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Reaction of Salicylamine with α-Dicarbonyl Compounds. I. Transamination Reaction

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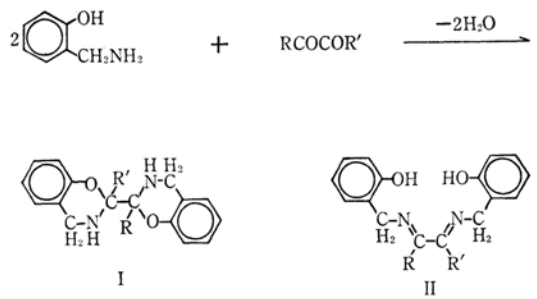
The reactions of salicylamine with α-dicarbonyl compounds were examined in the hope of obtaining 2,2′-bibenzoxazine derivatives I or Schiff bases II as two-to-one condensation products; however, salicylidenesalicylamine was isolated in every case. It was found that the reaction proceeded through transamination, followed by *trans*-Schiffization between salicylamine and α-dicarbonyl compounds. The mechanism and the conditions under which the reactions take place were investigated.

It has previously been reported by one of the present authors[1] that the condensation of *o*-aminophenols with α-dicarbonyl compounds proceeded with the formation of 2,2′-bibenzoxazoline and its derivatives, and that it did not afford ordinary Schiff base derivatives. It was further noted that the oxazoline could isomerize to a Schiff base-type anion by ring opening in the presence of bivalent metal ions and formed metal chelates where the anion was coordinated as a tetradentate ligand. Therefore, the Schiff base can exist only as a ligand anion of the metal chelate in this case.

The present investigation was undertaken to study whether a similar type of condensation occurs when salicylamine (*o*-hydroxybenzylamine) reacts with α-dicarbonyl compounds. The compounds expected as the condensation products were 2,2′-bibenzoxazines of the type I or Schiff bases of the type II.

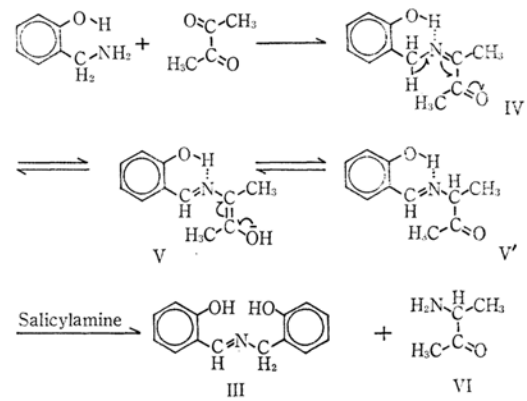


I II

The reaction of salicylamine with diacetyl was examined. When a mixture of two moles of the former and one mole of the latter was heated in methanol, yellow crystals, mp 183—184°C, were isolated. However, the compound with a molecular formula of $C_{14}H_{13}NO_2$, was neither the oxazine I nor the Schiff base II. It was easily confirmed to be salicylidenesalicylamine (III) from its infrared spectrum and by means of a mixed-melting point determination with an authentic sample.[2]

Accordingly, the mechanism of this unexpected reaction was first investigated in this paper.

Seto *et al.*,[3] have reported that salicylidenesalicylamine was isolated from an aqueous methanol solution of salicylamine by prolonged heating. The reaction was found to proceed by air oxidation, in which the amine was converted to aldimine, which was then readily hydrolized to salicylaldehyde. The aldehyde then reacted with unoxidized salicylamine to afford the Schiff base III. Although, in the present experiments, the reaction was carefully conducted under a nitrogen stream to avoid the otherwise inevitable air oxidation, the Schiff base III was always isolated in about a 40% yield.



Scheme I

1) I. Murase, This Bulletin, **32**, 827 (1959); **33**, 59, 607 (1960).

2) M. Yamaguchi, *Nippon Kagaku Zasshi* (*J. Chem. Soc. Japan, Pure Chem. Sect.*), **74**, 261 (1953).

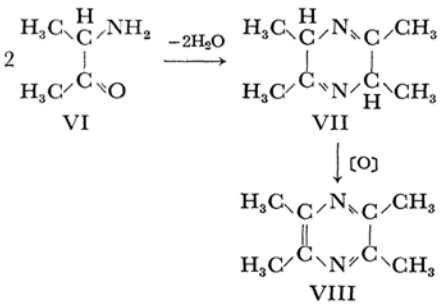
3) A. Takahashi and S. Seto, *Kogyo Kagaku Zasshi* (*J. Chem. Soc. Japan, Ind. Chem. Sect.*), **58**, 796 (1955).

Thus, the reaction did not proceed by the air oxidation of salicylamine; rather, diacetyl must have taken part in this reaction. The postulated reaction mechanisms are shown in Scheme I.

The formation of the Schiff base IV is the first step of an equimolar condensation between salicylamine and diacetyl. IV undergoes deprotonation from the methylenic group and protonation at the carbonyl oxygen, accompanied by a simultaneous electron shift, to form V, which is in equilibrium with its keto form, V′. The amine moiety of the two Schiff bases, V and/or V′, is then replaced by unreacted salicylamine to give salicylidenesalicylamine (III). Thus, the overall reaction can be assumed to be transamination, followed by *trans*-Schiffization between salicylamine and diacetyl.

A similar reaction involving salicyamine has been reported by Witkop and Beiler,[4] who also isolated salicylidenesalicylalmine from the reaction mixture of salicylamine and pyridoxal. They claimed that the reaction proceeded through transamination, followed by a Schiff base exchange reaction which they termed "*trans*-Schiffization."

According to our reaction mechanism, the α-aminoketone VI should be liberated as a by-product of the *trans*-Schiffization; the determination of VI is another evidence of this mechanism. It should be noted, however, that an aliphatic α-aminoketone such as VI is, in general, very unstable and readily undergoes self-condensation to form dihydropyrazine VII, which is then readily air-oxidized to a pyrazine VIII. Thus, the formation of the α-aminoketone VI can be proven by the detection of either VII or VIII.

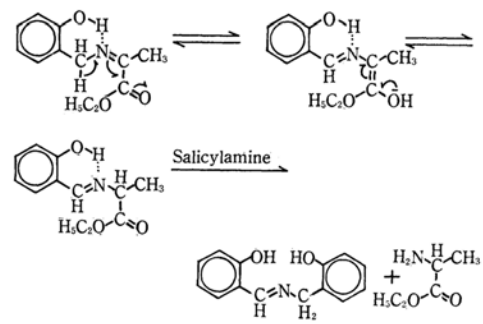


VI VII VIII

In our experiments, tetramethylpyrazine (VIII) was isolated from the reaction mixture; it was identified with an authentic sample[5] by means of the infrared spectra and by a mixed-melting point determination. The formation and isolation of VIII can be explained as resulting from the air-oxidation of VII, which has been formed from α-aminoketone VI in the reaction mixture, since the isolation and purification were unavoidable in an air atmosphere.

Different α-dicarbonyl compounds were also examined with salicylamine; the same type of reaction was found to proceed with methylglyoxal, acetylpropionyl, acetylisobutylyl, phenylglyoxal, acetylbenzoyl, and benzil, always giving rise to salicylidenesalicylamine. Among these, the reaction proceeded without a solvent for acetylbenzoyl; with the exception of acetylpropionyl and acetylisobutylyl, the others gave salicylidenesalicylamine in poor yields. Glyoxal was also examined, but no crystalline material was isolated. 5-Chlorosalicylamine as well as salicylamine reacted with diacetyl; 5-chlorosalicylidene-5′-chlorosalicylamine was thus obtained in about a 40% yield.

It was also found that the α-keto acid ester, *i. e.*, pyruvic acid ethyl ester, underwent the same type of reaction with salicylamine, and that salicylidenesalicylamine was thus obtained in a good yield. Since the amine moiety after *trans*-Schiffization should consist of the α-amino acid ester in this case, the determination was carried out by paper chromatography; α-alanine was detected in the reaction mixture from which salicylidenesalicylamine was isolated. It is clear that the reactions proceed in the same manner as in the case of the α-diketones. They are shown in Scheme II.



Scheme II

It is interesting with respect to this reaction to note that Nakahara *et al.*[6] have found the transamination reaction to occur from a salicylamine-pyruvic acid Schiff base to a salicylaldehyde-α-alanine Schiff base through the copper chelate. Since both Schiff bases can exist only as metal chelate ligands, the role of the metal ion may be to stabilize the azomethine linkage through the formation of a chelate ring. In the case of the ester, the Schiff base exists without any metal chelate formation; therefore, transamination could occur smoothly in the absence of metal ions.

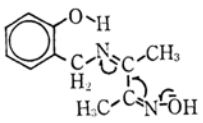
It can be seen from these pieces of evidence that

4) B. Witkop and T. W. Beiler, *J. Am. Chem. Soc.*, **20**, 5589 (1954).

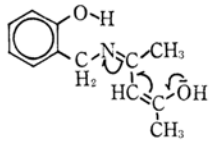
5) H. Gutknecht, *Ber.*, **12**, 2291 (1879); E. Braun, *ibid.*, **22**, 559 (1889).

6) Y. Nakao, S. Sasaki, K. Sakurai and A. Nakahara, This Bulletin, **40**, 241 (1967).

these types of transamination and *trans*-Schiffization proceed between salicylamines and α-dicarbonyl compounds except in the case of α-dialdehyde. The transamination may be due to a mesomeric effect of the carbonyl group in the Schiff base IV; this effect causes simultaneously an electron shift from the azomethine double bond to the C–C bond and deprotonation from the methylenic hydrogen. Accordingly, if there is any substituent to prevent the carbonyl group from exerting the electron-withdrawing effect, the transamination reaction will not occur. This was confirmed by the reaction of salicylamine and diacetyl monoxime, where a Schiff base IX was isolated in a good yield and where no further reactions were observed. It is clear that the electron-withdrawing effect of the carbonyl group was very much weakened by the oximino substitution and that, consequently, a further electron shift was prevented.



IX



X

The significant role of the α-carbonyl group of the Schiff base IV in the transamination was further supported by the fact that transamination did not occur on a Schiff base such as X with a β-carbonyl group. The Schiff base X which was obtained by the reaction of salicylamine with acetylacetone is stable in boiling methanol; the enol structure was suggested from its infrared spectrum which exhibited strong absorptions at 1603 cm^{-1} and 1540 cm^{-1}. Since the enol group enhances the negative charge at the azomethine nitrogen atom, as is shown in the case of X, deprotonation from the methylenic hydrogen becomes difficult.

Metzler *et al.*[7] have extensively studied non-enzymatic transamination between α-amino acid and α-keto acid catalyzed by pyridoxal and by pyridoxamine. They found that the reaction was accelerated by metal chelate formation with the Schiff bases of pyridoxal-amino acid or pyridoxamine-keto acid and claimed that the significance of the nitrogen atom of the pyridine ring of pyridoxal or pyridoxamine was that it caused an electron shift from the azomethine linkage towards the pyridine ring. The role of the metal ion was explained as enhancing the electronegativity of the azomethine nitrogen; however, no mention was made concerning the role of the carboxylate group adjacent to the azomethine linkage.

The fact that the transamination could occur even between salicylamines and α-dicarbonyl compounds in the absence of metal ion may be somewhat inconsistent with their explanation. As has been stated above, the significant role of the α-carbonyl group should be taken into consideration as an electron-withdrawing source towards its own sites.

The presence of the ortho hydroxyl group in salicylamine is favorable for transamination by facilitating the formation of the Schiff base IV through intramolecular hydrogen bonding with the azomethine nitrogen. This was evidenced by the fact that benzylamine with no hydroxyl group, did not react with either the diacetyl or the pyruvic acid ester.

The effect of the metal ion, through chelate formation, on this transamination is now being investigated; the synthesis of the initially-proposed compounds, I and II, will be reported in a subsequent paper.

Experimental

Reaction of Salicylamine with Diacetyl (Transamination and *trans*-Schiffization). Under a nitrogen stream, 3.7 g (0.03 mol) of salicylamine which had been carefully purified by sublimation and by recrystallization from ethanol were dissolved in 70 m*l* of methanol, and then 1.5 g (0.018 mol) of diacetyl were added. The solution was gently refluxed under a nitrogen stream for thirty minutes and then kept in a refrigerator overnight. The resulting yellow needles were filtered, and the filtrate was concentrated to about 15 m*l*; additional crystals were thus obtained. When they were recrystallized from methanol, 1.4 g of a pure sample, mp 183—184°C, were obtained in a yield of 41.3% based on the salicylamine. The mixed-melting point with salicylidenesalicylamine was 183°C, and their infrared spectra were identical, both exhibiting a C=N absorption at 1640 cm^{-1} (KBr disk).

Found: C, 73.39: H, 5.82; N, 6.20%. Calcd for $C_{14}H_{13}NO_2$: C, 73.54: H, 5.72: N, 6.16%.

After salicylidenesalicylamine had been isolated from the reaction mixture, the mother liquor was evaporated to dryness on a water bath; the remaining resinous material was then sublimed at 80°C under reduced pressure (30 mmHg). The colorless sublimates were collected and recrystallized from water. The melting point was 81—82°C; it showed no depression upon being mixed with an authentic sample of tetramethylpyrazine, and their infrared spectra were identical.

The reaction of salicylamine with acetylpropionyl, acetylisobutylyl, methylglyoxal, phenylglyoxal, and benzil were carried out in the same manner as above; salicylidenesalicylamine was isolated in every case. The yields for acetylpropionyl and acetylisobutylyl were almost the same as those cited above; however, those of the last three substances were less than 10%.

For acetylbenzoyl, the reaction proceeded without any solvent; thus, 0.12 g (0.001 mol) of salicylamine and 0.15 g (0.001 mol) of acetylbenzoyl were mixed and heated on a water bath under a nitrogen stream. The mixture soon melted and yellow needles were gradually deposited over a ten-minute period. After the mixture

7) D. E. Metzler, M. Ikawa and E. E. Snell, *J. Am. Chem. Soc.*, **76**, 648 (1954).

had been heated for thirty minutes, the resulting salicylidenesalicylamine was isolated by treating the mixture with ethanol.

Reaction of 5-Chlorosalicylamine with Diacetyl. This reaction was carried out in the same manner as in the case of salicyalmine; 5-chlorosalicylidene-5′-chlorosalicylamine, mp 201—203°C, was isolated in a 40% yield. IR: 1665 cm^{-1} (C=N).

Found: C, 56.88; H, 3.81; N, 4.66%. Calcd for $C_{14}H_{11}NO_2Cl_2$: C, 56.79; H, 3.72; N, 4.73%.

Reaction of Salicylamine with Ethyl Pyruvate. A mixture of 0.12 g (10^{-3} mol) of pure salicylamine and 0.06 g (5×10^{-4} mol) of ethyl pyruvate in 5 m*l* of methanol was gently refluxed under a nitrogen stream for one hour. The solution turned red orange, and salicylidenesalicylamine was crystallized on cooling. The yield was 0.04 g (40% based on the salicylamine) and a mixed-melting point determination with an authentic sample showed no depression (183°C). After the filtrate of salicylidenesalicylamine had been evaporated, the resinous residue was treated with a small amount of water and filtered. To the filtrate there was added one drop of concentrated hydrochloric acid; the mixture was refluxed for one hour and then evaporated to dryness. The residue was dissolved in a small amount of water, and the solution was subjected to paper chromatography. The R_f value of the sample was 0.38, identical with that of *d,l*-alanine ($R_f=0.38$; solvent, butanol : acetic acid : water=4 : 1 : 2).

Schiff Base of Salicylamine with Diacetyl Monoxime IX. A mixture of 0.48 g (0.039 mol) of pure salicylamine and 0.4 g (0.04 mol) of diacetyl monoxime in 25 m*l* of dry benzene was refluxed for one hour under a nitrogen stream. The solution was then concentrated to 10 m*l* under reduced pressure, and the resulting precipitates were recrystallized from benzene. Colorless crystals, mp 106—108°C; yield 0.6 g (80%). IR: 3250 cm^{-1} (NOH), 1645 cm^{-1} (C=N), 1609 cm^{-1} (C=NOH).

Found: C, 63.78; H, 6.79; N, 13.67%. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58%.

Schiff Base of Salicylamine with Acetylacetone (X). A mixture of 1.2 g (0.01 mol) of pure salicylamine and 1 g (0.01 mol) of acetylacetone in 10 m*l* of methanol was refluxed for one hour under a nitrogen stream. On cooling, 1.7 g of an almost pure Schiff base was obtained as colorless needles in a yield of 83%; it was recrystallized from methanol; mp 141—142.5°C. IR: 1603 cm^{-1}, 1540 cm^{-1} (probably C=N and C=C of enol).

Found: C, 69.88; H, 7.27; N, 6.99%. Calcd for $C_{11}H_{13}NO_2$: C, 70.21; H, 7.37; N, 6.84%.