

CXCIV.—*The Condensation of Salicylaldehyde and Benzamide.*

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THE condensation of salicylaldehyde with amides has been studied by Cebrian (*Ber.*, 1898, **31**, 1592), who described a series of cyclic derivatives, which he named "coumarazines," and to which he gave the

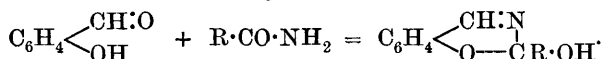
general formula  $\text{C}_6\text{H}_4 \begin{smallmatrix} \text{CH:N} \\ \diagup \quad \diagdown \\ \text{O} \cdots \text{CR} \cdot \text{OH} \end{smallmatrix}$ . Owing to the similarity in

structure of these coumarazines to the metoxazone derivatives which one of the authors has shown represent the tautomeric form of *O*- and

*N*-acylsalicylamides,  $\left( \text{C}_6\text{H}_4 \begin{smallmatrix} \text{CO} \cdot \text{NH} \\ \diagup \quad \diagdown \\ \text{O} \cdots \text{CR} \cdot \text{OH} \end{smallmatrix} \right)$ , where there is a similar

hydroxylated metoxazine skeleton present, it was thought desirable to submit Cebrian's derivatives to close study. Auwers (*Ber.*, 1907, **40**, 3510), in criticising the theory of metoxazone tautomerism as applied to the acylsalicylamides, drew attention to the difference between the crystalline character of the latter and the amorphous properties of the coumarazines, and considered that this difference precluded the possibility of the acylsalicylamides appearing in a metoxazone form.

Repetition of Cebrian's work, however, brought to light the fact that his so-called coumarazines are not really cyclic in structure, but that they are simply open-chain condensation derivatives, having a phenolic character similar to the condensation product (benzylidene-salicylamide) obtained by the action of benzaldehyde on salicylamide (Titherley, *Trans.*, 1907, **91**, 1420). Cebrian, who considered the possibility of an open-chain formula,  $\text{HO} \cdot \text{C}_6\text{H}_4 \cdot \text{CH:N} \cdot \text{COR}$ , for his products, was led to adopt a ring formula according to the reaction :



His reasons were based on the properties of the resulting "coumarazines," namely: (1) the difficulty with which they are hydrolysed; (2) their behaviour on oxidation, yielding when  $\text{R} = \text{H}$  or

$\text{CH}_3$  the ring compound  $\text{C}_6\text{H}_4 \begin{smallmatrix} \text{CH:N} \\ \diagup \quad \diagdown \\ \text{O} \quad \text{CO} \end{smallmatrix}$ , whilst, when  $\text{R} = \text{C}_6\text{H}_5$  practically no oxidation occurs. In support of the ring formula, moreover, Cebrian cites the inability of *o*-ethoxybenzaldehyde,  $\text{EtO} \cdot \text{C}_6\text{H}_4 \cdot \text{CHO}$ , to condense with acetamide. On the other hand, he notes the easy solubility of the coumarazines in alkalis, and shows how various salts can be prepared, from which he concludes that "ein aromatisches hydroxyl nachgewiesen ist." By this it is evident that he assumes a phenolic character for the hydroxyl group in the ring

$\text{C}_6\text{H}_4 \begin{smallmatrix} \text{CH:N} \\ \diagup \quad \diagdown \\ \text{O} \quad \text{CR} \cdot \text{OH} \end{smallmatrix}$ . This assumption is, however, unwarranted, and,

although there are no exactly similar compounds of certain constitution known for comparison, it can hardly be doubted that a hydroxyl group in such a substance attached to an alkylated carbon atom situated between an oxygen and nitrogen atom would possess secondary or tertiary alcoholic characters rather than phenolic. If this is so the various alkylated and acetylated coumarazines which Cebrian has described are really open-chain compounds of the structure  $\text{R}'\text{O} \cdot \text{C}_6\text{H}_4 \cdot \text{CH:N} \cdot \text{CO} \cdot \text{R}$  and  $\text{AcO} \cdot \text{C}_6\text{H}_4 \cdot \text{CH:N} \cdot \text{CO} \cdot \text{R}$  respectively.

The present authors have not repeated the whole of Cebrian's work, but have confined themselves merely to the condensation which occurs between salicylaldehyde and benzamide, and the results make it clear that not only is no ring compound produced, but also that the amorphous product which Cebrian described as hydroxyphenyl-

coumarazine,  $\text{C}_6\text{H}_4 \begin{smallmatrix} \text{CH:N} \\ \diagup \quad \diagdown \\ \text{O} \quad \text{CPh} \cdot \text{OH} \end{smallmatrix}$ , is a mixture of two open-chain

salicylidenebenzamides,  $\text{HO} \cdot \text{C}_6\text{H}_4 \cdot \text{CH:N} \cdot \text{CO} \cdot \text{C}_6\text{H}_5$ . Both these substances have the amorphous and other properties attributed to them by Cebrian, but they differ in solubility in acetone, by means of which they were separated. They give the intense purple ferric chloride reaction characteristic of most salicylic derivatives, and possess normal phenolic properties. It is possible that they stand to each other as *syn*- and *anti*-geometrical isomerides, analogous to the corresponding benzylidenesalicylamides (*loc. cit.*), but it is also possible that one is a polymeric modification of the other. Owing to the troublesome amorphous character of the substances, and their lack of special interest, they have not been submitted to further investigation, but in the meantime it may be regarded as certain that, although they may appear in the tautomeric ring-form attributed to them by Cebrian and thus range themselves with the acylsalicylamides as substances exhibiting metoxazone tautomerism, they must be regarded as simple open-chain derivatives, and thus arguments based on the assumed cyclic structure of the "coumarazines" fall through.

It appeared to be of interest incidentally to ascertain whether the true ring compound  $C_6H_4 \begin{smallmatrix} \text{CH:N} \\ | \\ \text{O}-\text{CPh}\cdot\text{OH} \end{smallmatrix}$  could be prepared either from the above compounds or direct from the condensation of salicylaldehyde and benzamide by modifying the conditions; and accordingly a number of experiments have been made, but without success. At the same time, some interesting results have been obtained which show that the same kind of tautomeric change occurs during the process of condensation as occurs in the acylsalicylamide group, resulting in the migration of the benzoyl group (see p. 1937).

By analogy with the production of phenylbenzometoxazone (*loc. cit.*) in the condensation of salicylamide and benzaldehyde under the influence of hydrogen chloride, it was thought that the above ring compound would be formed from salicylaldehyde and benzamide, using the same catalyst. Carrying out the reaction in benzene solution, hydrogen chloride being passed in, a ready condensation occurs, and a crystalline compound melting at  $198^\circ$  was easily obtained, which gave no ferric chloride reaction, and which at first was assumed to be the desired derivative,  $C_6H_4 \begin{smallmatrix} \text{CH:N} \\ | \\ \text{O}-\text{CPh}\cdot\text{OH} \end{smallmatrix}$ , because, on analysis, the values for carbon, hydrogen, and nitrogen agreed with this. A study of the properties of the substance showed, however, that no hydroxyl group was present, and that on cautious hydrolysis a benzoyl group could be eliminated, leaving a compound of phenolic properties still containing benzoyl; whilst a molecular weight determination showed that the value was double that required for the above formula, from which it was evident that the condensation had proceeded on unexpected lines. The references\* in the literature to the condensation between amides and aldehydes make it clear that different results may be expected, but there is not sufficient evidence available to correlate these differences with structure of the reacting substances, on the one hand, and conditions of condensation, on the other. In general, the following main types of change have been observed:

- (a)  $-\text{CH:O} + \text{NH}_2\cdot\text{COR} \rightarrow -\text{CH(OH)}\cdot\text{NH}\cdot\text{COR};$   
 (b)  $-\text{CH:O} + 2\text{NH}_2\cdot\text{COR} \rightarrow -\text{CH} \begin{smallmatrix} \text{NH}\cdot\text{COR} \\ | \\ \text{NH}\cdot\text{COR} \end{smallmatrix};$   
 (c)  $-\text{CH:O} + \text{NH}_2\cdot\text{COR} \rightarrow -\text{CH:N}\cdot\text{COR}.$

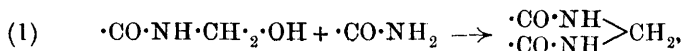
\* Roth, *Annalen*, 1870, **154**, 72; Schuster, *Annalen*, 1870, **154**, 80; Medicus, *Annalen*, 1871, **157**, 44; Nencki, *Ber.*, 1874, **7**, 158; Hofmann and Meyer, *Ber.*, 1892, **25**, 209; Pulvermacher, *Ber.*, 1892, **25**, 314; Michael and Jeanprêtre, *Ber.*, 1892, **25**, 1678; Bülow, *Ber.*, 1893, **26**, 1972; Cebrian, *Ber.*, 1898, **31**, 1592; Einhorn, *Annalen*, 1905, **343**, 207, 272; Keane and Nicholls, *Trans.*, 1907, **91**, 264; Burrows and Keane, *Trans.*, 1907, **91**, 269; Titherley, *Trans.*, 1907, **91**, 1419.

In all cases the observed results can be explained by assuming an aldol-like condensation (*a*) to occur first. In restricted cases only, as Einhorn's observations show, can such aldol-like derivatives be isolated, namely, with formaldehyde, chloral, and bromal as aldehydes, or with halogen substituted aliphatic amides.

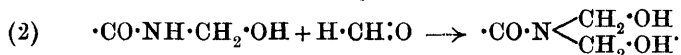
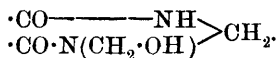
Einhorn has shown that a quite general reaction occurs in presence of alkaline or acid catalysts between formaldehyde, on the one hand, and amides of all kinds, on the other (of monobasic and dibasic aliphatic and aromatic acids), yielding definite aldol-like additive compounds of a type (*a*), namely, methylol derivatives:



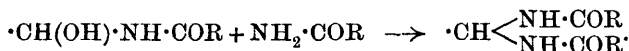
Such methylol derivatives are capable of condensing with (1) a second molecule of amide, or (2) probably with a second molecule of formaldehyde:



which may now condense further with formaldehyde, yielding



Apparently in the case of most amides and aldehydes such aldol-like additive compounds cannot be obtained, but Einhorn's researches have thrown considerable light on the mechanism of the condensation, and there can be little doubt that such hydroxy-derivatives are, in all cases, first formed. In the majority of condensations recorded, further action appears to have occurred between the aldol-compound and a second molecule of amide, giving the type of reaction represented in (*b*):

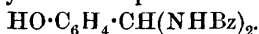


This type of reaction (*b*) occurs in the following condensations: between benzaldehyde and acetamide, as well as other fatty amides and benzamide (Roth); between anisaldehyde and acetamide, as well as benzamide (Schuster); between benzaldehyde and formamide (Bülow); between heptaldehyde and benzamide (Medicus); between acetaldehyde and carbamide, yielding the compound  $\text{CH}_3\cdot\text{CH} \begin{array}{c} < \text{NH} \\ < \text{NH} \end{array} > \text{CO}$  (Nencki)—in each case by simply heating the two substances together; also between acetaldehyde and benzamide (Nencki); between formaldehyde and acetamide in aqueous solution (Pulvermacher); between benzaldehyde and *o*-methoxybenzamide (Keane and Nicholls);

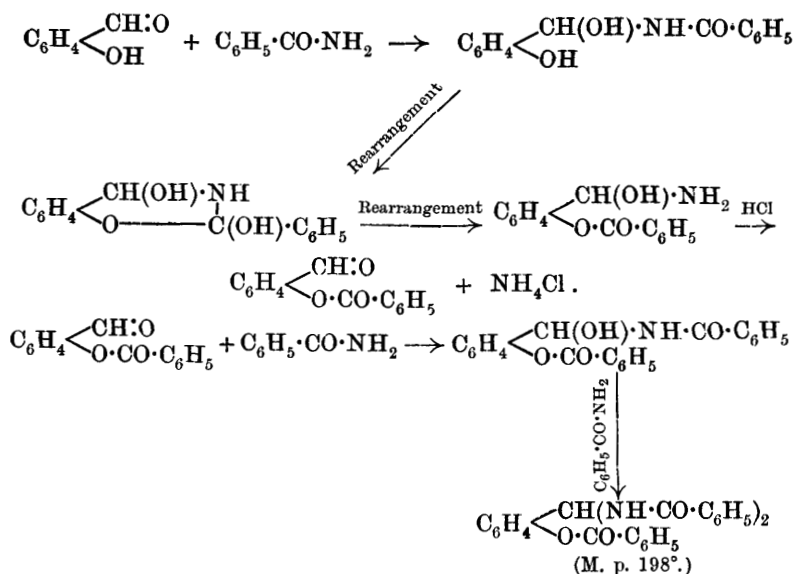
between benzaldehyde and diethylmalonamide, yielding 4:6-diketo-2-phenyl-5:5-diethylhexahydropyrimidine,  $\text{CEt}_2 \begin{smallmatrix} \text{CO} \cdot \text{NH} \\ \text{CO} \cdot \text{NH} \end{smallmatrix} \text{CH} \cdot \text{C}_6\text{H}_5$  (Burrows and Keane)—in each case in presence of hydrochloric acid as a catalyst; also between formaldehyde and benzamide under the influence of dilute sulphuric acid, producing dibenzoylmethylene-diamine,  $\text{CH}_2(\text{NHBz})_2$  (Pulvermacher).

The type of change (*c*) has been observed in the condensation between benzaldehyde and mandelamide simply by heating (Michael and Jeanprêtre), giving the compound  $\text{C}_6\text{H}_5 \cdot \text{CH}(\text{OH}) \cdot \text{CO} \cdot \text{N} \cdot \text{CH} \cdot \text{C}_6\text{H}_5$ ; between salicylaldehyde and amides in presence of sodium acetate (Cebrian and the authors); between benzaldehyde and salicylamide in presence of sodium acetate or hydrogen chloride (Keane and Nicholls; Titherley), yielding the compound  $\text{HO} \cdot \text{C}_6\text{H}_4 \cdot \text{CO} \cdot \text{N} \cdot \text{CH} \cdot \text{C}_6\text{H}_5$ , and, by rearrangement, the isomeride  $\text{C}_6\text{H}_4 \begin{smallmatrix} \text{CO} \cdot \text{NH} \\ \text{O} - \text{CH} \end{smallmatrix} \cdot \text{C}_6\text{H}_5$ .

From the above condensations, it is impossible to trace fully the influences at play, and predict what would happen in the case of salicylaldehyde and benzamide under the influence of hydrogen chloride. The crystalline derivative obtained was finally proved to be *O-N-N*-tribenzoylsalicylidenediamine,  $\text{BzO} \cdot \text{C}_6\text{H}_4 \cdot \text{CH}(\text{NHBz})_2$  (M.W. 450), from the fact that on cautious hydrolysis with alcoholic potassium hydroxide it yielded the phenolic compound

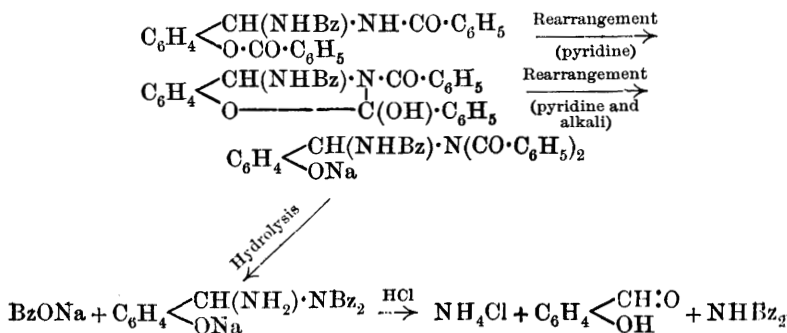


The production of such a tribenzoyl derivative in this unexpected manner furnishes evidence that during the condensation the benzoyl group wanders in a similar manner to that which has been observed by one of the authors in the acylsalicylamide group, and that the same kind of cyclic metoxazone tautomerism is at play. Moreover, the hydrogen chloride acts, not only as a catalyst, but also as a remover of ammonia, which was proved by the fact that a considerable quantity of ammonium chloride is produced, and that the yield is dependent on the continuous passage of the gas, whilst in the preparation of phenylbenzometoxazone by an analogous method a small quantity of hydrogen chloride suffices. The changes which occur in the condensation may be represented thus:



It has been shown, moreover, that a similar wandering of benzoyl occurs when this tribenzoyl derivative is hydrolysed by pyridine and alkali in the cold. Only one benzoyl group is eliminated as benzoic acid, the two others appearing attached to nitrogen in the form of dibenzamide, which is produced together with ammonia and salicylaldehyde. The production of dibenzamide was so unexpected, having regard to the constitution of the original substance, that it was at first assumed from its analysis to be the desired "coumarazine,"

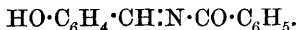
$\text{C}_6\text{H}_4 \begin{array}{l} \text{CH:N} \\ \text{O} \end{array} \text{---} \text{CPh} \cdot \text{OH}$ , which by chance is isomeric with dibenzamide, but close investigation revealed its identity with the latter. The hydrolysis is evidently accompanied by a wandering of benzoyl, and may be expressed thus:



The intermediate amino-derivative, which appeared as an oily mass, could not be isolated, owing to its instability.

# EXPERIMENTAL.

## *Preparation of the Isomeric Salicylidenebenzamides,*



Following the method of Cebrian (*loc. cit.*), 10 grams of salicylaldehyde, 10 grams of benzamide, and 6 grams of anhydrous sodium acetate, intimately mixed, were heated at 140° for five hours. The green, semi-solid mass was allowed to cool, and the resulting solid powdered and digested with water. The insoluble, crude material, weighing, after washing and drying, 15 grams, was purified by dissolving in aqueous sodium hydroxide, filtering, and adding acetic acid.

The amorphous, discoloured precipitate, consisting of the two isomerides, was dried and digested three times with an excess of acetone in the cold, by which a nearly complete separation was effected. The insoluble isomeride remained as an amorphous precipitate, which, after washing and drying, was further purified by repeated solution in pyridine and precipitation with acid. The isomeride soluble in acetone was regained from the filtrate by precipitating with faintly acidified water, and purified as far as possible by repeated solution in hot alcohol and precipitation with acidified water. The two compounds, which were produced in approximately equal quantity, have very similar properties.

## *Salicylidenebenzamide (soluble in acetone) :*

0.2024 gave 0.5305 CO<sub>2</sub> and 0.1023 H<sub>2</sub>O. C = 71.48 ; H = 5.66.

0.2304, by Kjeldahl's method, required 9.4 c.c. N/10 HCl. N = 5.71.

C<sub>14</sub>H<sub>11</sub>O<sub>2</sub>N requires C = 74.66 ; H = 4.89 ; N = 6.22 per cent.

The substance is a pale yellow powder, which does not melt but darkens at 190°. It is very soluble in cold acetone, fairly so in hot alcohol or pyridine, sparingly so in benzene or chloroform, and insoluble in ether, ethyl acetate, or light petroleum. From solution in hot glacial acetic acid, it separates in a gelatinous form on cooling. In acetone or alcohol solution, it gives a dark purple coloration with ferric chloride, whilst in alkali hydroxides it dissolves readily, yielding a yellow solution, from which it is precipitated in a gelatinous form by acids.

*Salicylidenebenzamide* (insoluble in acetone):

0.3338 gave 0.9098 CO<sub>2</sub> and 0.1572 H<sub>2</sub>O. C = 74.35; H = 5.27.

0.2337, by Kjeldahl's method, required 10.5 c.c. N/10 HCl. N = 6.28.

C<sub>14</sub>H<sub>11</sub>O<sub>2</sub>N requires C = 74.66; H = 4.89; N = 6.22 per cent.

The substance forms a yellow, amorphous powder, which does not melt but decomposes at about 200°. It is soluble in pyridine, but insoluble in chloroform, benzene, alcohol, or ether; it is sparingly soluble in hot acetic acid, and, on cooling, separates with difficulty in a gelatinous form. Its behaviour with acetone is curious; with a little acetone, it mixes to form a homogeneous liquid, doubtless consisting of a solution of acetone in the substance; on adding more acetone, however, the substance at once separates as a thick, flocculent precipitate, which is only very slightly soluble in, and may be washed by, acetone. The substance in presence of acetone gives a strong purple colour with alcoholic ferric chloride. It dissolves at once in alkali hydroxide, forming a yellow solution, from which acids precipitate it in a yellowish-white, gelatinous form.



A mixture of 40 grams of salicylaldehyde and 80 grams of benzamide, dissolved in about 200 c.c. of benzene, was heated to boiling in a reflux apparatus while a steady stream of hydrogen chloride was passed in. The clear solution rapidly became turbid, owing to the formation of water, which also showed itself as drops in the condenser.

At the same time, ammonium chloride continually separated, and collected at the bottom of the flask. After an hour, on cooling, the mass of white crystals which separated was filtered off, washed with benzene, and dried. The mass consisted chiefly of a mixture of the tribenzoyl derivative, benzamide, and ammonium chloride, and the former was separated by boiling the mixture with water and washing thoroughly with hot water. The filtrate, on cooling, deposited benzamide, which was thus recovered. The insoluble tribenzoyl derivative contained small quantities of an amorphous phenolic compound,\* which was removed by digestion with 5 per cent. sodium hydroxide.

\* This substance was recovered from the alkaline filtrate as a white, gelatinous precipitate by acidifying. Two analyses gave N = 3.48 and 3.45 per cent. It was soluble in alcohol, acetone, pyridine, ethyl acetate, or hot acetic acid, and insoluble in benzene, chloroform, or cold acetic acid. The compound was not further investigated.



0.1763 gave 0.4794 CO<sub>2</sub> and 0.0828 H<sub>2</sub>O. C = 74.16; H = 5.26.  
 0.3663, by Kjeldahl's method, required 16.57 c.c. *N*/10 HCl. N = 6.33.  
 0.3165                   "                   "                   "                   14.3 c.c. *N*/10 HCl. N = 6.32.  
 0.3760 gave 19.8 c.c. N<sub>2</sub> (moist) at 21° and 762 mm. N = 6.01.  
 C<sub>38</sub>H<sub>22</sub>O<sub>4</sub>N<sub>6</sub> requires C = 74.66; H = 4.89; N = 6.22 per cent.

0.2893 in 39.5 chloroform gave  $\Delta t$  0.055°. M.W. = 487.  
 0.6008, ,, ,,  $\Delta t$  0.122°. M.W. = 456.  
 $C_{28}H_{22}O_4N_2$  requires M.W. = 450.

#### Hydrolysis of O-N-N-Tribenzoylsalicylidenediamine.

By hydrolysis in the cold with alkali hydroxide in the presence of pyridine, dibenzamide was produced, as was shown by repeated experiments under varying conditions. In one case the procedure was as follows: Twelve grams of the tribenzoyl derivative were mixed with 12 c.c. of 50 per cent. potassium hydroxide and 2 c.c. of pyridine, and the mixture was well triturated for nearly an hour. An orange-red colour was first produced, which changed to yellow, and the mass was treated with 200 c.c. of water, in which it dissolved to a clear solution. The latter, on acidifying, became milky, and, on extracting with ether, salicylaldehyde and benzoic acid were isolated, whilst the aqueous

portion, on standing, deposited needles (5.7 grams) which, after recrystallisation from hot water, melted at 146—147°:

0.2346, by Kjeldahl's method, required 10.1 c.c.  $N/10$  HCl.  $N = 6.03$ .

0.2279 gave 12.7 c.c.  $N_2$  (moist) at 26° and 764 mm.  $N = 6.22$ .

$C_{14}H_{11}O_2N$  requires  $N = 6.22$  per cent.

The needles, although colourless, were soluble in sodium hydroxide to a yellow solution, but otherwise possessed all the properties (solubility, &c.) of dibenzamide. Repeated crystallisation from alcohol eliminated the impurity causing the yellow colour, and gave stout prisms, the identity of which with dibenzamide was established (1) by the fact that a mixture with the latter showed no depression in melting point, and (2) by showing that the rate and products (benzamide and benzoic acid) of cautious hydrolysis of the substance in presence of hot alkali were the same as those of dibenzamide.

The production of dibenzamide in the alkali-pyridine hydrolysis of the tribenzoyl derivative is accompanied by formation of ammonia, which was proved thus: The acid liquor containing pyridine, etc., from which the dibenzamide had separated, was evaporated to dryness, the residue extracted while hot with alcohol to remove pyridine hydrochloride, and the insoluble solid was then dissolved in water, rendered alkaline, and distilled into dilute hydrochloric acid, which was then evaporated. About one gram of ammonium chloride was isolated in this way.

In the above alkali-pyridine hydrolysis, there was evidence in several experiments of the presence of an oily intermediate amino-derivative, probably  $HO \cdot C_6H_4 \cdot CH(NH_2) \cdot NBz_2$ , which appeared to be decomposed by hydrochloric acid, forming ammonium chloride, salicylaldehyde, and dibenzamide.

By the cautious hydrolysis of the tribenzoyl derivative with aqueous alcoholic sodium hydroxide, one benzoyl group may be eliminated forming:



Twelve grams of *O-N-N*-tribenzoylsalicylidenediamine were mixed with 50 c.c. of water, 25 c.c. of 10 per cent. aqueous sodium hydroxide, and 150 c.c. of alcohol. The mixture, the colour of which was at first deep red and then changed to yellow, was agitated in the cold continuously until the solid had completely passed into solution, which required about one and a-half hours. The solution was kept cool while very dilute hydrochloric acid was stirred in. The dibenzoyl derivative was obtained in this way in a fairly pure state as a white, amorphous precipitate, which was washed. Ethyl benzoate was formed during the

hydrolysis, and was isolated by extracting with ether, etc. The precipitate weighed 6.5 grams, melted at  $185^{\circ}$ , and was further purified by dissolving in a mixture of 10 per cent. aqueous alcoholic sodium hydroxide and reprecipitating cautiously with dilute hydrochloric acid.

The solid, which melted at  $192^{\circ}$ , was practically pure, and was crystallised from hot methyl or ethyl alcohol or acetone by adding light petroleum gradually and allowing to stand. By either of these methods, which are very wasteful, it was obtained in small, prismatic needles:

0.3777, by Kjeldahl's method, required 21.8 c.c.  $N/10$  HCl.  $N = 8.08$ .

0.1442 gave 9.7 c.c.  $N_2$  (moist) at  $20^{\circ}$  and 760 mm.  $N = 7.69$ .

$C_{21}H_{18}O_3N_2$  requires  $N = 8.09$  per cent.

*N-N-Dibenzoylsalicylidenediamine* is soluble in cold pyridine, acetone, hot alcohol, or acetic acid, and is insoluble in ether, benzene, chloroform, or light petroleum. It is only very slowly soluble in cold dilute aqueous sodium hydroxide, forming a light yellow, sparingly soluble sodium salt, but it is much more readily soluble in alkali in presence of aqueous alcohol. In acetone solution it gives a characteristic green coloration with alcoholic ferric chloride, and the colour changes to purple on heating, owing apparently to decomposition.

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