Studies on 5-Aminosalicylaldehyde Derivatives. II.[1] Reduction of 5-(*p*-Sulfophenylazo)salicylaldehyde through Poly(5-nitrilosalicylidene) to 5-Aminosalicylaldehyde Derivatives

Mitsunori TANAKA

The Faculty of Education, Kagawa University, Takamatsu, Kagawa

(Received January 11, 1967)

Derivatives of 4-aminosalicylaldehyde over a wide range have been synthesized and characterized for medical purposes by several workers[2] in recent years. Only a few derivatives of 5-aminosalicylaldehyde have, however, been studied. In the previous paper,[1] it was reported that the attempted synthesis of 5-aminosalicylaldehyde (II) by the reduction of 5-(*p*-sulfophenylazo)salicylaldehyde (I)

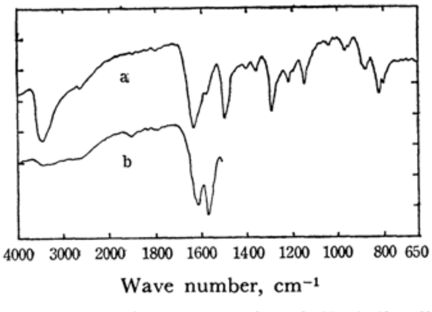


Fig. 1. Infrared spectra of poly(5-nitrilosalicylidene).

a, KBr disk

b, Hexachlorobutadiene mull method.

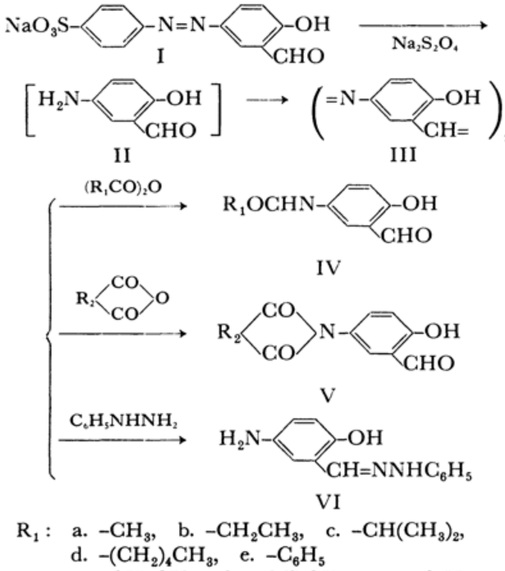
---

[1] Part I: M. Tanaka, This Bulletin, **37**, 1210 (1964).

[2] For instance, T. Ikeda, S. Hirai, M. Ishikawa and M. Yoshioka, *Ann. Repts. Shionogi Research Lab.*, 1 (1953); A. A. Goldbergand and H. A. Walkerm, *J. Chem. Soc.*, **1954**, 2540; R. Justoni, R. Pessina and C. Pirola, *Chem. Abstr.*, **47**, 6944 (1953); Ch. Gausser and P. Rumpf, *Helv. Chim. Acta*, **37**, 437 (1964).

TABLE 1. 5-ACYLAMINO- OR CYCLIC DICARBONYLAMINO-SALICYLALDEHYDE

Protected amino group	Mp °C	Reaction temp. °C	Method of preparation	Recryst. solvent	Yield %	Appearance	Formula		Analysis, % C	H	N
Acetamido	148	60—70	a	Benzene	65	Orange yellow needles	$C_9H_9O_3N$	Found	60.44	5.07	8.05
								Calcd	60.33	5.06	7.82
Propionamido	152	75—85	b	Benzene	52	Pale yellow needles	$C_{10}H_{11}O_3N$	Found	62.23	5.63	7.16
								Calcd	62.16	5.74	7.25
Isobutyramido	125.5—126	80—85	b	Benzene	53	Pale yellow needles	$C_{11}H_{13}O_3N$	Found	63.94	6.24	6.75
								Calcd	63.75	6.32	6.76
Caproamido	92	90—100	b	Benzene	42	White needles	$C_{13}H_{17}O_3N$	Found	66.61	7.34	5.86
								Calcd	66.36	7.28	5.95
Benzamido	205	70—80	b	Benzene	48	Yellow powder	$C_{14}H_{11}O_3N$	Found	69.43	4.84	5.49
								Calcd	69.70	4.59	5.80
Maleinimido	over 300	70—75	b	Ethyl alcohol		Yellow powder	$C_{11}H_7O_4N$	Found	60.61	3.38	6.48
								Calcd	60.83	3.25	6.45
Succinimido	268 (decomp.)	130—135	c	Ethyl alcohol		Brownish yellow powder	$C_{11}H_9O_4N$	Found	60.17	3.75	6.67
								Calcd	60.27	4.14	6.39
Phthalimido	243	140—150	c	Ethyl alcohol	56	Brownish yellow needles	$C_{15}H_9O_4N$	Found	67.05	3.44	5.04
								Calcd	67.41	3.39	5.24



R_1: a. $-CH_3$, b. $-CH_2CH_3$, c. $-CH(CH_3)_2$, d. $-(CH_2)_4CH_3$, e. $-C_6H_5$

R_2: a. $-CH{=}CH-$, b. $-CH_2CH_2-$, c. $-C_6H_4-$

with sodium hydrosulfite gave only an insoluble red substance (III).

The present work attempted to determine the structure of III and to establish a new route for obtaining 5-aminosalicylaldehyde derivatives from III. From the analytical data, the empirical formula $(C_7H_5ON)_n$ was given for III. The infrared spectra of III are shown in Fig. 1a (KBr) and Fig. 1b (H.C.B.). In Fig. 1a, the peak around 1600 cm^{-1} shows the presence of the $-CH{=}N-$ group. In addition, the absence of absorption bands around 3200 cm^{-1} for N–H and around 1650 cm^{-1} for $\rangle C{=}O$ suggests that III may be poly(5-nitrilosalicylidene). In order to confirm this structure, III was treated with acetic anhydride containing a small amount of pyridine and then with water. The cleaved product was 5-acetamidosalicylaldehyde (IVa), which was identified by its infrared spectrum and by a mixed-melting-point determination with an authentic sample prepared by the method of Ichibagase *et al.*[3] By an analogous method, propionic, isobutyric, caproic, and benzoic anhydrides, as well as succinic, maleic, and phthalic anhydrides, also gave the corresponding 5-acylaminosalicylaldehydes (IV) as well as cyclic dicarbonylaminosalicylaldehydes (V). The red substance (III) was cleaved also by phenylhydrazine and yielded 5-aminosalicylaldehyde phenylhydrazone (VI), which was identified by its infrared spectrum and by a mixed-melting-point determination with an authentic sample prepared by the method of Weil *et al.*[4] and Oddo *et al.*[5] Similarly, the reaction of III with hydrazine hydrate gave bis(5-aminosalicylaldehyde)azine.

From the facts mentioned above, the red substance (III) was confirmed to be poly(5-nitrilosalicylidene). As this substance is readily cleaved by acid anhydrides or by hydrazines, the synthesis of some 5-aminosalicylaldehyde derivatives may be facilitated by this new route through the polymer.

Experimental

The Infrared Spectra. The infrared spectra were measured with a Hitachi IR spectorophotometer, model EPI-S2.

Sodium Salt of 5-(*p*-Sulfophenylazo)salicylaldehyde (I). This salt was prepared by Tummely's method.[6]

Found: C, 42.80; H, 3.60; N, 7.48; Na, 5.93%. Calcd for $C_{13}H_9O_5N_2SNa \cdot 2H_2O$: C, 42.83; H, 3.60; N, 7.69; Na, 6.31%.

Poly(5-nitrilosalicylidene) (III). To a stirred solution of 3.8 g of sodium salt of I and 1.6 g of sodium hydroxide in 100 m*l* of water, 3.8 g of sodium hydrosulfite were added at 60—70°C. The precipitate was collected and washed thoroughly with water. Reddish powder, insoluble in various solvents; yield, 1.16 g (85%).

Found: C, 70.64; H, 4.15; N, 11.72%. Calcd for C_7H_5ON: C, 70.58; H, 4.23; N, 11.76%.

Cleavage of Poly(5-nitrilosalicylidene) by Acid Anhydrides. Poly(5-nitrilosalicylidene) (0.01 mol) (III) was heated with acid anhydride (0.05—0.1 mol) containing a small amount of pyridine (0.1 m*l*) until it dissolved. The temperatures are listed in Table 1. Subsequent treatment was altered according to the kind of acid anhydride.

a) The reaction mixture was distilled under diminished pressure to remove an excess of acid anhydride and pyridine. The residue was then dissolved in a solution of sodium hydroxide (1.33 g) in water (100 m*l*), and acetic acid (3.5 m*l*) was added, after which the mixture was evaporated under diminished pressure.

b) The reaction mixture was poured into 150 m*l* of hot water and boiled for an hour. After cooling, the aqueous solution was neutralized with alkali, and the mixture was evaporated under diminished pressure.

c) The reaction mixture was poured into 150 m*l* of hot water and boiled for an hour. The hot mixture was filtered, and the precipitate was washed with hot water.

The residue obtained by these treatments was extracted with hot benzene or ethyl alcohol and recrystallized from the solvent specified in Table 1.

5-Aminosalicylaldehyde Phenylhydrazone. To 1.19 g of III, 5 g of phenylhydrazine were added. The mixture was then warmed on a water bath. After cooling, the precipitate was collected, washed with ethyl alcohol, and recrystallized from benzene. Yellowish needles. Mp 165—165.5°C.

Found: C, 68.73; H, 5.76; N, 18.61%. Calcd for $C_{13}H_{13}ON_3$: C, 68.70; H, 5.77; N, 18.49%.

Bis(5-aminosalicylaldehyde)azine. A mixture of 1.19 g of III with 5 g of hydrazine hydrate (80%) was slightly warmed on a water bath. After cooling, the reaction mixture was poured into dilute acetic acid. The precipitate was then collected, washed with ethyl alcohol, and recrystallized from dimethylformamide. Mp over 300°C. Yellow powder.

Found: C, 62.44; H, 5.36; N, 20.36%. Calcd for $C_{14}H_{14}O_2N_4$: C, 62.21; H, 5.22; N, 20.73%.

The author wishes to express his thanks to President Dr. Tokuichi Tsumaki of the Kyushu Institute of Technology and to Professor Dr. Tamotsu Yoshino and Dr. Masaru Yamaguchi of Kyushu University for their exceedingly kind direction of this work.

---

[3] Y. Kuwayama and H. Ichibagase, *Yakugaku Zasshi*, **78**, 659 (1958).

[4] H. Weil, M. Traun and S. Marcel, *Chem. Ber.*, **55**, 2664 (1958).

[5] G. Oddo and A. Giacalone, *Gazz. Chim. Ital.*, **58**, 290 (1928).

[6] E. Tummely, *Ann.*, **251**, 180 (1889).