639. *Mechanism of the Kolbe–Schmitt Reaction. Part II.*[1] *Influence of the Alkali Metal.*

By S. E. Hunt, J. Idris Jones, A. S. Lindsey, and (in part) D. C. Killoh and H. S. Turner.

A study has been made of the behaviour on heating of the alkali-metal mono- and di-salicylates and *p*-hydroxybenzoates, and of some related substances. Some rate studies are reported for these reactions.

When a mixture of ^{14}C-labelled potassium carbonate and dipotassium salicylate was heated at 200° appreciable exchange accompanied the rearrangement with formation of labelled *p*-hydroxybenzoate. The mechanism of these reactions is discussed

Differences in behaviour of the alkali metals in organic reactions have often been noted.[2,3,4] The Kolbe–Schmitt reaction provides a classical example.[1,2,5,6]

In 1875 Kolbe [7] and Ost [8] drew attention to the remarkable difference in behaviour between sodium and potassium salicylate at 220°. The former yielded disodium salicylate, the latter dipotassium *p*-hydroxybenzoate. There occur in the literature many conflicting reports concerning the thermal rearrangement of the alkali-metal salts of aromatic hydroxy-carboxylic acids. In large measure, these are due to the use of carbon dioxide as a supposedly inert atmosphere in the early studies of these rearrangements,[9,10] for under these conditions it is possible for carboxylation to intervene.

More recent studies have revealed differences not only in the ratio of *ortho*- to *para*-substitution, but also in the extent of carboxylation and in the tendency to form hydroxy-dicarboxylic acids, particularly at higher temperatures.[6,11] In the Marasse procedure also differences have been observed [11,12,13] and these distinctions hold in the phenol, naphthol, and heterocyclic series.[6]

In order to establish how far purely thermal rearrangements are involved in the Kolbe–Schmitt reaction, a study of the behaviour on heating of various alkali-metal derivatives of salicylic acid and other aromatic hydroxy-carboxylic acids was undertaken.

Most of our experiments were conducted *in vacuo*; this served to minimise oxidation, and in those cases where carbon dioxide was evolved eliminated the possibility of re-carboxylation. From our studies on the monoalkali-metal salts the following facts have emerged. Monosodium salicylate at 300° yields equimolecular amounts of phenol, carbon dioxide, and disodium salicylate. A mixture of sodium phenoxide and monosodium salicylate at 140° gives equimolecular amounts of free phenol and disodium salicylate.

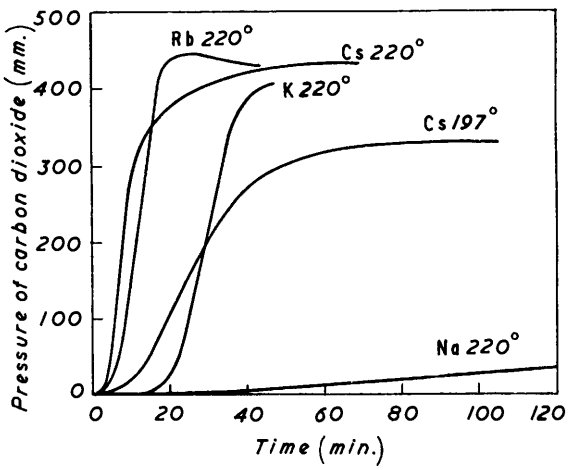
[1] Part I, *J.*, 1954, 3145.
[2] Brady and Jakobovits, *J.*, 1950, 767.
[3] Morton and Letsinger, *J. Amer. Chem. Soc.*, 1945, **67**, 1537.
[4] Brändström, *Arkiv Kemi*, 1953, **6**, 155; 1954, **7**, 81; *Acta Chem. Scand.*, 1953, **7**, 223.
[5] Widequist, *Arkiv Kemi*, 1954, **7**, 229.
[6] Lindsey and Jeskey, *Chem. Rev.*, 1957, **57**, 583.
[7] Kolbe, *J. prakt. Chem.*, 1875, **11**, 24.
[8] Ost, *ibid.*, 1875, **11**, 385.
[9] Kupferberg, *ibid.*, 1876, **13**, 103.
[10] den Velden, *ibid.*, 1877, **15**, 151.
[11] Baine, Adamson, Barton, Fitch, Swayampati, and Jeskey, *J. Org. Chem.*, 1954, **19**, 510.
[12] Cameron, Jeskey, and Baine, *ibid.*, 1950, **15**, 233.
[13] Wessely, Benedikt, Benger, Friedrich, and Prillinger, *Monatsh.*, 1950, **81**, 1071.

Monosodium *p*-hydroxybenzoate at 250° gives substantially disodium *p*-hydroxybenzoate, together with phenol and carbon dioxide.

In contrast monopotassium salicylate at 250° yields phenol, carbon dioxide, and *p*-hydroxybenzoic acid with small amounts of 4-hydroxy*iso*phthalic and 6-hydroxytrimesic acid and unchanged salicylic acid. The same products are obtained by heating equimolecular mixtures of mono-sodium and -potassium salicylate. However monopotassium *p*-hydroxybenzoate at 340° gives dipotassium *p*-hydroxybenzoate, phenol, and carbon dioxide.

The thermal decomposition of mono-lithium, -sodium, -potassium, -rubidium, and -cæsium salicylate at fixed temperatures was also examined in a closed, partly evacuated system, the extent of decomposition being measured by the carbon dioxide pressure. The results are presented graphically in Figs. 1 and 2. The threshold temperature for the decomposition decreases and the rate of decomposition at any one temperature increases

FIG. 1.

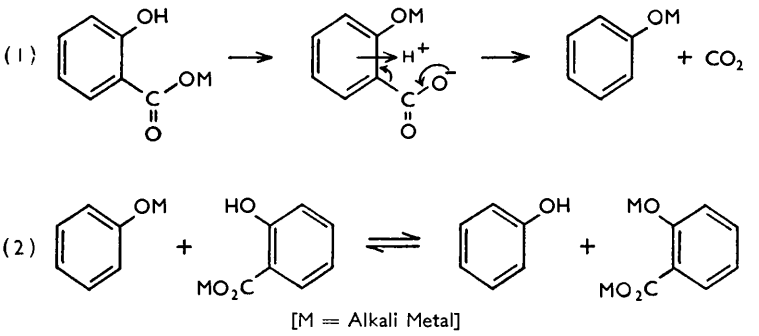


through the series Li, Na, K, Rb, Cs. The slight decrease in pressure towards the end of some experiments suggests that some recarboxylation occurs at this stage. From the lithium and sodium salts only salicylic acid was detected in the products; in the cases of potassium, rubidium, and cæsium, the product was substantially *p*-hydroxybenzoic acid.

The thermal decomposition of the monoalkali-metal salicylates, as well as of monosodium and -potassium *p*-hydroxybenzoate, probably proceeds by heterolysis of the anionic form after migration of the metal cation.[14] Some support for this view is given by the observation that heating monosodium salicylate in phenol leads to almost complete decarboxylation. The second stage involves reaction of the metal phenoxide with a second molecule of the metal salicylate to yield phenol and the dimetal salicylate, which itself may undergo rearrangement when the metal is potassium, rubidium, or cæsium. In the case of sodium this second step occurs at temperatures as low as 140° and presumably occurs to a slight extent during the industrial synthesis of salicylic acid from sodium phenoxide and carbon dioxide. The possibility of intermolecular transfer of the CO_2Na unit in the second stage may be excluded since, for example, when a mixture of monosodium salicylate and sodium *p*-tolyloxide is heated only free *p*-cresol is obtained. In reactions with monopotassium salicylate intermolecular transfer has frequently been observed. Thus, Isemer [15] has shown that 2-hydroxy-3-phenylbenzoic acid accompanies *p*-hydroxybenzoic acid when monopotassium salicylate is heated with the potassium derivative of 2-hydroxydiphenyl. Similarly, we have found that, in addition to *p*-hydroxybenzoic acid and small amounts of salicylic acid, 6-hydroxytrimesic acid is obtained when

[14] Brown, *Quart. Rev.*, 1951, **5**, 131.
[15] Isemer, Doctoral Thesis, Halle, 1951.

tripotassium 4-hydroxy*iso*phthalate is heated with monopotassium salicylate; 3-carbamoyl-4-hydroxybenzoic acid is obtained from salicylamide, and 3-phenyl hydrogen



[M = Alkali Metal]

4-hydroxy*iso*phthalate from salol. This transfer is almost certainly a part of the subsequent rearrangement of the dipotassium and higher alkali-metal salicylates, and it has not been observed in the absence of the salicylate–*p*-hydroxybenzoate conversion.

In the past the importance of the equilibrium reaction (2) above has not always been sufficiently appreciated. In the original Kolbe reaction this accounts for the conversion of only half the phenol into salicylate. Under Kolbe–Schmitt conditions the equilibrium determines the extent of conversion and accounts for the formation of certain by-products, since carboxylation of the dialkali-metal salicylate can give both 2- and 4-hydroxy*iso*phthalic acid which are found as by-products in the industrial carboxylation of sodium phenoxide.[16] The existence of this equilibrium has been clearly recognised in the synthesis of long-chain alkyl salicylates from the corresponding phenols.[17]

Addition of sodium hydride at the end of the first carboxylation stage of 2-naphthol has also been claimed to give increased yields of 2-hydroxy-3-naphthoic acid.[18]

Our studies on the dialkali-metal salts have given the following information. Contrary to the claims of Kupferburg,[9] disodium salicylate remains unchanged at 360°. Dipotassium salicylate, however, undergoes the well-known rearrangement to dipotassium *p*-hydroxybenzoate [19] at 200—240°. That the product is dipotassium *p*-hydroxybenzoate and not some complex which when dissolved in water and acidified gives *p*-hydroxybenzoic acid was established by the identity of its infrared spectrum with that of authentic dipotassium *p*-hydroxybenzoate. The reaction, however, is subject to a number of factors which have been disregarded previously. One is the influence of moisture. The dipotassium derivative when prepared from aqueous solutions contains water of crystallisation which is difficult to remove completely. In the present work very dry specimens of the dipotassium salt were prepared and all manipulations were carried out in a dry box. There was no detectable rearrangement when the dry salt was heated at 250°/0·1 mm. for 6 hr. but a trace of phenol was liberated. After exposure of the sample to the atmosphere for a short time rearrangement proceeded readily, as was also the case with less rigorously dried dipotassium salicylate. The main product of the rearrangement was *p*-hydroxybenzoic acid accompanied by small amounts of 4-hydroxy*iso*phthalic and 6-hydroxytrimesic acid. The results of a kinetic study of the rearrangement of dipotassium salicylate at 250° are shown graphically in Fig. 3. The sigmoid curve is typical of a solid-state autocatalytic reaction. Invariably traces of phenol sublimed from the system during the rearrangement and phenol may well serve as a catalytic factor.

A limited study has also been made of the effect of substituents in the benzene ring on

[16] Hunt, Jones, and Lindsey, *J.*, 1956, 3099.
[17] B.P. 738,359/1955.
[18] B.P. 736,476/1955.
[19] *Org. Synth.*, Coll. Vol. II, 1943, p. 341.

the rearrangement products. Heating disodium or dipotassium 4-hydroxy*iso*phthalate at 250° for 6 hr. led in the former case to decomposition with partial conversion into salicylic and 6-hydroxytrimesic acid, in the latter case to partial conversion into *p*-hydroxybenzoic and 6-hydroxytrimesic acid. Heating dipotassium 3-methyl-2-hydroxybenzoate (*o*-cresotinate) under the same conditions gave the potassium derivatives of 4-hydroxy-5-methyl-benzoic and -*iso*phthalic acid. The rearrangement was analogous therefore to that of dipotassium salicylate, the presence of the dicarboxylic acid suggesting an easier transfer of carboxylate group. Carboxylation of potassium *o*-tolyloxide with carbon dioxide under pressure [20] led to the formation of *o*-cresotinic and 4-hydroxy-5-methyl-*iso*phthalic acid in approximately equal quantities, together with a small amount of

FIG. 2.

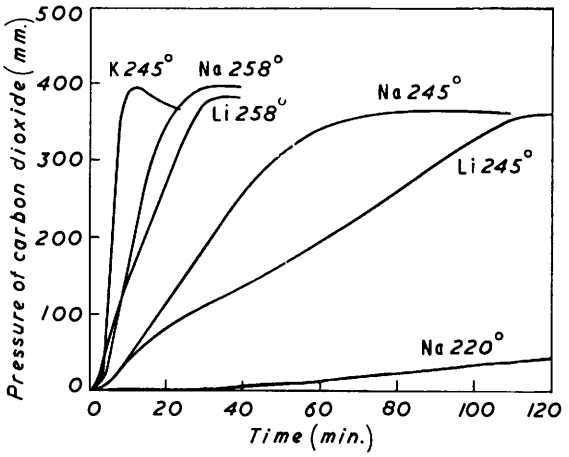
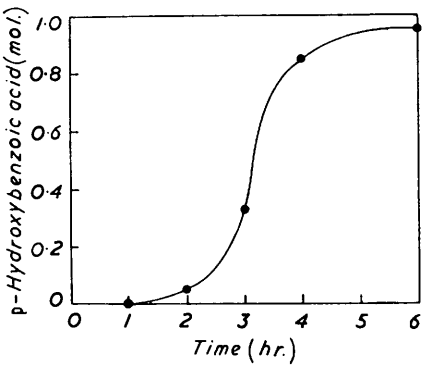


FIG. 3.



4-hydroxy-5-methylbenzoic acid. Heating 4-amino-2-hydroxypotassium benzoate at 160° led to decarboxylation with formation of free and bound *m*-aminophenol; no acidic product was obtained other than a little unchanged 4-aminosalicylic acid.

In order to study the mechanism, a tracer investigation of the rearrangement of dipotassium salicylate in admixture with potassium [^{14}C]carbonate was undertaken (by H. S. T. and D. C. K.). In a vacuum (0·1 mm.) pure dry dipotassium salicylate either alone or in admixture with approximately 5% of potassium carbonate was unchanged after 6 hr. at 250°, but at 200° in an atmosphere of dry nitrogen the rearrangement could be carried out reproducibly to 50% completion in about 30 min. Even in the presence of carbonate, rearrangement was always accompanied by a loss in weight of about 5%, most of which was due to free phenol distilling from the mixture. The product was worked up for *p*-hydroxybenzoic acid and carbon dioxide (from the carbonate). It was found that exchange had occurred to about 4·7% of the maximum (assuming the carboxylate group alone to be capable of exchange). In blank experiments (i) in which the original mixture was worked up without having been heated and (ii) in which the working up procedure was applied to a mixture of dipotassium *p*-hydroxybenzoate and [^{14}C]carbonate the extent of apparent exchange was negligible, less than 0·005% of the activity in the carbonate being found in either acid. Although an intimate mixture of the salicylate and carbonate was prepared by grinding, it is obvious that at the molecular level the mixture must have been extremely heterogeneous. An overall exchange of about 5% may therefore correspond to extensive, if not complete, exchange in the regions of intimate contact.

Ost [8] reported that conversion of dipotassium salicylate into *p*-hydroxybenzoate was

[20] Ihle, *J. prakt. Chem.*, 1876, **14**, 443.

inhibited at 250° by the addition of a further mol. of potassium hydroxide. We have detected no rearrangement after heating an equimolecular mixture of dipotassium salicylate and potassium methoxide at 250° for 6 hr. However, a similar mixture, after 6 hr. at 340°, contained *p*-hydroxybenzoic and 4-hydroxy*iso*phthalic acid, in addition to unchanged salicylic acid. It is significant that in the commercial preparation of *p*-hydroxybenzoic acid from dipotassium salicylate it is customary to use a small excess of potassium hydroxide. Further, we have observed that addition of 5% of potassium carbonate has no noticeable effect on the rate of rearrangement. This evidence suggests that the reaction is not proton-catalysed. The inhibition of the rearrangement as a result of adding 1 mol. of potassium methoxide or hydroxide may be due to the formation of an ortho-salt *o*-KO·C_6H_4·C(OK)$_2$·OMe or *o*-KO·C_6H_4·C(OK)$_2$·OH. It is pertinent that phenyl-lithium interacts with lithium benzoate to give $Ph_2C(OLi)_2$ [21] and Bender [22] has demonstrated the existence of addition compounds of carboxylic acid derivatives with sodium alkoxides.

Our investigations were not taken far enough to permit a completely unequivocal decision on the mechanism of the rearrangement of dipotassium salicylate. Nevertheless some reasonable suggestions may be advanced. We have demonstrated that the reaction is catalysed by traces of water and of phenol, that it is facilitated by electron-releasing substituents in the ring, that it is probably not proton-catalysed (in contrast to the marked effect observed in the analogous rearrangement of aminonaphthalenesulphonates [23]), and that the migrating fragment is capable of exchange with carbonate. Our experiments *in vacuo* strongly suggest that the rearrangement does not proceed by way of a decarboxylation–recarboxylation involving free carbon dioxide. Apart from the isolation of a little oxalic acid from one reaction product we have failed to isolate the by-products which would be expected in a free-radical reaction. We therefore suggest that the most likely mechanism is that the migrating group is $^+CO_2K$, which is only loosely held to the nucleus during the transition stage, perhaps by a π-bond. The reaction may be either intra- or inter-molecular, depending on the precise spatial relation of adjoining molecules. The group $^+CO_2K$ will, on this view, be capable of exchange with carbonate, though under the conditions of our tracer experiments extensive overall exchange would not be expected. It is highly probable that similar considerations apply to the rearrangements of alkali-metal salts of unsubstituted aromatic carboxylic acids recently reported by Raecke.[24] We have discussed the mechanism of this reaction and some views upon it in a recent memoir.[25]

Chelation has been postulated in the alkali-metal salicylates [26] and Widequist [5] has suggested that the difference in behaviour of the alkali-metal salicylates towards heat could be related to the chelating tendency of the cations. Martel and Calvin [27] have pointed out that the chelating strengths can be correlated with the e^2/r values of the ions. For the alkali-metal ions the values are Li^+ 1·7, Na^+ 1·05, K^+ 0·75, Rb^+ 0·68, Cs^+ 0·60. Lithium and sodium salicylate, which do not rearrange, are more strongly chelated than the potassium, rubidium, and cæsium salts. Some evidence for the participation of a chelation effect is given by the results obtained by heating (i) a mixture of monosodium salicylate and potassium phenoxide at 245° and (ii) a mixture of monosodium salicylate and potassium carbonate at 250°. In both cases an appreciable quantity of *p*-hydroxybenzoic acid was found in the product, indicative of the intermediate formation of *o*-KO·C_6H_4·CO_2Na with subsequent rearrangement. A mixture of dipotassium *p*-hydroxybenzoate and disodium salicylate, both of which are thermally stable alone at 340°, when

[21] Bluhm, Donn, and Zook, *J. Amer. Chem. Soc.*, 1955, **77**, 4406.
[22] Bender, *ibid.*, 1953, **75**, 5986.
[23] Shilov, Bogdanov, and Shilov, *Doklady Akad. Nauk S.S.S.R.*, 1953, **92**, 93.
[24] Raecke, *Angew. Chem.*, 1958, **70**, 1.
[25] Jones, Lindsey, and Turner, *Chem. and Ind.*, 1958, 659.
[26] Sidgwick, "The Electronic Theory of Valency," Oxford, 1927, p. 242.
[27] Martel and Calvin, "Chemistry of the Metal Chelate Compounds," Prentice-Hall, New York, 1952, p. 191.

heated at 320° for 6 hr. gave a product containing appreciable amounts of 4-hydroxy-*iso*phthalic and 6-hydroxytrimesic acid. Thermal migration of carboxylate groups must therefore arise consequent on interchange of cations.

In addition to the chelation effect it is possible that other effects, notably polarisation effects, are also operative. Clearly further studies are needed before the precise mechanism of these solid-state reactions can be elucidated.

Experimental

General.—Microanalyses were carried out by Miss M. Corner and her staff of this laboratory.

Ultraviolet absorption spectra were measured for ethanolic solutions with a Unicam S.P. 500 spectrophotometer, which had been calibrated against an alkaline solution of potassium chromate.[28]

Infrared measurements were made on a modified Hilger D 209 double-beam instrument.[29]

Hygroscopic materials were weighed and manipulated in a dry box.

Preparation of Materials.—Monolithium, monosodium, and monopotassium salicylate were of reagent grade (B.D.H.) quality. After drying at 130° *in vacuo* satisfactory alkali-metal analyses were obtained.

Disodium salicylate was prepared by heating the monosodium salt at 300° for 6 hr. *in vacuo*. The identity of the product was confirmed by infrared spectroscopy.

Most other salts were prepared by neutralisation of aqueous or aqueous-alcoholic solutions, followed by evaporation and drying at 140° *in vacuo*. Dipotassium salicylate and dipotassium *o*-cresotinate were particularly difficult to dry and so were prepared by reaction of anhydrous methanolic solutions of potassium methoxide and the dry acid. Good analyses were obtained in all cases.

Thermal Rearrangement Experiments.—The salts were heated in a Pyrex tube which was attached by a cone-and-socket joint to a tared U-tube. The latter was packed in powdered carbon dioxide. A vacuum was applied, *ca.* 0·1 mm. (oil-pump) or 16 mm. (water-pump). Experiments carried out at the latter pressure are marked W.P. in the Tables.

Procedure for Separation of Products.—The solid residue was dissolved in water and made up to a standard volume. " Bound phenol " (present as a metal phenoxide) was liberated from an aliquot portion by passage of carbon dioxide, and recovered by continuous ether-extraction.

Acidification of the aqueous phase followed by continuous ether-extraction and then by removal of the solvent and drying gave the total acids, which were then separated by silica-gel chromatography. The mixed acids (*ca.* 400 mg.) were washed on to the column and eluted with dry benzene. Fractions of 100 ml. each were collected, and the solid acids recovered by evaporation of the solvent. The column was successively washed with 5, 10, 12, 15, and 50% ether in benzene, then with 100% ether, and finally with anhydrous methanol.

The solid acids were identified by m. p. and coloration with ferric chloride solution. Efficient and quantitative separation of salicylic, *p*-hydroxybenzoic, 4-hydroxy*iso*phthalic, and 6-hydroxytrimesic acid was attained in this way.

Effect of Phenol on the Decomposition of Monosodium Salicylate.—Monosodium salicylate (8·8 g.) was boiled with excess of phenol (52·3 g.) for 5 hr., then cooled. Water was added and the free phenol removed by steam-distillation. " Bound " phenol (5·7 g.) and salicylic acid (0·15 g.) (confirmed by ferric chloride test and m. p.) were isolated as before. Thus 98% decarboxylation had occurred.

Carboxylation of Salicylamide using Monopotassium Salicylate.—An intimate mixture of salicylamide (0·1 mole) and monopotassium salicylate (0·1 mole) was heated slowly to 220° and kept there for 1¼ hr. Frothing occurred and phenol distilled, the pressure being reduced at the end to assist the removal of phenol. The residue was dissolved in water and ether-extracted. Acidification of the aqueous phase gave a coloured precipitate (13·2 g.) from which crude *3-carbamoyl-4-hydroxybenzoic acid* was isolated, m. p. 297° (decomp.) after recrystallisation from dioxan (Found: C, 53·3; H, 4·0; N, 7·4. $C_8H_7O_4N$ requires C, 53·0; H, 3·9; N, 7·7%).

Carboxylation of Phenyl Salicylate using Monopotassium Salicylate.—Phenyl salicylate.

[28] Haupt, *J. Res. Nat. Bur. Stand.*, 1952, **48**, 414.
[29] Hale, *J. Sci. Instr.*, 1949, **26**, 359; 1953, **30**, 52.

Results of thermal rearrangement experiments.

Expt.	Reactant(s) and mols. %	Experimental conditions	Products (mols. %) Phenol Free	Phenol Bound	CO_2	SA	pHBA	4HIPA	6HTA
1	A(100)	360°/24 hr.; W.P.†	6	—	—	83	—	—	—
2	B(100)	250° raised to 360° 7 hr.; W.P.	50	—	51	50	—	—	—
3	B(100)	300°/6 hr.†	49	—	53	49	—	—	—
4	C(100)	250°/6 hr.	Trace	2	—	—	99	—	—
5	D(100)	250°/6 hr.	10	26	38	—	61	—	—
6	B(50) + E(50)	140°/2 hr.; W.P.	53	—	—	47	—	—	—
7	B(50) + F(50)	140°/6 hr.; W.P.	44 *	3 *	—	48	—	—	—
8	G(100)	250°/1 hr.	<1	—	—	90	—	—	—
9	G(100)	250°/2 hr.	3	2	—	88	5	—	—
10	G(100)	250°/3 hr.	3	1	—	62	34	—	—
11	G(100)	250°/4 hr.	2	2	—	16	85	—	—
12	G(100)	250°/6 hr.	1	3	—	<2	96	—	—
13	G(100)	250°/7 hr.; W.P.	1	23	2	1	51	9	6
14	G(50) + H(50)	250°/6 hr.	—	—	—	47	—	—	—
15	G(50) + H(50)	340°/6 hr.	—	12	—	65	2	4	2
16	G(82) + J(18)	250°/3 hr.; W.P.	12	20	—	29	28	7	—
17	K(100)	250°/7 hr.; W.P.	50	—	32	4	29	10	3
18	K(100)	250°/5 hr.	52	Trace	49	—	48	3	—
19	K(50) + B(50)	250°/7 hr.; W.P.	55	—	50	22	17	6	—
20	K(50) + B(50)	320°/5 hr.; W.P.	51	9	51	6	7	19	3
21	K(50) + L(50)	250°/6 hr. W.P.	29	—	57	1	24	18	18
22	M(100)	340°/6 hr.	53	—	40	—	42	—	—
23	N(100)	250°/6 hr.	10	3	92	6	—	62	8
24	P(100)	250°/6 hr.	15	7	67	—	40	31	7
25	B(50) + R(50)	245°/4 hr.	40	32	55	15	13	—	—
26	B(100) + S(200)	230—250°/0·5 hr. 250—260°/2 hr.	34	4	—	18	41	—	—
27	T(50) + A(50)	320°/6 hr.	Trace	24	2	15	4	35	11

Code:

A Disodium salicylate.
B Monosodium salicylate.
C Disodium *p*-hydroxybenzoate.
D Monosodium *p*-hydroxybenzoate.
E Sodium phenoxide.
F Sodium *p*-tolyloxide.
G Dipotassium salicylate.
H Potassium methoxide.
J Phenol.
K Monopotassium salicylate.
L Tripotassium 4-hydroxy*iso*phthalate.
M Monopotassium *p*-hydroxybenzoate.
N Disodium 4-hydroxy*iso*phthalate.
P Dipotassium 4-hydroxy*iso*phthalate.
R Potassium phenoxide.
S Potassium carbonate.
T Dipotassium *p*-hydroxybenzoate.
SA Salicylic acid.
pHBA *p*-Hydroxybenzoic acid.
4HIPA 4-Hydroxy*iso*phthalic acid.
6HTA 6-Hydroxytrimesic acid.
W.P. Vacuum induced by water-pump.
* *p*-Cresol.
† Some charring occurred.

(42·8 g.) and monopotassium salicylate (70·8 g.) were heated, under slightly reduced pressure, at 240° for 4 hr. Phenol (27 g.) distilled and the residue yielded bound phenol, salol (31 g.), and 3-phenyl hydrogen 4-hydroxy*iso*phthalate (6 g.); after recrystallisation from methanol (charcoal) the acid had m. p. 235° (Found: C, 65·1; H, 4·1. Calc. for $C_{14}H_{10}O_5$: C, 65·1; H, 3·9%).

Rate of Thermal Decomposition of the Monoalkali-metal Salicylates.—The apparatus employed is shown diagrammatically (Fig. 4). The salt (approx. 2 millimoles) was introduced into *A* and spread along the bulb, and the trap *B* cooled to 0° in ice. The system was evacuated to about 20 mm., then tap *C* was turned so as to isolate the system. The bulb *A* was heated to the required temperature in a vapour bath. The liquids used and the temperatures obtained were as follows: diethylene glycol monoethyl ether monoacetate 197°, dipropylene glycol 220°, butyl benzoate 245°, 1 : 6-dimethylnaphthalene 258°. While the reaction was in progress readings were taken of pressure against time. The rates of decomposition, as measured by the rate of evolution of carbon dioxide, of all the alkali-metal salicylates is graphically shown in Figs. 1—3.

The solid residues were worked up. From lithium and sodium salicylate the product was salicylic acid; in the case of potassium, rubidium and cæsium salicylates the ferric chloride test was negative, showing that no unchanged salicylic acid was present, and that no 4-hydroxy*iso*phthalic acid had been formed. The m. p. and mixed m. p. confirmed the presence of *p*-hydroxybenzoic acid.

Infrared Spectroscopic Examination of the Solid Products obtained by heating Dipotassium Salicylate.—The infrared spectra of the products from experiments 12 and 18 (Table), and from similar experiments not recorded, were taken from KCl discs. The spectra were compared directly with those of authentic samples of dipotassium salicylate, *p*-hydroxybenzoate, and 4-hydroxy*iso*phthalate, and in each case were closely similar to that of dipotassium *p*-hydroxybenzoate.

Action of Heat on Dipotassium o-*Cresotinate.*—Dipotassium *o*-cresotinate (10 g.) was heated under reduced pressure for 6 hr. at 250°. No loss of weight occurred. The mixed acid obtained from the product was extracted with cold chloroform to remove unchanged *o*-cresotinic acid (confirmed by m. p. and ferric chloride test). Sublimation of the residue under reduced pressure gave a sublimate shown to be 4-hydroxy-3-methylbenzoic acid, m. p. 174—175° (no colour with

FIG. 4.

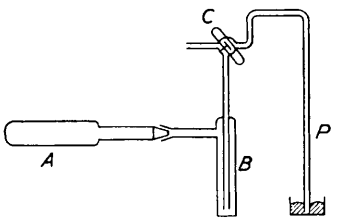
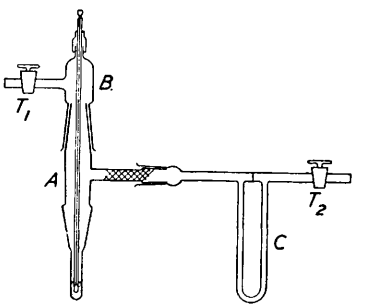


FIG. 5.



alcoholic ferric chloride), by comparison with an authentic specimen (Found: C, 63·0; H, 5·7. Calc. for $C_8H_8O_3$: C, 63·2; H, 5·3%).

Recrystallisation of the non-sublimable residue from ethanol–water gave 4-hydroxy-5-methyl*iso*phthalic acid, m. p. 294—295°, no colour with alcoholic ferric chloride, red colour with aqueous ferric chloride (Found: C, 55·1; H, 4·2. Calc. for $C_9H_8O_5$: C, 55·1; H, 4·1%).

Action of Heat on Potassium 4-Amino-2-hydroxybenzoate.—The salt (10·5 g.) was heated for 6 hr. at 160° *in vacuo* (water-pump). Some *m*-aminophenol (0·4 g.) (m. p. and mixed m. p. 123°) distilled into the trap, and the residue (8·98 g.) in water (100 ml.) was continuously extracted with ethyl acetate to give more *m*-aminophenol (4·5 g.) (m. p. and mixed m. p.). The aqueous phase contained *m*-aminophenol (" bound phenol ") (0·3 g.). After adjustment to pH 4 the aqueous phase was continuously extracted with ethyl acetate, to yield a brown solid [1·55 g.; m. p. 112° (decomp.)] which gave a hydrochloride recrystallising from aqueous ethanol [m. p. 233° (decomp.)]. There was no depression of m. p. on admixture with the hydrochloride of *p*-aminosalicylic acid. The infrared spectrum confirmed the identity.

Isotope Experiments on the Rearrangement of Dipotassium Salicylate.—Preparation of materials. Potassium [^{14}C]carbonate was prepared by absorbing [^{14}C]carbon dioxide in a slight deficiency of 0·1N-potassium hydroxide and adjusted to a suitable specific activity by addition of more potassium carbonate. The solution was evaporated to dryness, ground to a fine powder, and dried at 140° *in vacuo*.

Dipotassium salicylate, prepared as above, was dried at 120°/0·1 mm. for several hours.

Thermal rearrangement. The reaction vessel *A* (see Fig. 5) could be closed for weighing by means of two tapered Polythene plugs. A plug of glass wool in the side-arm prevented the carrying over of particles into the trap *C*. The head *B*, which bore a side-arm through which dry nitrogen could be introduced, also carried an Anschütz thermometer the bulb of which, symmetrically disposed out of contact with the walls of the bottom of *A*, was just covered by the normal charge.

In preparing the charge every effort was made to exclude moisture. The apparatus was rigorously dried and all manipulations were carried out in a dry box over phosphoric anhydride. The dipotassium salicylate (300—400 mg.) and potassium [^{14}C]carbonate (15—20 mg.) were weighed separately in weighing tubes and intimately mixed by grinding for 20 min. in an agate mortar. The mixture was transferred to the bottom of *A* by means of a small funnel with a long stem, and the weight introduced obtained by difference. The head *B* was then attached and the combined unit removed from the dry box and weighed. A current of dry nitrogen was

passed in through T_1 and out through the side-arm of A, which was then connected to the trap C. The air within the powder was replaced by nitrogen by several times evacuating the apparatus and re-admitting nitrogen. The trap C was then cooled to $-80°$ and the lower half of A was lowered into a vapour-bath. After a suitable time at the desired temperature the bath was removed and the mixture cooled rapidly to room temperature. Whenever rearrangement occurred a small sublimate of phenol collected in the side-arm of A. This was caused to pass into C by gentle warming. C was then detached, the side-arm of A closed by a plug, T_1 closed, and the whole re-weighed.

The product, which was usually pink, was washed into a flask with carbon dioxide-free water (total 15 ml.) and diluted with 0·382N-potassium carbonate (10·00 ml.). The flask was attached to an apparatus in which carbon dioxide-free dilute sulphuric acid was added while the carbon dioxide liberated was swept from the cold, stirred solution in a current of nitrogen into a series of traps containing aqueous barium hydroxide at ~95°. The barium carbonate was collected and dried out of contact with atmospheric carbon dioxide. The acid liquors were again made alkaline by addition of a slight excess of potassium hydroxide solution, and a stream of carbon dioxide was passed in order to liberate phenol. After extraction with ether (2 × 15 ml.) the aqueous phase was again acidified with sulphuric acid, and the hydroxy-acid extracted by ether (4 × 15 ml.). The combined extracts were dried by refluxing over anhydrous calcium sulphate in a Soxhlet apparatus, and afterwards evaporated to dryness.

The acids were separated on a " sulphuric acid " column,[30] the progress of the separation being followed by ultraviolet spectroscopy. Salicylic and *p*-hydroxybenzoic acid were cleanly separated. 6-Hydroxytrimesic acid travelled with salicylic acid, and 4-hydroxy*iso*phthalic acid with *p*-hydroxybenzoic acid.

In preliminary experiments it was found that no rearrangement took place *in vacuo* (~0·1 mm.) even at ~250° during 6 hr., but under nitrogen at atmospheric pressure the reaction was about half complete in 30 min. at the temperature of boiling benzyl alcohol. The results were somewhat variable even when the greatest care was taken to exclude moisture.

In a blank run, designed to test the possibility of exchange during working-up, dipotassium salicylate (0·2976 g.) and potassium [^{14}C]carbonate (0·0153 g.) were mixed and the normal procedure followed, with the sole difference that the mixture was not heated. The product from the chromatographic separation was purified by sublimation, giving salicylic acid, m. p. 158—158·5° (0·179 g.; specific activity $3·4 \times 10^{-11}$ curies per millimole). The carbon dioxide had a specific activity of $4·9 \times 10^{-6}$ curies per millimole corresponding to $8·9 \times 10^{-5}$ curies per millimole for the carbonate *before* dilution. Thus the transfer of carbon from carbonate to salicylate during working up was $4·8 \times 10^{-4}$%.

A further rough control was carried out to test the exchange of *p*-hydroxybenzoic acid and potassium carbonate during the solution stages of working up. Here the transfer from carbonate to *p*-hydroxybenzoate was $\sim 2·5 \times 10^{-4}$%.

In the tracer run a mixture of dipotassium salicylate (0·3956 g.) and potassium [^{14}C]carbonate (0·0196 g.) was heated for 30 min. at 202·5°. The loss in weight during the rearrangement was 0·0278 g. The *p*-hydroxybenzoic acid fraction (0·1464 g.) was further purified by sublimation to give the acid (specific activity $3·00 \times 10^{-7}$ curies per millimole), m. p. 214—215° (pure *p*-hydroxybenzoic acid melted at 214·5—215·5° under the same conditions). The carbon dioxide collected had a specific activity of $5·45 \times 10^{-6}$, corresponding to $7·86 \times 10^{-5}$ for the carbonate in the reaction product *before* dilution. If exchange between the carbonate and the carboxyl group of the original salicylate had been complete the specific activity would have been $6·35 \times 10^{-6}$ curies per milliatom of exchangeable carbon, or per millimole of recovered hydroxybenzoic acid. The specific activity observed is therefore equivalent to 4·7% attainment of complete exchange.

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[30] Martin and Webb, cited by Cornforth, Hunter, and Popjak, *Biochem. J.*, 1953, **54**, 597.