Anal. Calcd. for $C_{23}H_{31}N_5O_{10}S$: C, 48.49; H, 5.49; N, 12.29; S, 5.63. Found: C, 48.64; H, 5.37; N, 12.30; S, 5.74.

1-(9-Adenyl)-1,1-dideoxy-1-ethylthio-*aldehydo*-D-galactose Aldehydrol (VIII).—Crystalline penta-*O*-acetyl-1-(6-acetamido-9-purinyl)-1,1-dideoxy-1-ethylthio-*aldehydo*-D-galactose aldehydrol (IV, 5.0 g.) was dissolved in 75 ml. of hot, dry methanol to which 1.5 ml. of *n*-butylamine[15] was added and the solution refluxed for 6 hr. A crystalline solid (VIII) separated upon cooling the solution; yield 2.66 g. (91%). The material was redissolved in water, treated with carbon, and evaporated to a sirup. Addition of ethanol and storing at 0° induced crystallization; yield 2.59 g. (88%), m.p. 217–218°, $[\alpha]^{22}D$ −114° (*c* 0.53, water); absorption spectra data[11,12]: $\lambda_{max}^{H_2O}$ 262 mμ; λ_{max}^{KBr} 2.86, 3.00 μ (OH, NH); 6.02, 6.18, 6.30, 6.72 μ (NH_2, NH, and purine ring); 7.34 (methyl hydrogen); 9.00, 9.38, 9.74 μ (COC, COH); x-ray powder diffraction data[13]: 10.10 vs (1), 6.68 vw, 6.17 vw, 5.56 m, 5.11 s (2), 4.68 w, 4.23 s (3), 3.75 w, 3.59 vw, 3.37 w.

Anal. Calcd. for $C_{13}H_{21}N_5O_5S$: C, 43.44; H, 5.89; N, 19.49; S, 8.92. Found: C, 44.02; H, 5.88; N, 19.57; S, 8.96.

The product VIII was also obtained by deacetylation of penta-*O*-acetyl-1-(adenyl)-1,1-dideoxy-1-ethylthio-*aldehydo*-D-galactose aldehydrol (X) with boiling methanolic *n*-butylamine solution as described above.

Penta-*O*-acetyl-1-(9-adenyl)-1,1-dideoxy-1-ethylthio-*aldehydo*-D-glucose Aldehydrol (XI).—Sirupy penta-*O*-acetyl-1-bromo-1,1-dideoxy-1-ethylthio-*aldehydo*-D-glucose aldehydrol (II) was prepared by Weygand's method[6] as described above for the D-galactose derivative, and added to an azeotropically dried mixture of 6-acetamido-9-chloromercuripurine, 11 g. of cadmium carbonate, 4 g. of Celite,[10] and 300 ml. of toluene. The mixture was refluxed for 2.5 hr. with stirring and filtered. The product was isolated as described above for the D-galactose derivative (IV); yield 17.7 g. of a sirupy penta-*O*-acetyl-1-(6-acetamido-9-purinyl)-1,1-dideoxy-1-ethylthio-*aldehydo*-D-glucose aldehydrol (V). The substance was purified through the crystalline picrate (VII) as described above for the D-galactose derivative (VI); yield 14.5 g. (63%) of VII, dec. 155–165°.

The substance (XI) was regenerated from its picrate (VII, 12.8 g.) by the procedure described above for the corresponding D-galactose derivative (VI); yield 8.33 g. (91%) of crystalline XI. Recrystallization from toluene produced pure material; m.p. 134–135°, $[\alpha]^{21}D$ −109° (*c* 0.74, chloroform); absorption spectra data[11,12]: λ_{max}^{EtOH} 262 mμ, λ_{max}^{KBr} 2.95, 3.10 μ (NH_2, NH), 5.68 μ (ester carbonyl), 5.95, 6.08, 6.22, 6.32, 6.73 μ (NH_2, NH, and purine ring), 7.30 μ (methyl hydrogen), 8.30 μ (*COC* of acetate), 9.32, 9.70 μ (*COC*); x-ray powder diffraction data[13]: 11.05 vw, 8.59 w, 7.44 vs (1), 6.94 m, 6.42 vw, 5.52 m (3), 5.20 vw, 4.99 vw, 4.44 m (2), 4.18 w, 3.48 w, 3.10 vw, 2.98 w, 2.76 w, 1.97 w.

Anal. Calcd. for $C_{23}H_{31}N_5O_{10}S$: C, 48.49; H, 5.49; N, 12.29; S, 5.63. Found: C, 49.17; H, 5.32; N, 12.14; S, 5.38.

1-(9-Adenyl)-1,1-dideoxy-1-ethylthio-*aldehydo*-D-glucose Aldehydrol (IX).—Crude crystalline XI (6.12 g.) was dissolved in 80 ml. of dry methanol and 4 ml. of *n*-butylamine and refluxed for 5.5 hr. The resulting solution was evaporated thrice from methanol and the residue washed with boiling chloroform to give a glassy material; yield 3.91 g. (91%). Crystallization was effected from methanol and recrystallization from ethanol produced pure material (IX): m.p. 149–150°, $[\alpha]^{16}D$ −123° (*c* 0.45, water); absorption spectra data[11,12]: $\lambda_{max}^{H_2O}$ 261 mμ, λ_{max}^{KBr} 2.86, 2.95, 3.05 μ (OH, NH), 5.98, 6.18, 6.32, 6.74 μ (NH_2, NH, and purine ring), 7.27 μ (methyl hydrogen), 9.00, 9.14, 9.57μ (COH); x-ray powder diffraction data[13]: 13.00 m, 10.40 vw, 7.73 vs (1), 6.63 vw, 5.92 m (3), 4.87 w, 4.35 vs (2), 3.94 vw, 3.71 vw, 3.51 vw, 3.34 vw.

Anal. Calcd. for $C_{13}H_{21}N_5O_5S$: C, 43.44; H, 5.89; N, 19.49; S, 8.92. Found: C, 43.17; H, 5.76; N, 18.25; S, 8.55.

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Preparation of Salicylic Acids by the Hydroxylation of Benzoic Acids

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Received April 23, 1962

Basic cupric salts of benzoic and the toluic acids decompose at 200–220° to give the corresponding salicylic acids. The hydroxyl group enters the ring at a position adjacent to the carboxyl group.

The carbonation of phenols to give aromatic hydroxy acids by the Kolbe-Schmitt reaction is well known. An excellent review by Lindsey and Jeskey has appeared recently.[1] The position adjacent to the hydroxyl group on the aromatic ring is the preferred place of entry. However, a small amount of *para* substitution frequently occurs and conditions are known which favor entry of the carboxyl group at the *para* position.[2]

A method has now been discovered for the preparation of salicyclic acids by the hydroxylation of the corresponding benzoic acid derivative. This was accomplished by the thermal decomposition of the basic cupric salt of the acid.

Copper Salts of Benzoic Acids.—Cupric salts of aromatic carboxylic acids have been prepared by the combination of equivalent amounts of the sodium or potassium salts of the acid and a soluble inorganic cupric salt in water solution.[3] The insoluble product was purified by thorough washing with water. Only certain *ortho*-substituted products were soluble enough in common organic solvents to permit a recrystallization.

We have found that cupric benzoate prepared in this manner was a mixture of normal cupric

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TABLE I

PHYSICAL PROPERTIES OF VARIOUS CUPRIC SALTS[a]

	Normal salt				Basic salt					
Acid	M.p., °C.	% Cu Calcd.	% Cu Found	Infrared absorption peaks in 12–16-μ region	Gray color, °C.	Dark color, °C.	M.p., °C.	% Cu Calcd.	% Cu Found	Infrared absorption peaks in 12–16-μ region
Benzoic	280–282 dec.	20.78	20.79	12.3 (w) 13.8 (s) 14.1 (s) 14.7 (s)	210–220	240–250	257–259 dec.	31.51	31.47	14.3 (s) 14.6 (s)
o-Toluic	254–255 dec.	19.06	18.93	12.4 (w) 12.7 (w) 13.6 (s) 14.9 (m)	185	205	248 dec.	29.49	29.30	12.4 (w) 12.7 (w) 13.7 (s) 15.0 (m)
m-Toluic	248–250 dec.	19.06	18.36	12.7 (s) 13.3 (s) 14.8 (s)	195	205	227–229 dec.	29.49	29.25	12.6 (s) 13.4 (s) 14.7 (s)
p-Toluic	280–282 dec.	19.06	18.95	12.8 (w) 13.1 (s) 13.2 (s)	200	210–215	245–248 dec.	29.49	28.91	13.3 (s) 14.6 (w)

[a] The normal salts were purified by recrystallization from dry acetone. The basic salts were prepared by adding water to an acetone solution of the normal salt.

TABLE II

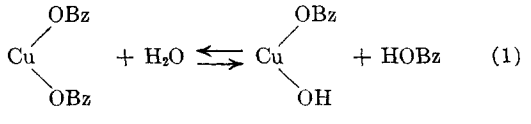
PYROLYSIS OF BASIC CUPRIC SALTS

Acid	Basic salt, mmole	Medium,[a] ml.	Temp., °C.	Time heated, min.	Salicylic acid dvt., mmole	Recovered starting acid, mmole	CO_2, mmole	Yield, %
Benzoic	137	NB-100	212	7	17	95[b]	1.7	40
Benzoic	198	NB-150	212	16	47	123[b]	3.5	63
Benzoic	40	DPM-100	212	12	5.1	31	0.7	57
o-Toluic	37	DPM-100	212	12	1.7	30	3.0	24
o-Toluic	37	None	212	5	1.1	34	0.2	37
o-Toluic	37	None	220	6	3.3	24	...	25
o-Toluic	47	None	278	1	0.5	34	0.9	4
o-Toluic	47	None	230	12	1.0	16	7.8	3
m-Toluic	42	None	220	45	1.6	30	2.3	13
m-Toluic	47	None	220	32	3.4	37	1.5	34
p-Toluic	47	None	220	25	2.0	27	3.4	10
p-Toluic	47	None	220	30	5.7	28	2.5	30

[a] NB—nitrobenzene, DPM—diphenylmethane. [b] Calculated from analysis by titration with base.

benzoate, basic cupric benzoate,[4] and benzoic acid. The compounds were present in proportions to give an analysis for copper equal to that required for the normal salt. The brilliant emerald green normal salt and free acid were extracted from the pale blue basic salt with dry boiling acetone.

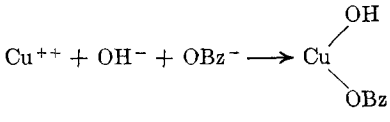
When water was added to a hot acetone solution of the normal salt, very pure basic salt precipitated. Furthermore, the basic salt redissolved to regenerate the normal salt when quantities of benzoic acid were added. This suggests that an equilibrium exists as shown in equation 1, and could account for the mixture obtained when aqueous solutions were used to prepare the various cupric salts.



(1)

(4) In this paper, normal cupric salts contain two carboxyl groups per copper atom and basic salts contain one carboxyl and one hydroxyl group per copper atom, as indicated by analysis for copper.

Basic salts may also be prepared by the combination of equivalent amounts of cupric, hydroxyl, and benzoate ions as shown in equation 2. An



(2)

identical product was obtained by this method as shown by the infrared spectra and crystalline *d*-spacings and intensity ratios obtained from powder X-ray diffraction measurements. The infrared spectra of all of the basic salts have a characteristic strong hydroxyl bending absorption frequency in the 10.5–11.5-μ region as well as the hydroxyl stretching absorption frequency at 2.8 μ, both of which were absent for all of the corresponding normal salts. Characteristic absorption bands appeared in the 12–16-μ region. The properties of various salts are summarized in Table I.

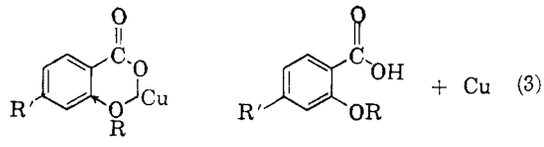
Pyrolysis of Basic Salts.—The basic salts were heated directly as the dry powder or suspended in

an inert heat transfer liquid. The reaction cell was heated by means of a refluxing liquid to ensure that the prescribed maximum temperature was not exceeded. The blue salt turned gray and then dark in color. Best yields were obtained when the dry salt was heated at the maximum temperature for fifteen to thirty minutes. The results are summarized in Table II.

The recovered carboxylic acid fraction contained a mixture of starting acid and various amounts of the corresponding salicylic acid. The latter was isolated by a counter current extraction system utilizing aqueous ferric chloride as the transfer agent. A water-soluble complex formed only with the salicylic acid derivative.

Basic salts of the three toluic acid isomers were prepared and pyrolyzed in a similar manner. The hydroxyl group became attached to the ring at a position adjacent to the carboxyl group. Thus, *o*- and *p*-toluic acids gave 6- and 4-methylsalicylic acids, respectively. With *m*-toluic acid, the principal product isolated was 5-methylsalicylic acid with only a trace of the 3-methyl isomer. This could indicate that orientation was quite sensitive to steric requirements.

This orientation was entirely analogous with that observed previously for the thermal decomposition of the normal cupric salt to give phenyl benzoate (or phenol) and carbon dioxide.[5] The hydroxyl group appeared at a position adjacent to the original carboxyl group. A cyclic intermediate (R = —COC_6H_5) was proposed involving a nucleophilic attack by oxygen to account for the products obtained and the steric course of the reaction.



(3)

A similar mechanism is proposed for the basic salt decomposition reaction (R = H) as shown in equation 3. Normally, copper metal did not appear as a product of reaction unless relatively vigorous conditions of reaction were used. At present, it has not been possible to determine whether a pair of cupric atoms carry out the oxidation with a single electron change for each or whether copper metal is formed, as shown in equation 3, which then rapidly reacts with another cupric atom to produce the cuprous salt.

With the process for the production of phenol in molten benzoic acid solution, the normal cupric salt is the key intermediate in the absence of water. However, when steam is used, and when magnesium benzoate is present to reduce substantially the concentration of free benzoic acid, the equilibrium, equation 2, is undoubtedly shifted in favor of the basic salt. Furthermore, the latter decomposes at a temperature significantly lower than the normal salt. This strongly suggests that the basic salt is the key intermediate in the new Dow process[5b] for converting benzoic acid to phenol.

We have been unable to find any references describing either the structure or the chemistry of aromatic basic cupric salts. The structures of inorganic and simple aliphatic basic cupric salts are usually portrayed as combinations of normal salts, cupric hydroxide, cupric oxide, and water.

The attachment of both hydroxyl and carboxylate groups to the same copper atom appears to be novel and evidence of this structure would support the mechanism proposed.

Experimental

Normal Cupric Salts of Aromatic Acids. Method IA.—Approximately 4 equivalents of molten acid at 200–210° were combined with 2 equivalents of basic cupric carbonate. The hot slurry was stirred for a few minutes and then emptied into 10 volumes of methylene chloride. Unchanged acid dissolved and the crude product was separated by filtration.

Brilliant emerald green crystals were obtained by recrystallization from acetone, which appeared to contain acetone of crystallization. The latter was easily removed by reducing the pressure in a drying apparatus.

Method IB.—Equivalent amounts of cupric sulfate and the sodium or potassium salt of the acid in aqueous solution, at room temperature, were combined with vigorous agitation. The blue-green precipitate was washed with water until the filtrate no longer gave a test for sulfate. The normal salt was extracted from the dry solid with boiling acetone in a manner similar to that described above.

Preparation of Basic Cupric Salts of Aromatic Acids. Method IIA.—A dry, boiling acetone solution of the normal salt was treated with water until a substantial amount of light blue, basic salt precipitated. The displaced free acid could be recovered from the acetone filtrate by dilution with water. All of the basic salts were light blue, finely divided powders.

Method IIB.—An aqueous solution of 1 mole of cupric sulfate was added to an agitated solution of 2 moles of sodium hydroxide and 1 mole of the organic acid at room temperature. After 30 min., the solid was washed with water until the filtrate was free of sulfate.

The dry solid had a copper content required by the theory for the basic salt and was identical to that made by method IIA in both physical and chemical properties.

Runs in Nitrobenzene.—A suspension of the basic salt in nitrobenzene was heated with vigorous agitation, cooled, diluted with ether, and filtered. The solid was treated with ammonia and after digestion, acidified with hydrochloric acid, extracted with ether, and combined with the original filtrate. The combined filtrates were extracted with dilute hydrochloric acid to remove copper and then with saturated aqueous bicarbonate to remove the free carboxylic acids. The latter were isolated by extraction with methylene chloride after acidification.

The solvent was removed by distillation and a sample of the pale tan solid titrated to determine the total equivalents of acid present. A second sample was treated with bromate–bromide solution, acidified, and back-titrated with thiosulfate to determine the amount of salicylic acid present. Salicylic acid was converted to tribromophenol and carbon

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dioxide.[6] The amount of unchanged benzoic acid was calculated by difference.

Runs Made in Diphenylmethane or without Solvent.—A cylindrical glass reaction chamber with an operating volume of 125 ml. was sealed to the top of a 3-l. flask, by a flat ground glass joint. The flask contained a thermometer well and outlet which led to a condenser. The temperature of the reaction cell was determined by a refluxing liquid with the desired boiling point. High surface temperatures produced by heating directly with a mantle were avoided by this technique. The reaction chamber contained a thermowell and gas inlet tube which extended to the bottom, and a gas exit tube at the top.

The reaction chamber, with the nitrogen bubbler attached was inserted in the vigorously refluxing bath liquid; nitrobenzene (212°), isopropyl benzoate (220°). When a dry solid was used, the portion near the walls of the vessel came up to temperature very rapidly. Approximately 15–20 min. were required for the temperature to reach the desired level in the interior part of the sample. No attempt was made to mix the solid physically.

The products of reaction were cooled, dry ether was added, and the suspension treated with an excess of dry hydrogen chloride. The copper was converted to the insoluble chloride (CuCl) and was removed. Some oxidation of the copper salt took place on contact with air. The ether solution was extracted with dilute acid to remove this soluble copper. The organic carboxylic acids were then extracted with aqueous, saturated sodium bicarbonate solution. In some cases, this solution was treated with charcoal to remove a light amber color. This treatment lowered the yield considerably. Acidification of the bicarbonate solution released the organic acids and they were extracted with methylene chloride. Evaporation of the latter gave the crude acid product, which was analyzed by the titration method described above or subjected to the countercurrent separation procedure.

Countercurrent Extraction Method for Separating Salicylic and Benzoic Acids.—A 0.1 *M* aqueous ferric chloride solution saturated with methylene chloride and a similar amount of methylene chloride saturated with this solution were prepared. About 4–5 g. of the crude benzoic–salicylic acid mixture was dissolved in 200 ml. of the methylene chloride solution and placed in the first 500-ml. separation funnel. After shaking vigorously with 200 ml. of the ferric chloride solution, the phases were allowed to separate and the methylene chloride phase transferred to the second funnel. Methylene chloride was added to the first funnel and ferric chloride to the second funnel and the process repeated until twelve transfers were made. The salicylic acid formed a brilliant dark purple complex in the aqueous phase and its presence could be readily determined by the intensity of color.

The aqueous ferric chloride phases for the first seven to eight funnels were combined, made alkaline, and heated to 45°. The precipitate was removed by filtration and washed with a small amount of base. The filtrate was acidified and extracted with methylene chloride, and the latter dried with magnesium sulfate. Evaporation of the solvent produced from 0.2 to 1 g. of salicylic acid. The latter was further purified by recrystallization from water.

The methylene chloride phases from funnels 9–12 were combined, dried with magnesium sulfate, and heated to remove the solvent. The residue remaining was the recovered, unreacted starting acid.

Identification of Products. Basic Cupric-*o*-toluate.—After the countercurrent separation, the crude salicyclic acid product was recrystallized from water, using activated charcoal, produced brilliant white micro needles, m.p. 170–172°, identified as 6-methylsalicylic acid (lit.,[7] m.p., 168°). The infrared spectrum was identical with an authentic sample.

Basic Cupric-*m*-toluate.—The salicylic acid products isolated by the countercurrent extraction method were pale amber, micro crystalline needles, m.p. 133–142° (crude product). The infrared spectrum was virtually identical with that of an authentic sample of 5-methylsalicylic acid (lit.,[8] m.p., 151–153°). 3-Methylsalicylic acid (lit.,[9] m.p., 163–164°) has a very strong infrared absorption peak at 13.45 μ. The product isolated had a very slight shoulder at this point, indicating that a small amount of this isomer could be present.

Basic Cupric-*p*-toluate.—The crude salicylic acid product obtained from the pyrolysis of the basic salt of *p*-toluic acid was a pale amber solid m.p. 172–174°. Vacuum sublimation improved the color but not the melting point. Recrystallization from water treated with activated charcoal gave brilliant white micro needles, m.p. 175–178° (lit.,[10] m.p. 176°). The infrared spectrum was identical with an authentic sample of 4-methylsalicylic acid.

Acknowledgment.—We are indebted to Mrs. Veda Brink for assistance with the experimental work.

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