide. After a number of trials, it was found that much the best yield of the labile *O*-benzoyl derivative could be obtained by mixing the salicylamide and benzoyl chloride first, adding a strong aqueous solution of sodium carbonate gradually in slight excess, and allowing the action to proceed very slowly. The following experiment will illustrate the best conditions for the formation of the labile substance: 28 grams of salicylamide (1 mol.) were mixed with 28 grams of benzoyl chloride (1 mol.) and treated gradually with a 16 per cent. aqueous solution of 16 grams of sodium carbonate containing 92 per cent. Na_2CO_3 (representing $1\frac{1}{2}$ atoms of sodium). The addition of the sodium carbonate was regulated to occupy four hours and the operation was conducted in a large, shallow, glass dish, so as to offer the greatest possible surface of contact between the interacting materials. The mass soon became pasty and, with occasional stirring, almost granular in five hours. The whole was left for 24 hours, by which time the aqueous portion was quite neutral to litmus. The white, granular solid was filtered off at the pump, washed well with water, and dried on a porous plate at the ordinary temperature. It weighed 48 grams and consisted essentially of unchanged salicylamide and its labile *O*-benzoyl derivative together with some dibenzoylsalicylamide. The separation of these substances proved a difficult operation, and after several wasteful attempts to remove the unchanged salicylamide by digesting with ammonia or sodium carbonate the following process was finally adopted: the dry, finely-powdered mixture was digested with 70 grams of benzene, warmed to 50° , and allowed to cool and stand for three hours. In this way, the dibenzoylsalicylamide was dissolved out of the mixture, since, although when

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pure it is sparingly soluble in cold benzene, it is readily soluble in presence of salicylamide.

Dibenzoylsalicylamide.—The benzene solution was filtered at the pump and the benzene from the filtrate removed by distillation at 100°. The residual syrup, which solidified on cooling, contained essentially salicylamide and its dibenzoyl derivative; these were easily separated by treatment with 80 c.c. of ether, in which the former is readily and the latter sparingly soluble. On filtering and washing, dibenzoylsalicylamide remained as a nearly white, microcrystalline powder, which was purified by crystallisation from a small quantity of boiling alcohol. It weighed 3 grams and melted at 126°. After repeated crystallisation from alcohol, it melted at 129°, this being the highest melting point recorded.

O-Benzoylsalicylamide.—The portion which remained insoluble after digestion and washing with benzene consisted of a mixture of *O*-benzoylsalicylamide and salicylamide; it weighed 32 grams and gave an intense ferric chloride reaction. To separate these substances, the whole mass was dissolved in about 500 c.c. of cold absolute alcohol and filtered, and the filtrate was quickly diluted with about 1200 c.c. of water until permanently turbid. After five minutes, a thick precipitate of *o*-benzoylsalicylamide separated out as scaly, glistening plates having a snow-white, fatty lustre. It was quickly filtered off before the salicylamide began to separate, well washed, and dried at 15°; it weighed 19.5 grams (40 per cent. theoretical maximum), melted at 143°, gave no ferric chloride reaction, and was quite pure. By crystallisation from boiling benzene, or preferably from light petroleum containing 10 per cent. of benzene, it was obtained in the form of slender needles melting at 144°.

O-Benzoylsalicyliminohydroxide.—Under the conditions of the above experiment, practically no *O*-benzoylsalicyliminohydroxide was produced. When, however, the benzylation was assisted by mechanical mixing, and when the addition of sodium carbonate was not regulated carefully, this substance was produced as its sparingly soluble yellow sodium derivative, together with an increased quantity of the dibenzoyl compound, and little or none of the labile *O*-benzoyl derivative. The separation was carried out in the following manner: the granular solid at the close of the reaction (5–6 hours) was filtered off and washed with water. From the filtrate and washings, by acidifying with hydrochloric acid, a mixture of salicylamide and the *O*-benzoylsalicyliminohydroxide was obtained; these were separated by boiling water, in which the latter is practically insoluble. The above granular solid, after drying at 15°, was extracted with cold benzene, and from the benzene solution dibenzoylsalicylamide was obtained in quantity by the treatment previously described. The portion insoluble

in benzene was boiled with the latter and filtered. The benzene solution contained large quantities of salicylamide and varying small quantities (sometimes none) of the labile substance, which, if present in sufficient quantity, was separated as before. The portion insoluble in boiling benzene contained *O*-benzoylsalicyliminohydroxide, which was purified by dissolving in warm ammonia and precipitating by hydrochloric acid. The total quantity of this substance obtained was small and variable. It melted at 205° , and after repeated crystallisation from boiling alcohol at 208° . Owing to its sparing solubility in the ordinary solvents, its molecular weight was determined in ethylene dibromide by the ebullioscopic method. The above three benzoyl derivatives gave the following results on analysis and determination of molecular weights.

(1) *O*-Benzoylsalicylamide (m. p. 144°):

0.2685 gave 0.6852 CO_2 and 0.1170 H_2O . $\text{C} = 69.59$; $\text{H} = 4.84$.

0.3103 „ 16.1 c.c. nitrogen at 18° and 765 mm. $\text{N} = 6.02$.

0.6887 in 36.08 acetic acid gave $\Delta t = 0.30^{\circ}$. $\text{M. W.} = 247$.

$\text{C}_{14}\text{H}_{11}\text{O}_3\text{N}$ requires $\text{C} = 69.71$; $\text{H} = 4.57$; $\text{N} = 5.81$ per cent.; and $\text{M. W.} = 241$.

(2) *O*-Benzoylsalicyliminohydroxide (m. p. 208°):

0.2553 gave 0.6515 CO_2 and 0.1050 H_2O . $\text{C} = 69.60$; $\text{H} = 4.57$.

0.2042 „ 11.0 c.c. nitrogen at 18° and 765 mm. $\text{N} = 6.25$.

0.5230 in 38.08 ethylene dibromide gave $\Delta t = 0.36^{\circ}$. $\text{M. W.} = 241$.

$\text{C}_{14}\text{H}_{11}\text{O}_3\text{N}$ requires $\text{C} = 69.71$; $\text{H} = 4.57$; $\text{N} = 5.81$ per cent.; and $\text{M. W.} = 241$.

(3) *O*-N-Dibenzoylsalicylamide (m. p. 128°):

0.2278 gave 0.6129 CO_2 and 0.0957 H_2O . $\text{C} = 73.37$; $\text{H} = 4.66$.

0.2366 „ 8.3 c.c. nitrogen at 21° and 764 mm. $\text{N} = 4.01$.

0.7907 in 35.33 acetic acid gave $\Delta t = 0.25^{\circ}$. $\text{M. W.} = 347$.

$\text{C}_{21}\text{H}_{15}\text{O}_4\text{N}$ requires $\text{C} = 73.05$; $\text{H} = 4.34$; $\text{N} = 4.06$ per cent.; and $\text{M. W.} = 345$.

O-Benzoylsalicylamide, $\text{BzO}\cdot\text{C}_6\text{H}_4\cdot\text{CO}\cdot\text{NH}_2$, is insoluble in cold water and light petroleum, and sparingly soluble in cold ether and benzene, but fairly readily in boiling ether and benzene, from which it crystallises in glistening, pearly plates. It is fairly readily soluble in cold alcohol, and readily in the cold in chloroform, ethyl acetate, methyl alcohol, glacial acetic acid, and pyridine.

The pure substance on heating melts at 143 – 144° , but a few degrees above its melting point rapidly becomes solid owing to conversion into *O*-benzoylsalicyliminohydroxide. On prolonged heating below its melting point, it appears to undergo very little change pro-

vided it is perfectly dry, and the stability limit is coincident with its melting point. The transformation to the stable form does not proceed quantitatively, not because of a reversible equilibrium, but because during the change a small quantity of the labile substance undergoes general decomposition, forming resinous, apparently polymeric substances and a little benzoylsalicylonitrile, which were not obtained in sufficient quantity to admit of investigation. By heating the labile substance for an hour at 150°, at least 80 per cent. is converted into the stable substance, which can be isolated from the resulting mass by digesting with cold alcohol, in which it is sparingly soluble. The stable substance remains as a white, granular powder, melting before crystallisation at 203°.

O-Benzoylsalicylamide, on heating with water, dissolves, but, if the solution is kept at 100°, in about 60—80 seconds the stable substance separates out as a flocculent, microcrystalline precipitate melting at 205°, and the change is quantitative.

With alkalis, *O*-benzoylsalicylamide is transformed at the ordinary temperature more or less rapidly into the stable compound, and the change is very rapid if the substance is finely divided. With a cold freshly-prepared solution of sodium hydrogen carbonate, it is unaffected, but with aqueous ammonia, sodium carbonate, or sodium hydroxide intense yellow solutions result, which on acidification give a white, gelatinous precipitate of *O*-benzoylsalicyliminohydroxide melting at 203—205°. The change is quantitative if care be taken to avoid hydrolysis, which takes place on standing or warming. Although *O*-benzoylsalicylamide is thus changed by alkali and gradually passes into solution, it is quite evident that the substance itself is insoluble, dissolving only as a result of the change to the stable compound, as can be readily observed in the behaviour of the larger crystals, where, owing to the slowness of the change, the process can be closely followed. When, on the other hand, an alcoholic solution of the labile amide is treated with sufficient alkali, the transformation is instantaneous and quantitative, and the substance may be titrated, using phenolphthalein as an indicator (the *O*-benzoylsalicyliminohydroxide formed behaves like a monobasic acid, see p. 1223).

By adding to the resulting neutral solution of sodium *O*-benzoylsalicylimino-oxide a known considerable excess of sodium hydroxide and allowing to remain for 24 hours at 30°, the benzoyl derivative was completely hydrolysed. The following results were obtained:

- (1) 0.1725 *O*-benzoylsalicylamide required 7.0 c.c. *N*/10 NaOH (direct titration).
- (2) 0.1725 *O*-benzoylsalicylamide required 14.3 c.c. *N*/10 (after complete hydrolysis).

The change (1) $\text{BzO} \cdot \text{C}_6\text{H}_4 \cdot \text{CO} \cdot \text{NH}_2 + \text{NaOH} = \text{BzO} \cdot \text{C}_6\text{H}_4 \cdot \text{C}(\text{ONa}) \cdot \text{NH}_2 + \text{H}_2\text{O}$ requires 1 mol. = 7.15 c.c. *N*/10 NaOH. [View Article Online](#)

*The change (2) $\text{BzO} \cdot \text{C}_6\text{H}_4 \cdot \text{CO} \cdot \text{NH}_2 + 2\text{NaOH} = \text{NaO} \cdot \text{C}_6\text{H}_4 \cdot \text{CO} \cdot \text{NH}_2 + \text{C}_6\text{H}_5 \cdot \text{CO}_2\text{Na} + \text{H}_2\text{O}$ requires 2 mols. = 14.3 c.c. *N*/10 NaOH.

O-Benzoylsalicylamide spontaneously undergoes transformation to the iminohydroxide when dissolved in alcohol, pyridine, or other ionising solvents, slowly at the ordinary temperature, more rapidly on heating. In alcoholic solution at 20°, the change is inappreciable in a few minutes, but in three days the iminohydroxide begins to separate out as tufts of needles and the change is complete in less than seven days. A 5 per cent. solution in pyridine shows incipient change at 20° in 15 minutes, and on diluting with water a yellow solution results, containing traces of iminohydroxide (pyridine salt), but by neutralising the solution with hydrochloric acid, which precipitates the labile amide, the majority may be recovered unchanged. A pyridine solution of the labile amide, on standing several hours, assumes a bright yellow colour, and in less than ten days the change is complete. On treatment with water, part of the iminohydroxide is deposited as a white precipitate melting at 203°, and the remainder (m. p. 204°) from the aqueous pyridine solution by addition of hydrochloric acid.

O-Benzoylsalicylamide is not appreciably affected in acetic acid solution, and after a few hours is precipitated unchanged by adding water; it is also unaffected by benzoyl or acetyl chloride, in both of which it dissolves on warming, and crystallises unchanged on cooling. With benzoyl chloride in presence of pyridine it is readily benzoylated, yielding *O*-*N*-dibenzoylsalicylamide (see p. 1224), and with acetic anhydride it yields a mixture of benzoylsalicylonitrile and *O*-benzoyl-*N*-acetylsalicylamide (see p. 1227).

O-Benzoylsalicylamide is readily decomposed hydrolytically by cold concentrated sulphuric acid, forming salicylamide and benzoic acid.

O-Benzoylsalicyliminohydroxide, $\text{BzO} \cdot \text{C}_6\text{H}_4 \cdot \text{C}(\text{OH}) \cdot \text{NH}_2$, is the compound described by Gerhardt and Chiozza (*loc. cit.*) as benzoyl salicylamide and by Limpricht (*loc. cit.*) as benzoylsalicylamic acid (m. p. 200°). When perfectly pure, it melts at 208°; it is insoluble in cold water, and only very slightly in hot water; sparingly soluble in cold alcohol, not very soluble in hot alcohol, but crystallises well on cooling in very light, small needles. It is practically insoluble in ether, light petroleum, and benzene; very sparingly soluble in cold glacial acetic acid, but dissolves fairly readily in the hot solvent, from

* Salicylamide may be titrated practically as a monobasic acid, using phenolphthalein as an indicator, and therefore when neutral takes up 1 mol. of NaOH as in the equation. Exact determinations have shown that under the conditions of the above experiments 1 mol. of salicylamide requires 0.93 mol. of caustic soda.

which it separates in needles; it is readily soluble in pyridine, and gives no coloration with ferric chloride in presence of water, alcohol, or its other solvents. [View Article Online](#)

On heating at 270° , as Limpricht (*loc. cit.*) has shown, it slowly loses water and passes into "benzoysalicylimid," a polymeric form of benzoysalicylonitrile, which forms yellow needles very sparingly soluble in alcohol.

The iminohydroxide is readily soluble in alkali, forming intense yellow solutions, which, on acidifying, yield a bulky, gelatinous precipitate of the unchanged substance. With ammonia, a yellow ammonium salt is formed, which has not been isolated in the pure condition, but a mixture of the iminohydroxide and its ammonium salt, having a bright yellow colour, may be obtained by adding alcoholic ammonia to an alcoholic solution of the labile *O*-benzoysalicylamide and allowing the liquid to evaporate. The ammonium salt becomes white at 150° , losing ammonia and forming the iminohydroxide. In aqueous solution, the ammonium salt is unaffected by heating with excess of ammonia. *O*-Benzoysalicyliminohydroxide is unaffected by cold freshly prepared aqueous sodium hydrogen carbonate, but with sodium carbonate or sodium hydroxide is instantly turned bright yellow owing to its conversion into the sparingly soluble sodium salt, which dissolves on the addition of more water. The resulting yellow solution is unstable in presence of excess of alkali, hydrolysis slowly taking place at the ordinary temperature and rapidly on warming, with formation of sodium salicylamide and benzoate, and the progress of the change can easily be observed by the gradual disappearance of the yellow colour. The behaviour of *O*-benzoysalicyliminohydroxide in alcoholic solution with caustic soda was quantitatively studied. Using phenolphthalein as an indicator, 0.2174 required 9.0 c.c. *N*/10 NaOH.

The change $\text{BzO} \cdot \text{C}_6\text{H}_4 \cdot \text{C}(\text{OH}) \cdot \text{NH} + \text{NaOH} = \text{BzO} \cdot \text{C}_6\text{H}_4 \cdot \text{C}(\text{ONa}) \cdot \text{NH} + \text{H}_2\text{O}$ requires 1 mol. = 9.02 c.c. *N*/10 NaOH.

The resulting solution was treated with a known large excess of *N*/10 NaOH, allowed to remain at 18° for 24 hours, and the excess of alkali estimated.

0.2174 required 18.0 c.c. *N*/10 NaOH after hydrolysis.

The change $\text{BzO} \cdot \text{C}_6\text{H}_4 \cdot \text{C}(\text{OH}) \cdot \text{NH} + 2\text{NaOH} = \text{NaO} \cdot \text{C}_6\text{H}_4 \cdot \text{CO} \cdot \text{NH}_2 + \text{C}_6\text{H}_5 \cdot \text{CO}_2\text{Na} + \text{H}_2\text{O}$ requires 2 mols. = 18.04 c.c. *N*/10 NaOH.

When *O*-benzoyliminohydroxide was treated with exactly 2 mols. of caustic soda instead of an excess, only partial hydrolysis (69 per cent.) had occurred in 24 hours at 18° , and by taking varying amounts it was found that the velocity of hydrolysis is influenced in the usual way by the concentration of the alkali. After complete hydrolysis,

salicylamide and benzoic acid were extracted, after acidifying, by shaking with ether; on removing the ether, the two substances were separated by means of warm light petroleum, recrystallised, and readily identified by their melting points and properties.

O-Benzoylsalicyliminohydroxide in presence of aqueous alkali, preferably sodium carbonate, is readily benzoylated on treatment with benzoyl chloride. On stirring, the yellow colour slowly disappears and a pasty mass results which sets to a crystalline solid, which, after washing and drying, melts at 123°, and after crystallisation from alcohol fuses at 127–128°. The benzoyl derivative, the yield of which is practically theoretical, is identical with the product (dibenzoylsalicylamide) obtained in the wet benzoylation of salicylamide, and there can be no doubt that it is produced in this process through the intermediate formation of *O*-benzoylsalicyliminohydroxide. The same dibenzoyl derivative is obtained by the pyridine benzoylation of the iminohydroxide (see p. 1225).

O-Benzoylsalicyliminohydroxide is soluble without change in cold concentrated sulphuric acid (compare its labile isomeride) and is unaffected by acetyl chloride. With acetic anhydride, it is unaffected on heating, but dissolves and crystallises out on cooling; on prolonged boiling, however, with acetic anhydride, it is broken up into benzoic acid, salicylamide, and oily (apparently polymerised) products which have not been identified.

This compound has been obtained in the following ways: (a) by wet benzoylation of salicylamide; (b) by wet benzoylation of *O*-benzoylsalicyliminohydroxide; (c) by pyridine benzoylation of *O*-benzoylsalicylamide; (d) by pyridine benzoylation of *O*-benzoylsalicyliminohydroxide. Methods (a) and (b) have already been described.

(c) *Pyridine-benzoylation of O-Benzoylsalicylamide.*

Three grams of *O*-benzoylsalicylamide (1 mol.) dissolved in 8 grams of pyridine were treated gradually with 1.75 grams (1 mol.) of benzoyl chloride, and the mixture, which became warm, was kept cool and allowed to stand protected from moisture. It assumed a yellow tinge, but pyridine hydrochloride did not separate. After 24 hours, the mixture was treated with about 70 c.c. of pure ether, stirred well, and quickly filtered from the crystalline, semi-oily insoluble pyridine hydrochloride. The ethereal pyridine solution was allowed to evaporate for several hours; needles separated consisting of a mixture of dibenzoylsalicylamide and benzoylsalicylonitrile; these were filtered

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off at the pump from the syrup and washed with ether. After drying on a porous plate, these two substances were separated by digestion with cold benzene, in which the nitrile is readily and the other sparingly soluble. The impure nitrile was obtained by evaporation from the benzene filtrate, and was purified by digesting with cold caustic soda and washing. In this way, 0.4 gram of *benzoylsalicylonitrile* was obtained, which crystallised from boiling light petroleum in fine, white, silky needles (m. p. 106°).

0.1019 gave 5.6 c.c. nitrogen at 22° and 760 mm. $N = 6.28$.

$C_{14}H_9O_3N$ requires $N = 6.27$ per cent.

The above syrup, when treated with an excess of dry ether, slowly yielded a thick, crystalline precipitate of dibenzoylsalicylamide; this was separated and added to the crystals which remained after digesting the original needles with cold benzene. A further batch of the dibenzoyl derivative was obtained by dissolving in alcohol the oily pyridine hydrochloride residue after the original treatment with ether and allowing the solution to evaporate. The total yield of *dibenzoylsalicylamide* obtained weighed 1.5 grams (35 per cent. of theory); it was recrystallised from a boiling mixture of benzene and light petroleum, and finally from absolute alcohol, from which it separated in thick prisms melting at 126°.

0.1761 gave 6.4 c.c. nitrogen at 22° and 760 mm. $N = 4.11$.

$C_{21}H_{15}O_4N$ requires $N = 4.06$ per cent.

The complete identity of the substance with that obtained by the wet benzoylation of salicylamide and *O*-benzoylsalicyliminohydroxide was shown by a comparison of their properties and by the definite melting point given by mixtures of the two specimens.

(d) *Pyridine-benzoylation of O-Benzoylsalicyliminohydroxide.*

One mol. of *O*-benzoylsalicyliminohydroxide dissolved in three times its weight of pyridine was treated gradually with 1 mol. of benzoyl chloride. The mixture, which became warm and assumed a yellow colour, was cooled and allowed to stand protected from moisture for 12 hours to complete the benzoylation; it was then treated with an excess of pure ether, rapidly stirred, and filtered from the insoluble pyridine hydrochloride; the ethereal solution was allowed to evaporate, and finally heated on the water-bath to remove pyridine. On cooling, a mass of needles (dibenzoylsalicylamide) separated, which were digested and washed with ether* and recrystallised from boiling alcohol. It melted

* Although dibenzoylsalicylamide is practically insoluble in ether, it is readily soluble in presence of pyridine, and therefore removed by ether from the reaction product after benzoylation.

at 126°, and a further batch of the substance was obtained from the ethereal washings on evaporation, as well as from the pyridine hydrochloride, by dissolving in alcohol and allowing the solution to evaporate. The total amounted to an almost theoretical yield, and there was no benzoylsalicylonitrile formed (compare the pyridine-benzoylation of the labile isomeride). The substance was identical in every respect with that produced from the labile isomeride or by the other methods.

Dibenzoylsalicylamide when perfectly pure melts at 129°, and gives no coloration with ferric chloride; it is insoluble in cold water, not very soluble in cold, although readily so in hot, alcohol, and almost insoluble in ether. It is not very soluble in benzene, and almost insoluble in light petroleum, but dissolves fairly readily in chloroform, ethyl acetate, glacial acetic acid, and pyridine. Dibenzoylsalicylamide, on melting and quickly cooling, sets to a hard, transparent, brittle glass which is quite amorphous and even on standing shows no tendency to crystallise.

This amorphous modification is a distinct phase, and melts indefinitely between 55° and 60°, but on heating to about 80° the liquid sets to a crystalline solid which melts sharply at 128°. If the crystalline modification melting at 128° is melted, then cooled *slowly* and kept at 85° for about 40 minutes, it begins to solidify, and when completely solid it again melts sharply at 128°. These physical changes are interesting, inasmuch as they point to the existence of a labile isomeride. It is probable that the stable form (m. p. 128°) on fusion passes into a mixture of two forms,

in isodynamic equilibrium, which is disturbed by lowering the temperature 20°, so that if kept at this temperature sufficiently long only the stable form appears. When, however, the mixture of forms is quickly cooled, both isomerides may be expected to be present in the resulting amorphous solid in the ratio in which they existed in the equilibrium mixture, and it may therefore be found possible to isolate the unstable modification. Experiments with this object in view are proceeding, but it is impossible as yet even to say which of the two alternative formulæ corresponds to the stable form melting at 128°.

Dibenzoylsalicylamide is remarkably unstable in presence of alkali, being at once hydrolysed with the elimination of benzoic acid and the formation of *O*-benzoylsalicyliminohydroxide. Even ammonia effects this change, the crystals slowly dissolving in the cold to a yellow solution containing ammonium benzoate and the ammonium salt of the substance melting at 208°; the decomposition is more rapid on heating. Sodium carbonate behaves similarly; sodium hydroxide dissolves dibenzoylsalicylamide more readily with similar hydrolysis,

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which was observed quantitatively by using $N/10$ NaOH and titrating. Since dibenzamide dissolves in sodium hydroxide with inappreciable hydrolysis, unless the solution is warmed or allowed to stand, and is precipitated unchanged on acidification, this exceptionally easy hydrolysis of dibenzoylsalicylamide is very striking. All attempts to regain the unchanged substance by dissolving in sodium hydroxide in the cold and rapidly acidifying were unsuccessful, and these observations explain why all attempts to isolate N -benzoylsalicylamide by methods involving the use of alkaline media have failed.

The behaviour of the amorphous modification of dibenzoylsalicylamide with aqueous sodium hydroxide is similar to that of the stable form, but a yellow oil is first formed which sets to a granular solid consisting of the sodium derivative of O -benzoylsalicyliminohydroxide.

Dibenzoylsalicylamide is hydrolysed by cold strong sulphuric acid forming benzoic acid and O -benzoylsalicyliminohydroxide, which is precipitated on the addition of water. It is not affected by acetyl chloride, but with benzoyl chloride in presence of pyridine it yields tribenzoylsalicylamide (see p. 1228).

O-Benzoyl-N-acetylsalicylamide, $\text{BzO} \cdot \text{C}_6\text{H}_4 \cdot \text{CO} \cdot \text{NH} \cdot \text{CO} \cdot \text{CH}_3$.

O -Benzoylsalicylamide was boiled for half an hour with twice its weight of acetic anhydride, and the resulting liquid was evaporated by heating on the water-bath to remove acetic acid and excess of anhydride. The residual syrup, which did not crystallise on cooling, consisted essentially of benzoylsalicylonitrile and O -benzoyl- N -acetylsalicylamide, which were difficult to separate, since the difference in their solubilities in various solvents is slight. The mixture was stirred with an excess of light petroleum at 40° until the syrup changed to a white, granular solid, the light petroleum was decanted off, and the solid washed successively with cold light petroleum containing small quantities of benzene, alcohol, and finally ether. The washings containing the more soluble nitrile were collected and evaporated, and the impure crystalline solid recovered was digested with sodium hydroxide and washed in order to remove traces of the acetyl derivative present. In this way, pure benzoylsalicylonitrile was obtained, which, after crystallisation from boiling light petroleum, formed snow-white needles (m. p. 105°); it weighed one-fifth of the O -benzoylsalicylamide taken.

The insoluble white, granular residue which remained after the above treatment was dried on a porous plate and crystallised from boiling light petroleum, from which it separated on cooling in tufts of remarkably long, brittle needles; it consisted of pure

O-benzoyl-*N*-acetylsalicylamide and melted at 97°, the yield being about 40 per cent. [View Article Online](#)

0.2063 gave 9.1 c.c. nitrogen at 25° and 763 mm. $N = 4.95$.

$C_{16}H_{13}O_4N$ requires $N = 4.94$ per cent.

O-Benzoyl-*N*-acetylsalicylamide is fairly readily soluble in alcohol, less so in ether; it dissolves in benzene and is very soluble in chloroform. It does not give any coloration with ferric chloride, and is very similar in its properties to dibenzoylsalicylamide, being at once decomposed by sodium hydroxide to form a yellow solution from which *O*-benzoylsalicyliminohydroxide is precipitated by acids. Ammonia effects the same change slowly in the cold and readily on heating.

Tribenzoylsalicylamide, $BzO \cdot C_6H_4 \cdot CO \cdot NBz_2$.

This compound is formed by the pyridine benzylation of (*a*) *O*-benzoylsalicyliminohydroxide (using excess of benzoyl chloride) or of (*b*) dibenzoylsalicylamide. (*a*) *O*-Benzoylsalicyliminohydroxide (2.6 grams) dissolved in 10 grams of pyridine was treated gradually with 4 grams of benzoyl chloride, the mixture being cooled. The product, which assumed a deep port-wine tint, was left for 12 hours, and then treated with 80 c.c. of ether. After quickly stirring and filtering from the insoluble pyridine hydrochloride, the ethereal pyridine filtrate was allowed to evaporate, when hard, discoloured, crystalline crusts of impure tribenzoylsalicylamide separated. The crystalline mass was drained on a porous plate and digested first with ether, and finally with a mixture of absolute alcohol and ether, in which the tribenzoyl derivative is sparingly soluble. In this way, the colouring matter was mostly removed and a grey, granular powder (3 grams) remained, which was finally purified by crystallisation from a boiling mixture of equal parts of alcohol and ethyl acetate; it separated slowly on cooling as a white, crystalline powder melting at 186—188°.

(*b*) Three grams of dibenzoylsalicylamide (1 mol.) dissolved in 8 grams of pyridine were treated with 1.3 grams (1 mol.) of benzoyl chloride, the mixture, which darkened to a port-wine tint, being kept cool and left for 24 hours. At the end of this time, a considerable portion of the tribenzoyl derivative had separated out as a micro-crystalline powder in stellate tufts, and the majority of the remainder was deposited by treating the whole with 3 to 4 volumes of absolute alcohol. After two hours, the thick precipitate of the tribenzoyl derivative was collected and thoroughly washed with cold alcohol; it weighed 2 grams and was practically pure. On recrystallisation from boiling alcohol, in which it is not very soluble, it was obtained in woolly needles (m. p. 188°). The product was identical in every respect with that obtained by method (*a*).

0.1794 gave 5.0 c.c. nitrogen at 23° and 765 mm. [View Article Online](#) $N = 3.16$.

$C_{28}H_{19}O_5N$ requires $N = 3.11$ per cent.

Tribenzoylsalicylamide is insoluble in water, very sparingly soluble in alcohol and ether; it is moderately soluble in benzene, fairly readily in the hot solvent, crystallising out slowly on cooling or on addition of light petroleum, and it dissolves fairly readily in chloroform. It does not give any coloration with ferric chloride, is unaffected by aqueous sodium hydroxide even on boiling, but is decomposed by warming with concentrated sulphuric acid, yielding benzoic acid and *O*-benzoylsalicyliminohydroxide.

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