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96. Minoru Sekiya, Noboru Yanaihara, and Toshio Masui : Reaction of Amide Homologs. VI.[1] Aminomethylation of Salicylic Acid with N,N′-Methylenebisacetamide.

(*Shizuoka College of Pharmacy*[*1])

In continuation of our studies on aromatic α-acylaminoalkylation with N,N′-alkylidenebisamide, briefly stated in the preliminary communication[2], the present paper deals with aminomethylation of salicylic acid and related compounds. The compound, 5-aminomethylsalicylic acid, obtained in this work was found by E. Hayashi of this college to possess an analgetic activity. Its pharmacological data will be reported in the near future.

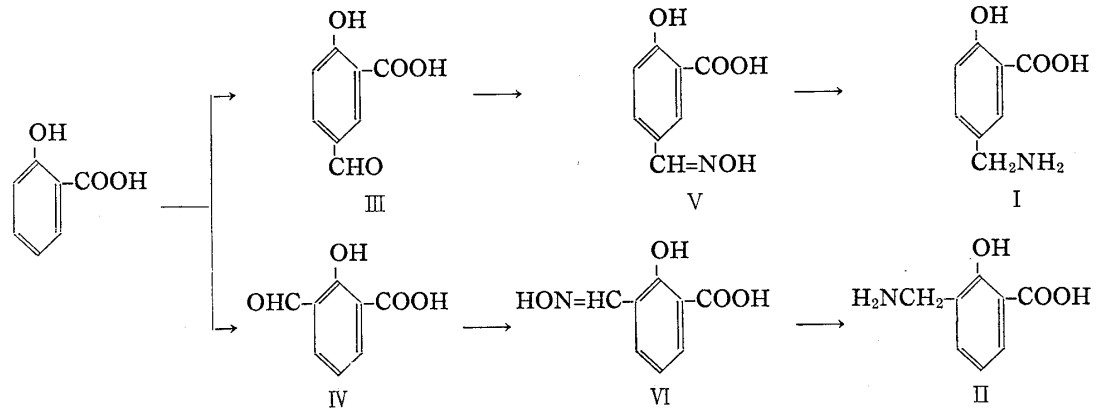
The acetamidomethylation of salicylic acid was carried out according to the method described in the previous paper by heating salicylic acid, N,N′-methylenebisacetamide, and phosphoryl chloride on a boilng water bath. Due to difficulty in crystallization of the reaction product, the crude acetamidomethyl compound was converted, without further purification, by hydrolysis with hydrochloric acid to aminomethylsalicylic acid hydrochloride, which decomposed at 245~246°. Its yield was 31 % of the theory from the starting salicylic acid, and the excess of salicylic acid was recovered almost quantitatively. Aminomethylsalicylic acid (I) obtained from its hydrochloride formed needles which did not melt on heating but underwent gradual decomposition at above 250°.

Both the compounds (I) and its hydrochloride gave correct values corresponding to those formulae by analyses. To determine the position of aminomethyl group in the structure, 5- and 3-substituted compounds were synthesized by another route, and I was identified as the former.

For the syntheses of I and 3-aminomethylsalicylic acid (II), 5- (III) and 3-formylsalicylic acid (IV) were used as the starting materials. According to the method reported by Duff, *et al.*,[3] these compounds were prepared by heating salicylic acid and hexamethylenetetramine in aqueous solution. Though the determination of the positions of aldehyde groups in the compounds was not described in their paper, their structure was later comfirmed by Horii, *et al.*[4] by identification with those synthesized by Reimer-Tiemann reaction of salicylic acid. Further, with the intention of getting more reliable data regarding their structure, III and IV were respectively oxidized with silver oxide to 4-hydroxyisophthalic acid,[5] m.p. 310°, and 2-hydroxyisophthalic acid,[5] m.p. 242°, which agreed in their m.p. and analytical values.

*1 Oshika, Shizuoka (関屋 実, 矢内原 昇, 増井俊夫).

1) Part V : This Bulletin, **9**, 945 (1961).
2) M. Sekiya, N, Yanaihara : *Ibid.*, **7**, 746 (1959).
3) J.C. Duff, E.J. Bills : J. Chem. Soc., **1932**, 1987.
4) Z. Horii, Y. Komiyama, K. Otsuki, Y. Yamamura : Yakugaku Zasshi. **72**, 1520 (1952).
5) F. Tiemann, K. Reimer : Ber., **10**, 1570 (1877).



I and II were synthesized from III and IV according to the following route.

The compounds, III and IV were converted into their oximes (V and VI), which respectively melted at 222° (decomp.) and 210° (decomp.). Fürth[6] recorded V as a monohydrate of m.p. 179°.

Then according to Sekiya's method,[7] V and VI were catalyticaly hydrogenated with Raney-nickel under high pressure of hydrogen in the presence of formamide and both the crude reaction products, which should be 5- and 3-formamidomethylsalicylic acid, were hydrolyzed with dil. hydrochloric acid to I and II, which respectively showed decomposition at above 250° and at 258°.

The aminomethylsalicylic acid obtained by aminomethylation of salicylic acid was identical with the 5-substituted compound derived from III. Infrared spectra of these samples were identical with each other and melting points of their methyl ester (VII) were not depressed on admixture.

Previously, VII and its hydrochloride were reported by Bauer, *et al.*[8] as an oily substance and crystals of m.p. 118~122°, respectively, but the two samples obtained as VII and its hydrochloride by either of the foregoing two routes were the crystals which respectively showed m.p. 135~136° and 200° (decomp.).

Experimental

5-Aminomethylsalicylic Acid (I)——i) A mixture of 50 g. of salicylic acid, 56.5 g. of N,N′-methylenebisacetamide, and 28 g. of $POCl_3$ was heated for 1 hr. on a boiling water bath, when HCl gas evolved. To the syrupy reaction mixture water was added and the whole was warmed cautiously. The separated oily material which should be the acetamidomethyl compound, was hydrolyzed without further purification. To this was added 300 cc. of 15% HCl and the mixture was refluxed for 3 hr. After removal of unchanged salicylic acid which deposited on cooling, the solution was concentrated under reduced pressure. The crystalline substance was collected and refluxed with benzene to remove remaining salicylic acid by extraction. Yield 22 g. Needles (from EtOH), m.p. 245~246° (decomp.). *Anal.* Calcd. for $C_8H_{10}O_3NCl$: C, 47.18; H, 4.95; N, 6.88. Found: C, 47.06; H, 4.95; N, 6.92. IR ν_{max}^{KBr} cm^{-1}: 1687, 1187 (COOH), 3006 (NH_3^+), 1203 (OH).

To an aqueous solution of the hydrochloride, equimolar amount of KOH solution was added, when the free amino acid precipitated. Recrystallization from H_2O gave needles, which did not melt on heating, but gradually decomposed at a temperature above about 250°. Addition of $FeCl_3$ gave violet color in aqueous solution. *Anal.* Calcd. for $C_8H_9O_3N$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.27; H, 5.57; N, 8.45. IR ν_{max}^{KBr} cm^{-1}: 1637, 1445 (COO^-), 3016 (NH_3^+), 1203, 3225 (OH).

ii) To a solution of 3.3 g. of 5-formylsalicylic acid oxime (V) dissolved in 40 cc. of EtOH, NH_3 was sufficiently absorbed to neutralize acidity of the solution. To this solution, 2.5 g. of formamide and Raney-Ni (1 g. as 50% alloy) were added in an authoclave. Under 100 atm. (21°C) of initial H_2 pressure, the whole was heated and constantly shaken at 100~102°. The absorption was nearly completed in

6) A. Fürth: Ber., **16**, 2182 (1883).
7) M. Sekiya: Yakugaku Zasshi, **70**, 524 (1950).
8) K. H. Bauer, K. Bühler., Arch. Pharm., **1924**, 135.

about 20 min. After removal of the catalyst, EtOH and an excess of $HCONH_2$ were distilled off under reduced pressure, and the residue was refluxed with 40 cc. of 15% HCl for 2 hr. Concentration of the resultant solution gave crystals of hydrochloride. Yield 3.4 g. Needles (from EtOH), which decomposed at 244~245°. The free amino acid was obtained by the same procedure as described in (i). Needles, which showed gradual decomposition at above 250°. *Anal.* Calcd. for $C_8H_9O_3N$: C, 57.48; H, 5.43; N, 8.38. Found : C, 57.45; H, 5.38; N, 8.55.

IR spectra of this compound and its hydrochloride were in agreement with those of the corresponding compounds obtained in (i).

Methyl 5-Aminomethylsalicylate (VII)——A mixture of 2 g. of 5-aminomethylsalicylic acid hydrochloride and 30 cc. of saturated MeOH-HCl was refluxed for 2 hr. on a water bath. At the end of the reaction the mixture became homogeneous. On evaporation of the solvent, crystals of hydrochloride were obtained. Yield 2 g. Needles (from MeOH), m.p. 200°(decomp.). *Anal.* Calcd. for $C_9H_{12}O_3NCl$: C, 49.66; H, 4.41; N, 6.43. Found : C, 49.18; H, 4.52; N, 6.21.

When NH_3 was passed through an aqueous solution of this substance, free amine precipitated. Recrystallization from MeOH gave needles, m.p. 135~136°. *Anal.* Calcd. for $C_9H_{11}O_3N$: C, 59.66; H, 6.21; N, 7.73. Found : C, 59.28; H, 6.02; N, 7.74.

Both of the methyl esters, one obtained through aminomethylation of salicylic acid and another through reduction of V, were found to be identical with each other by mixed melting point test.

4-Hydroxyisophthalic Acid——To a solution of 2 g. of 5-formylsalicylic acid (III), m.p. 249°, dissolved in 40 cc. of 5% NaOH, Ag_2O prepared from 4 g. of $AgNO_3$ was added and the mixture was heated at 60~70° with agitation. The reaction completed after a few minutes. After removal of Ag, acidification of the solution with HCl gave needle crystals (from EtOH), m.p. 310°(decomp.), which agreed well with that recorded in the literature.[5] *Anal.* Calcd. for $C_8H_6O_5$: C, 52.72; H, 3.30. Found : C, 52.67; H, 3.35.

2-Hydroxyisophthalic Acid——By the same method as described for 4-hydroxy compound, 2-hydroxy compound was obtained from 3-formylsalicylic acid, m.p. 177°, as needles, m.p. 242°, which agreed well with that recorded in the literature.[5] *Anal.* Calcd. for $C_8H_6O_5$: C, 52.72; H, 3.30. Found : C, 52.61; H, 3.36.

5-Formylsalicylic Acid Oxime (V)——To a solution of 4.2 g. of III dissolved in 30 cc. of *N*NaOH, 2.3 g. of NH_2OH-HCl in 150 cc. of H_2O was added. The reaction solution was allowed to stand at room temperature for 2 days. By acidification with HCl, the oxime precipitated. Yield, 4.3 g. Needles (from 70% EtOH), m.p. 222°(decomp.). *Anal.* Calcd. for $C_8H_7O_4N$: C, 53.04; H, 3.90; N, 7.73. Found : C, 53.11; H, 3.90; N, 7.62.

3-Formylsalicylic Acid Oxime (VI)——As described in V, 4.2 g. of IV in NaOH solution and 2.3 g. of NH_2OH-HCl were treated. Yield, 4.2 g, Needles (from 70% EtOH), m.p. 210°(decomp.). *Anal.* Calcd. for $C_8H_7O_4N$: C, 53.04; H, 3.90; N, 7.73. Found : C, 52.82; H, 3.83; N, 7.70.

3-Aminomethylsalicylic Acid (II)——From 2.5 g. of VI, this was prepared by the same procedure as that described for I. The absorption was nearly completed in about 20 min. Yield of hydrochloride, 2.6 g. Needles, m.p. 234~236°(decomp.). *Anal.* Calcd. for $C_8H_{10}O_3NCl$: C, 47.18; H, 4.95; N, 6.88. Found : C, 47.08; H, 5.04; N, 6.90.

With equimolar amount of KOH, the free amino acid was obtained as needles, m.p. 257~258° (decomp.). *Anal.* Calcd. for $C_8H_9O_3N$: C, 57.48; H, 5.43; N, 8.38. Found : C, 57.31; H, 5.50; N, 8.45.

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Summary

Aminomethylation of salicylic acid was carried out by heating together N,N′-methylenebisacetamide and phosphoryl chloride affording 5-aminomethylsalicylic acid. For the identification of this product, 5- and 3-aminomethylsalicylic acid were synthesized by another route using 5- and 3-formylsalicylic acid as starting materials.

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