Oxidation of Aromatic Acids. IV. Decarboxylation of Salicylic Acids

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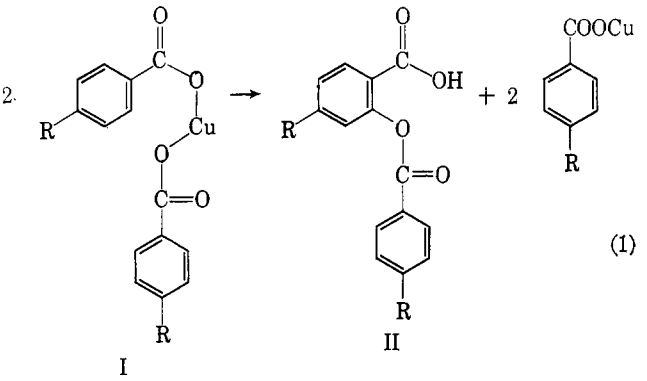
Pseudo-first-order rate constants for the decarboxylation of salicylic acid and a number of derivatives, in benzoic acid solutions, were measured. *ortho* and *para* substituents which tended to enrich the electron density of the aromatic ring produced an increase in rate. The converse was observed with electron-withdrawing groups. The decarboxylation rate also increased when soluble metal salts of benzoic acid were added. A difference in the ability of various metals to promote decarboxylation was observed. The mechanism is discussed in terms of an attack by a proton on the ring carbon atom which is bonded to the carboxylate group.

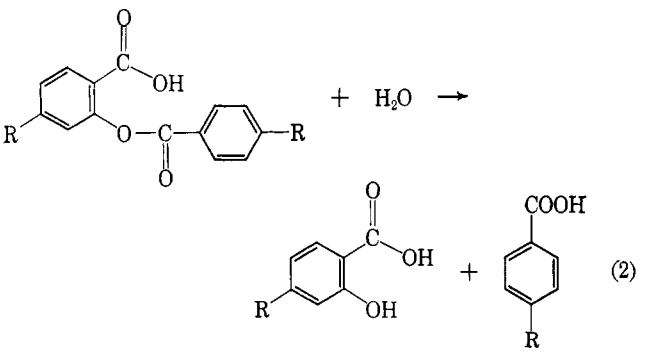
Previous papers of this series[1] have described the over-all procedure for the conversion of aromatic carboxylic acids to their corresponding phenols and carbon dioxide. The proposed initial step, eq. 1, involves the



(1)

I II

thermal rearrangement of the cupric salt of the acid (I). In a homogeneous solution of benzoic acid, the intermediate benzoyl salicylic acid (II) decarboxylated readily to give the corresponding phenyl benzoate derivative as the major product of reaction. Water is usually present in the system, however, and may hydrolyze any ester produced. Under these conditions, the intermediate may be converted to the corresponding salicylic acid derivative, shown in eq. 2 following.



(2)

Therefore, the desired phenol may be produced from II by decarboxylation followed by hydrolysis of phenyl benzoate, or by hydrolysis followed by decarboxylation of salicylic acid, or by a combination of both processes. The kinetics of the decarboxylation of salicylic acid in benzoic acid solution will be reported as the first step in the elucidation of this portion of the reaction mechanism.

(1) (a) Paper I: W. W. Kaeding, *J. Org. Chem.*, **26**, 3144 (1961); (b) paper II: W. W. Kaeding and A. T. Shulgin, *ibid.*, **27**, 3551 (1962); (c) paper III; W. W. Kaeding, *ibid.*, **28**, 1063 (1963).

Results

Salicylic acid decarboxylated to give phenol and carbon dioxide, at a convenient rate for kinetic measurements, at 200–230°, in a homogeneous solution of benzoic acid and certain other high-boiling solvents. Concentrations of salicylic acid at various time intervals

TABLE I

UNCATALYZED DECARBOXYLATION RATES OF SALICYLIC ACID

Run no.	Temp., °C.	Initial concn., moles/kg.	% reacted	k, min.$^{-1}$ × 10^5	Solvent
1	212.0	0.3620	25	181	BzOH[a]
2	212.0	0.7130	25	179	BzOH[a]
3	212.0	1.4456	27	179	BzOH[a]
46	211.8	0.7240	39	182	BzOH[a]
56	211.8	0.7240	41	184	BzOH[b]
47	211.6	0.7240	42	167	BzOH[b]
49	211.8	1.0860	42	183	BzOH[b]
53	211.8	0.7240	34	174	BzOH[b]
54	212.2	0.7240	29	182	BzOH[c]
60	211.8	0.7240	44	180	BzOH
48	211.8	0.7240	43	171	BzOH–BzOPh, 90:10[d]
50	211.8	0.7240	42	150	BzOH–BzOPh, 75:25[d]
51	211.8	1.4480	10	26	BzOPh
65	211.4	0.7240	33	109	BzOH–Bz_2O, 90:10[d]
55	212.0	0.7240	48	196	BzOH–PhOH, 90:10[d]
56	211.6	0.7240	49	218	BzOH–resorcinol, 90:10[d]
58	212.0	0.7240	50	492[e]	Resorcinol
59	211.8	1.4480	55	461[e]	Resorcinol
40	220	0.7240	29	286	BzOH[b]
43	232	0.7240	49	562	BzOH[b]
67	231.2	0.362	85	594	BzOH
66	231.2	0.7240	88	588	BzOH
68	231.2	1.4480	84	566	BzOH
86[f]	231.0	0.7000	37	119	BzOH
85[g]	231.1	0.6519	66	286	BzOH
84[h]	231.2	0.6940	..	I.s.[i]	BzOH
83[j]	231.2	0.7000	..	I.s.	BzOH
82[k]	212.0	0.7000	93	112	BzOH
80[l]	182.3	0.7000	..	I.s.	BzOH
79[m]	182.1	0.7000	58	185	BzOH
57[n]	211.7	0.7240	..	I.s.	BzOH

[a] Technical grade benzoic acid (Bz = $C_6H_5C{=}O$). [b] Reagent grade benzoic acid. [c] Primary standard grade benzoic acid was used unless otherwise designated. [d] Weight per cent. [e] Initial rate, serious departure from linearity. [f] 5-Nitrosalicylic acid. [g] 5-Bromosalicylic acid. [h] 3,5-Dinitrosalicylic acid. [i] Immeasurably slow. [j] *m*-Hydroxybenzoic acid. [k] 2,4-Dimethoxybenzoic acid. [l] 5-Hydroxysalicylic acid. [m] 4-Hydroxysalicylic acid. [n] 4-Hydroxybenzoic acid.

were calculated from the weight of carbon dioxide evolved. Rate constants, first order with respect to salicylic acid, are listed in Table I.

The reaction did not appear to be sensitive to minor amounts of organic impurities. No significant changes in rate were observed when either highly purified or technical grade benzoic acid solvent was used.

An analysis of the products of the reaction indicated that approximately equal amounts of phenol and of phenyl benzoate were present. Presumably, the latter was formed by a reaction between phenol initially produced and solvent benzoic acid. These two compounds accounted for over 98% of the salicylic acid consumed.

When the solvent benzoic acid was diluted with certain aprotic solvents, a reduction in the pseudo-first-order rate constant was always observed. The results are summarized in Table I.

A variety of benzoate salts, referred to as "catalysts," were added to the solvent to determine the effect on the rate of decarboxylation. An increase was always observed. The magnitude varied considerably with the metal and was directly proportional to the catalyst concentration. The results are summarized in Table II.

To ensure that carbon dioxide did not appear by decarboxylation of the solvent, the solution of catalyst and benzoic acid was heated at the reaction temperature for a period of 30–60 min. prior to the addition of the salicylic acid. Remarkable stability was observed with the notable exception of mercuric benzoate where decarboxylation to produce benzene occurred at a significant rate.

Usually the most stable oxidation state of the metal ion was utilized, both for convenience in preparation and to avoid oxidation–reduction side reactions and changes in the catalyst during the run. Kinetic runs proved to be a sensitive means for detecting changes in the oxidation states of the metal-ion catalysts under the conditions of reaction. Copper(II), mercury(II), iron(III), and silver(I) benzoates had a pronounced tendency to revert to lower oxidation states. This was first indicated by a departure from a linear rate plot and later by the obvious appearance of the free metal or a reduced form of the ion.

TABLE II

CATALYZED DECARBOXYLATION OF SALICYLIC ACID[a]

Run no.	—Metal benzoate[b]— Metal	Concn.	% reacted	k, min.$^{-1}$ × 10^4	$\frac{k}{0.00180}$
25	Ni(II)	0.120	98	461	25.6
26	Zr(IV)	0.120	95	380	21.1
19	Co(II)	0.120	98	377	20.9
4	Mg(II)	0.120	96	320	17.8
22	Ce(III)	0.120	97	307	17.1
24	Mn(II)	0.120	96	290	16.1
33	K(I)	0.120	96	290	16.1
37	Cs(I)	0.120	96	289	16.1
34	Sr(II)	0.120	93	235	13.1
39	Hg(II)	0.120	[c]	221[d]	12.3
35	Ba(II)	0.120	90	203	11.3
18	Na(I)	0.120	89	193	10.7
16	Fe(III)	0.120	92	169[d]	9.4
27	U(VI)	0.120	80	164	9.1
15	Zn(II)	0.120	86	147	8.2
30	Li(I)	0.120	96	141	7.9
23	In(III)	0.120	79	135	7.5
28	Cd(II)	0.120	75	121	6.7
36	Ca(II)	0.120	73	113	6.3
38	Pb(II)	0.120	63	83	4.6
12	Cu(II)	0.120	62	82[e]	4.6
72	Be(I)	0.120	83	68	3.8
20	Cr(III)	0.12	45	49	2.7
21	Th(IV)	<0.12[f]	39	43	2.4
11	Cu(I)	0.119	32	33	1.8
32	Al(III)	<0.12[f]	15	26	1.4
2[g]		0.7130	25	18	1.0
6	Mg(II)	0.0300	89	111	6.2
5	Mg(II)	0.0622	94	195	10.8
61	Mg(II)	0.0824	99	274	15.2
7	Mg(II)	0.0902	97	274	15.2
62	Mg(II)	0.1142	98	371	20.6
4	Mg(II)	0.1200	96	320	17.8
63	Mg(II)[h]	0.1711	99	472	26.2
64	Mg(II)[i]	0.2281	99	564	31.3
70	Mg(II)[j]	0.2287	98	169	9.4

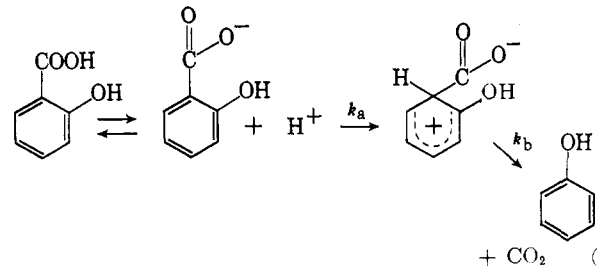
[a] 212.0°; benzoic acid solvent; initial concentration of salicylic acid was 0.7240 mole/kg. of benzoic acid. [b] Concentration expressed as moles of metal per kilogram of benzoic acid solvents. [c] >100% due to catalyzed decarboxylation of BzOH. [d] Considerable departure from linear rate plot. [e] Some departure from linear plot. [f] Saturated solution. [g] Uncatalyzed. [h] 211.6°. [i] 211.7°. [j] 193.5°.

Discussion

Approximately 15 years ago, there was a considerable amount of interest in the possibility of a bimolecular decarboxylation mechanism involving an attack by a proton on the free acid or its anion.[2] A variety of compounds such as anthracene-9-carboxylic acid,[3] substituted cinnamic acids,[4] mesitoic acid,[5] *p*-aminosalicylic acid,[6] and salicylic acid[7] appeared to represent examples of this type of decarboxylation mechanism. In most cases, pseudo-first-order rate constants were observed experimentally.

Willi and co-workers[6,7] have made a detailed study of the mechanism of decarboxylation of *p*-aminosalicylic acid in aqueous solution. Their system was extremely complicated because of the need to add many reagents to control pH and the ionic strength and especially by the amphoteric property of the substrate itself. After a detailed analysis of these factors, evidence was presented for a mechanism which involved a rate-determining attack by a proton on *p*-aminosalicylate ion.

This mechanism is also proposed for the decarboxylation of salicylic acid in benzoic acid solution. A competition between an oxygen atom and the terminal ring carbon atom for the proton to give either the undissociated acid or a σ-complex leading to products is shown by eq. 3.



(3)

(2) B. R. Brown, *Quart. Rev.*, **5**, 131 (1951).
(3) H. Schenkel *Helv. Chim. Acta*, **29**, 436 (1946).
(4) W. S. Johnson and W. E. Heinz, *J. Am. Chem. Soc.*, **71**, 2913 (1949).
(5) W. M Schubert, *ibid.*, **71**, 2639 (1949).
(6) (a) A. V. Willi and J. F. Stocker, *Helv. Chim. Acta*, **37**, 1113 (1954); (b) A. V. Willi, *ibid.*, **40**, 1053 (1957).
(7) A. V. Willi, *Trans Faraday Soc.*, **55**, 433 (1959).

The effect of substituents on the rate of decarboxylation of salicylic acid has been used to support a bimolecular mechanism. Electron-donating groups in the *ortho* or *para* positions have led to an increase in rate.[7,8] The increased electron density on the ring carbon atom bonded to the carboxyl group would presumably facilitate an attack by a proton at this position. Brown, Hammick, and Scholefield[8] have reported that the addition of hydroxyl groups in the 4- and in the 4- and 6-positions of salicylic acid has decreased energy of activation from 33,600 to 29,000 and 13,600 cal./mole, respectively, in resorcinol solution.[9]

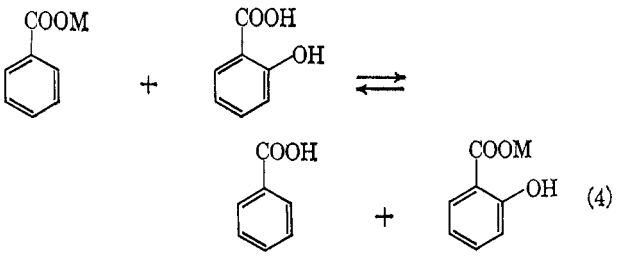
In benzoic acid solution, substituted salicylic acids with electron-withdrawing substituents have decreased rates of decarboxylation (runs 84–86, Table I). Conversely, an increase in rate was observed with the presence of a *para* hydroxyl group[10] (run 79, Table I).

In protic solvents, kinetic data do not permit a clear distinction between (a) a unimolecular decomposition of the free acid or its anion, or (b) a bimolecular reaction between the acid or anion and a proton. This system is further complicated by the equilibrium between salicylic acid and the ionized form. The concentrations of the proposed rate-determining species cannot be varied independently.

The benzoic acid solvent can reasonably be assumed to provide a large reservoir of protons required for decarboxylation by a bimolecular mechanism. Therefore, dilution of this solvent with an aprotic substance should depress the rate. With runs 48 and 50, Table I, the rate constants decreased by 5 and 17% when the benzoic acid solvent was diluted with 10 and 25 wt. % of phenyl benzoate. Furthermore, when phenyl benzoate was used as the solvent, the rate was decreased sevenfold (run 51). The only source of protons was salicylic acid itself.

If one can accept the premise that the drastic change in solvent medium from benzoic acid to phenyl benzoate effected the rate primarily by altering the concentration of available protons, the proposed bimolecular reaction is supported. More significant, perhaps, was the observation that a saturated solution of sodium and potassium salicylates in phenyl benzoate or benzoic anhydride were completely stable at 212°. Under these conditions, the salicylate ion was denied a proton and could not undergo a decarboxylation reaction.

Additional experiments were performed to test the proposed mechanism by significantly altering the concentration of the salicylate anion. The availability of protons would be expected to remain relatively constant by the use of benzoic acid as a solvent. An increase in salicylate ion concentration should then increase the decarboxylation rate. This was accomplished experimentally by the addition of various salts of benzoic acid. An equilibrium of the type shown by eq. 4 would be especially favorable with metals that are strongly

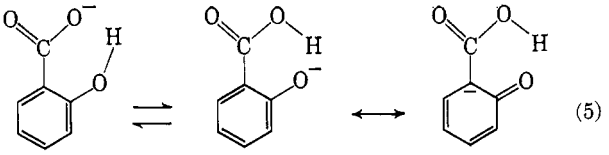


(4)

chelated. In every case where salts were added to the solvent, an increase in rate was observed. The results are summarized in Table II.

The catalytic effect produced by the addition of various salts of benzoic acid appears to be somewhat complicated, as indicated by the considerable variations in the effect on the rate of decarboxylation. On the other hand, the energy of activation calculated for runs catalyzed by magnesium benzoate at a concentration of 0.228 mole/kg. (runs 64 and 70) was 29,700 cal./mole. The value for the uncatalyzed reaction was 29,950 cal./mole. At 212°, the observed rate of decarboxylation was increased over 31-fold by the presence of the magnesium salt. This suggests that decarboxylation occurs by the same mechanism, the difference resulting from a substantial increase in salicylate ion by the presence of the magnesium salt.

An attack by a proton on the terminal ring carbon atom of the salicylate ion would appear, at first glance, to be extremely unfavorable because of the close proximity of a formal negative charge. Any interaction should merely lead to undissociated acid. The hydroxyl group in the *ortho* position appears to influence the distribution of the charge because of the steric configuration. Resonance and tautomeric forms, eq. 5, which



(5)

do not involve an extensive shift of atoms, can be drawn which would distribute the charge in a manner favorable to the proposed mechanism, eq. 3. This unique steric arrangement is not possible with *m*- or *p*-hydroxybenzoic acid, the effect of which is borne out by the fact that these two acids did not decarboxylate at a measurable rate in benzoic acid solution at 212°. Since inductive and resonance effects would be expected to be similar for the *ortho* and *para* isomers, the steric effect appears to exert a critical influence. It is of interest to observe that decarboxylation occurs with the presence of an *ortho* methoxy group (run 82, Table I), but at a diminished rate.

Experimental

Materials.—Benzoic acid, Baker's primary standard grade, m.p. 121.5°, and salicylic acid, Dow resublimed, m.p. 159°, were used directly without purification. The following Eastman chemicals were recrystallized, with solvent and melting points indicated: phenyl benzoate, hexane, 69°; 5-bromosalicylic acid, water, 171–172°; 2,4-dimethoxybenzoic acid, water, 108–109°; 3,5-dinitrosalicylic acid, water, 174°; 2,4-dihydroxybenzoic acid, water, 224–225° dec.; 2,5-dihydroxybenzoic acid, water, 208–209°; *m*-hydroxybenzoic acid, water, 203–204°; and 5-nitrosalicylic acid, water, 235°. The following chemicals from Matheson Coleman and Bell were recrystallized, with solvent and

(8) B. R. Brown, D. L. Hammick, and A. J. B. Scholefield, *J. Chem. Soc.*, 778 (1950).

(9) With the technique described herein, two runs were made utilizing resorcinol as a solvent (runs 58 and 59, Table I). In our hands, a severe deviation from a linear pseudo-first-order plot was observed. An initial rate constant was calculated by dividing the slope of a plot of concentration *vs.* time, at zero time by the initial concentration. Values of 0.6 and 0.8 × 10^{-4} sec.$^{-1}$ were similar to that obtained by Brown, *et al.*, 2 × 10^{-4} sec.$^{-1}$. The observed decreasing slope suggests a competing side reaction.

(10) The rate constant for the decarboxylation of salicylic acid at 182° was 23 × 10^{-6} min.$^{-1}$, calculated by means of the energy of activation, 29,950 cal./mole.

melting points indicated: benzoic anhydride, hexane, 43°; resublimed resorcinol, used directly, 108°; and *p*-hydroxybenzoic acid, used directly, 215°.

Apparatus and Method.—A schematic drawing of the apparatus is shown in Fig. 1. Constant temperature (±0.1°) was maintained by a stable refluxing liquid (*m*-diethylbenzene, 182°; *cis*-decalin, 193°; nitrobenzene, 212°; isopropyl benzoate, 220°; and *n*-propyl benzoate, 232°). The 3-l. flask was filled with approximately 1500 ml. of liquid. The temperature was measured with a mercury thermometer with 0.2° divisions, calibrated against a bureau of standards reference.

The solvent and catalyst were accurately weighed and transferred to the inner reaction chamber, bottom section 45 × 120 mm., top section 28 × 230 mm., and then placed in the refluxing liquid. The stability of the solvent could be checked by measuring the evolution of carbon dioxide at this point. When the temperature had equilibrated, the salicylic acid, pelletized for convenience, was added and the system was immediately closed.

A slow stream of purified nitrogen (approximately 100 ml./min.), line A, was bubbled through the solution to provide agitation and to carry the carbon dioxide from the reaction chamber. A fivefold change in flow rate did not significantly alter the calculated rate constant. Temperature readings, measured by a thermocouple inserted through the well sealed in the cap, indicated that the desired temperature of reaction was re-established within 5 min. after the addition of the salicylic acid. One hundred grams of solvent and the appropriate molar amounts of salicylic acid and catalyst were used with all concentrations expressed in moles per kilogram of solvent.

The gas emerging from the reactor was diverted to Dry Ice trap F, calcium chloride trap G, and Ascarite absorber H, by stopcock C. After exactly 10 min., stopcock C was turned to divert the gas to an identical adsorption train F′, G′, H′.

Stopcock D was turned to direct a second stream, B, of purified nitrogen (approximately 1.5 l./min.) through absorption system F, G, H. This was done to sweep all of the carbon dioxide produced during the first 10 min. into the Ascarite trap H. The lines leading from the reactor to stopcock C were kept as short as possible. After 18 min., stopcock E was turned to vent nitrogen from stream B to the atmosphere, trap H was removed and weighed to the nearest 0.1 mg. and immediately replaced in the system.

At exactly 20 min., stopcock C was turned toward absorption train F, G, H, then stopcock D was turned toward absorption train F′, G′, H′, and stopcock E was closed to begin sweeping train F′, G′, H′. The cycle was repeated. The increase in weight of the Ascarite absorber was recorded as the weight of carbon dioxide produced during the corresponding time interval.

A sensitive manometer (filled with Silicon 710 liquid) at the inlet side of nitrogen stream A indicated the development of back pressure in the system. A pressure difference when switching between the two absorption trains could not be tolerated. It could usually be avoided by the use of freshly prepared Ascarite traps.

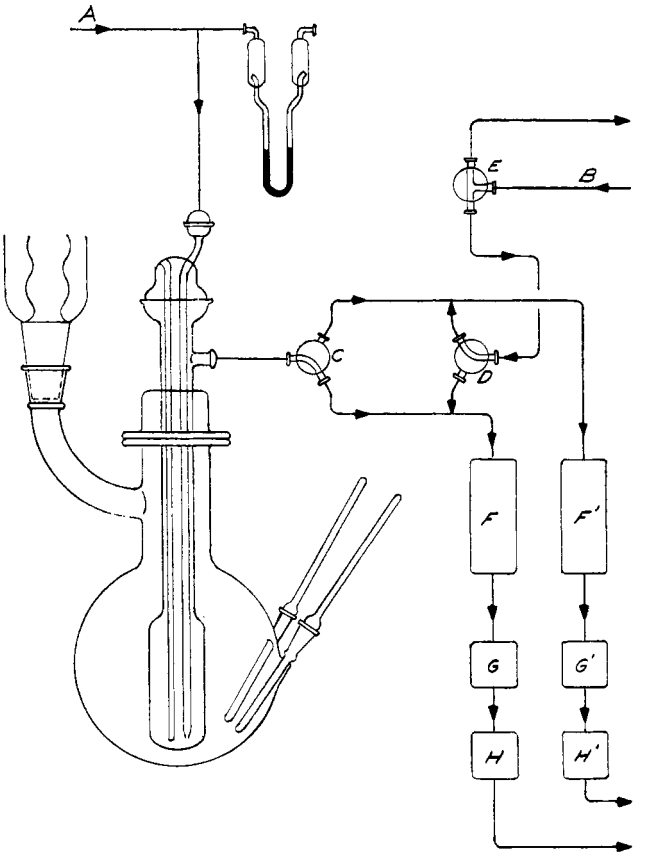


Figure 1.

Pseudo-first-order rate constants, k ($k = -\frac{1}{c}\frac{dc}{dt}$), were determined graphically by measuring the slope of the straight line obtained by plotting the logarithm of the salicylic acid concentration, c, *vs.* time, t.

Acknowledgment.—W. W. K. is indebted to Mrs. Veda Brink for assistance with the experimental work, to Dr. J. P. Surls and Mr. D. L. Bauer for making the run utilizing beryllium benzoate as the catalyst, and to Professor R. G. Rinker for stimulating discussions.

Glycolic Acid Metabolites of Desoxycorticosterone. Assignment of Configuration at C-20[1]

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For two epimeric glycolic (20-hydroxy-21-oic) acid metabolites of desoxycorticosterone assignment of configuration at C-20 cannot be made by measuring changes in molecular rotation after acetylation. Their absolute configurations have been determined by chemical and microbiological transformations which relate the configuration of one epimer both to 20β,21-dihydroxypregn-4-en-3-one and to two 11-oxygenated glycolic acids which possess a 20β-oxygen function. The preparation of a number of free and acetylated derivatives of the 20α- and 20β-epimers of 20,21-dihydroxypregn-4-en-3-one and 20-hydroxy-3-oxopregn-4-en-21-oic acid is described. The significance of differences in their molecular rotations is discussed.

Recently one of us reported that incubation of desoxycorticosterone with surviving guinea pig liver slices resulted in the formation of four acidic metabolites.[2] Two of these were the C-20 epimeric glycolic acids Va and Vb (Fig. 1), originally designated the polar and mobile acids, respectively. Their configurations at

(1) This work was supported by a research grant (AM 01255) from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Public Health Service.

(2) J. J. Schneider, "Proceedings of the First International Congress on Hormonal Steroids," Vol. I, Academic Press, New York, N. Y., 1964, pp. 127–135.