

TABLE III  
FRACTIONAL ELECTROLYSIS (GALLIC ACID)

Cell no.	P <sub>H</sub> of cell after electrolysis	Percentage of total gallic acid in cell	Percentage of total pantothenic acid in cell		
			Test 1 (2 cc.)	Test 2 (1 cc.)	Test 3 (0.5 cc.)
1	2.75	5.5	7.7	4.6	5.2
2	3.45	30.6	32.2	28.3	30.8
3	3.85	55.3	45.5	53.9	53.9
4	4.55	6.5	14.5	13.2	10.2
5-8	5.25-9.0	0	0	0	0

TABLE IV  
FRACTIONAL ELECTROLYSIS (GALLIC ACID)

Cell no.	P <sub>H</sub> of cell after electrolysis	Percentage of total gallic acid in cell	Percentage of total pantothenic acid in cell		
			Test 1 (2 cc.)	Test 2 (1 cc.)	Test 3 (0.5 cc.)
1	3.55	16.7	9.5	13.4	14.9
2	3.65	32.2	31.0	28.4	29.5
3	4.50	37.9	36.5	37.6	37.7
4	4.75	13.1	23.1	20.8	18.0
5-8	4.35-7.50	0	0	0	0

spectively, of gallic acid ( $K_A = 3.9 \times 10^{-5}$ ) were electrolyzed in the presence of the standard rice bran material. It will be noted that the migration of the gallic acid is parallel to that of the pantothenic acid except that in each case the gallic acid migrates appreciably farther toward the acid end, indicating that it is appreciably stronger as an acid. Results exactly similar to these were obtained in four different electrolyses when 5 mg. of gallic acid was electrolyzed in the presence of the rice bran material, for eighteen, twenty-four, thirty and thirty-six hours, respectively. In

every one of these electrolyses as in the ones detailed in Tables III and IV, gallic acid migrated a little farther toward the acid end of the system.

The fact that the ionization constant of pantothenic acid appears to be somewhat lower than  $3.9 \times 10^{-5}$ , is of considerable significance when it is realized that all  $\alpha$ -hydroxy acids which have been studied have ionization constants of  $10^{-4}$  or higher.<sup>4</sup> Evidently pantothenic acid is not an  $\alpha$ -hydroxy acid. The approximate value obtained does not preclude its having beta or gamma hydroxyl groups since beta (and gamma) hydroxy acids are actually somewhat weaker than gallic acid.

### Summary

1. A new method involving fractional electrolysis has been applied to the approximate determination of the ionization constant of a physiologically potent substance (pantothenic acid).

2. The ionization constant of pantothenic acid is found to be approximately that of gallic acid ( $3.9 \times 10^{-5}$ ) although slightly lower.

3. From comparison with the ionization constants of acids of known structure, it is concluded that pantothenic acid cannot be an alpha hydroxy acid but may possess beta or gamma hydroxyl groups.

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(4) Scudder, "Conductivity and Ionization Constants of Organic Compounds," 1914.

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

## The Pinacol-Pinacolone Rearrangement. V. The Rearrangement of Unsymmetrical Aromatic Pinacols

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Recently<sup>2</sup> an investigation of the rearrangement of unsymmetrical pinacols was begun; three pinacols of the type  $RR(OH)CC(OH)R'R'$ , in which R and R' are aryl groups, were subjected to rearrangement and the extent to which each of the two groups migrated was determined. We are now reporting the results obtained by rearrangement of seven new pinacols of this kind. In Table I are shown the percentage migration of the two groups in each pinacol; for comparison there is shown the migration of the same groups

when situated in the symmetrical pinacol  $RR'(OH)CC(OH)RR'$ .

It is apparent that the groups migrate differently when situated in the two types of pinacols. In a number of cases the order of migration is reversed; that is, the group that migrates to the greatest extent in the symmetrical molecule migrates least when situated in the unsymmetrical pinacol. There is no simple relationship between the two sets of values.<sup>3</sup> This is even more apparent from a comparison of the series

(1) Submitted in partial fulfillment of the requirements for the Ph.D. degree.

(2) Bachmann, *THIS JOURNAL*, **54**, 2112 (1932).

(3) For comparison with pinacols containing the biphenylene group see Bachmann and Sternberger, *ibid.*, **55**, 3819 (1933).

TABLE I  
 MIGRATION OF GROUPS

Groups R, R'	Pinacol	
	Unsym. Migration, %	Sym. %
C <sub>6</sub> H <sub>5</sub>	46	8
<i>p</i> -C <sub>6</sub> H <sub>4</sub> C <sub>6</sub> H <sub>4</sub>	54	92
C <sub>6</sub> H <sub>5</sub>	57	60
<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	43	40
C <sub>6</sub> H <sub>5</sub>	67	2.5
<i>p</i> -C <sub>6</sub> H <sub>4</sub> OC <sub>6</sub> H <sub>4</sub>	33	97.5
C <sub>6</sub> H <sub>5</sub>	91	35
<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	9	65
<i>p</i> -C <sub>6</sub> H <sub>4</sub> C <sub>6</sub> H <sub>4</sub>	58	87
<i>m</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	42	13
<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	45	96.7
<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	55	3.3
<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	35	
<i>m</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	65	
C <sub>6</sub> H <sub>5</sub> <sup>2</sup>	72	1.4
<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	28	98.6
C <sub>6</sub> H <sub>5</sub> <sup>2</sup>	51	6
<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	49	94
C <sub>6</sub> H <sub>5</sub> <sup>2</sup>	50	34
<i>m</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	50	66

representing the relative migration aptitudes of the groups on the basis of phenyl as unity. For the unsymmetrical pinacols the following series holds: *p*-biphenyl, 1.18; phenyl, 1.0; *m*-tolyl, 1.0; *p*-tolyl, 0.96; *p*-chlorophenyl, 0.75; phenetyl, 0.49; anisyl, 0.39; *p*-fluorophenyl, 0.099. The corresponding series for the symmetrical pinacols is: anisyl, 70+, phenetyl, 39; *p*-tolyl, 15; *p*-biphenyl, 11.5; *m*-tolyl, 1.95; *p*-fluorophenyl, 1.85; phenyl, 1.0; *p*-chlorophenyl, 0.66. It is seen that there is much less variation in the series of migration aptitudes in the unsymmetrical pinacols.

It is possible to calculate the course of the rearrangement of a pinacol containing the groups R<sub>2</sub> and R<sub>3</sub> from the results obtained by rearrangement of the pinacols containing a mutual third group R<sub>1</sub> with R<sub>2</sub> and R<sub>1</sub> with R<sub>3</sub>. Bachmann and Moser<sup>4</sup> have found that in symmetrical pinacols such predictions agree closely with the experimental results. In Table II is given a comparison of the calculated and the experimental results obtained with three unsymmetrical pinacols.

Although the calculated figures are of the same order as the experimentally determined values, they do not agree closely and it appears that more than one factor is involved in the rearrangement of an unsymmetrical pinacol.

(4) Bachmann and Moser, *ibid.*, **54**, 1124 (1932).

TABLE II

CALCULATED MIGRATION OF GROUPS		
In each case the mutual group R <sub>1</sub> was the phenyl group		
Groups R <sub>2</sub> R <sub>3</sub>	Calcd. Migration	Found
<i>p</i> -Biphenyl: <i>m</i> -tolyl	54:46	58:42
Anisyl : <i>p</i> -tolyl	29:71	45:55
Anisyl : <i>m</i> -tolyl	28:72	35:65

### Experimental

**Preparation of the Pinacols.**—The seven new pinacols were synthesized by the action of a Grignard reagent on the methyl ester of benzoic acid or a substituted benzoic acid. To the solution of Grignard reagent from 0.25 gram mole of aryl halide in 100 cc. of ether was added 100 cc. of benzene and then 0.062 gram mole of ester in portions. After being refluxed the mixture was cooled and hydrolyzed. The crude products were usually digested with cold alcohol or a mixture of alcohol and acetone in order to remove oily impurities before recrystallization. In all cases the pinacols were obtained as colorless crystals. Most of the pinacols hold solvent of crystallization tenaciously; the melting points were determined on samples that had been dried at 60° under reduced pressure. The essential data are presented in Table III.

**Preparation of Anisilic Acid.**—This acid was prepared by a modification of the Schönberg and Keller<sup>5</sup> method. Forty grams of anisil was added to a cooled solution of 24 g. of potassium hydroxide in 150 cc. of absolute alcohol in a 500-cc. bottle; absolute ether was added to fill the bottle. The mixture was shaken for two weeks, one week being found insufficient for complete reaction; yield, 35.8 g. (90%); m. p. 159–160°.

**Methyl Anisilate, (CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>C(OH)COOCH<sub>3</sub>.**—The ester was produced in 85% yield by treatment of the acid with a solution of diazomethane. The methyl anisilate was obtained as colorless crystals by recrystallization from a mixture of benzene and petroleum ether; m. p. 110.0–110.5°.

*Anal.* Calcd. for C<sub>17</sub>H<sub>15</sub>O<sub>3</sub>: C, 67.5; H, 6.0. Found: C, 67.6; H, 5.9.

Esterification methods which proved unsatisfactory included refluxing the acid with methanol alone or in presence of hydrogen chloride, treatment of the acid with dimethyl sulfate and reaction of the sodium salt with ethyl iodide.

**Preparation of 4,4'-Diphenylbenzoic Acid, (C<sub>6</sub>H<sub>5</sub>-C<sub>6</sub>H<sub>4</sub>)<sub>2</sub>C(OH)COOH.**—This acid has been prepared previously only in small amounts. We have worked out a procedure for preparing the compound which depends on the reaction of carbon dioxide with the diiodium derivative<sup>6</sup> of 4,4'-diphenylbenzophenone. Fifteen grams of 4,4'-diphenylbenzophenone<sup>7</sup> was suspended in a mixture of 150 cc. of anhydrous ether and 150 cc. of ordinary dry benzene in a 350-cc. bottle of the kind employed on a Parr hydrogenation apparatus. Five grams of sodium ribbon was introduced and the reaction was initiated by pressing portions of the sodium with a glass rod until an intense green color developed; if the reaction was not

(5) Schönberg and Keller, *Ber.*, **56**, 1638 (1923).

(6) Schlenk, Appenrodt, Michael and Thal, *ibid.*, **47**, 473 (1914).

(7) Bachmann, *This Journal*, **55**, 773 (1933).

TABLE III  
YIELDS AND PROPERTIES OF PINACOLS  
Abbreviations: alc, alcohol; ac, acetone; bz, benzene; ch, chloroform

No.	<i>as</i> -benzopinacol	Reactants		Time, hrs.	Yield, %	Recryst. solv.	Cryst. form	M. p., °C.
		Methyl ester of acid	Grignard reagent from					
1	3,3'-Dimethyl-4'',4'''- dimethoxy-	Anisilic	<i>m</i> -Bromotoluene	8	49	Ac + alc	Plates	153.3-154.5
2	4,4'-Dimethyl-4'',4'''- dimethoxy-	Anisilic	<i>p</i> -Bromotoluene	8	69	Ac + alc	Heavy needles	159.5-161.0
3	4,4'-Diethoxy-	Benzilic	<i>p</i> -Bromophenetole	9	73	Ac	Prisms	162.0-163.0
4	4,4'-Diphenyl <sup>a</sup>	Benzilic	Bromobenzene	15	86	Ch	Fine needles	190.5-191.0
5	3,3'-Dimethyl-4'',4'''- diphenyl-	Diphenylbenzilic	<i>m</i> -Bromotoluene	19	69	Ch + alc	Needles	160.0-161.0
6	4,4'-Dichloro-	Benzilic	<i>p</i> -Chlorobromobenzene	24	69	Ac <sup>b</sup>	Broad needles	143.0-144.5
7	4,4'-Difluoro-	Benzilic	<i>p</i> -Fluorobromobenzene	24	67	Ac <sup>c</sup>	Needles	166.5-167.5

  

No.	ac	alc	Solubility bz	ch	Empirical formula	Analyses, %		
						C	H	Found
1	vs	sls			C <sub>30</sub> H <sub>30</sub> O <sub>4</sub>	79.3	6.7	79.1
2	vs	sls			C <sub>30</sub> H <sub>30</sub> O <sub>4</sub>	79.3	6.7	78.8
3	vs	sls			C <sub>30</sub> H <sub>30</sub> O <sub>4</sub>	79.3	6.7	78.9
4	sls		sls	s(h)	C <sub>38</sub> H <sub>30</sub> O <sub>2</sub>	88.0	5.8	87.1
5	s	sls	vs(h)	vs(h)	C <sub>40</sub> H <sub>34</sub> O <sub>2</sub>	87.9	6.3	87.3
6	sls	sls	s		C <sub>26</sub> H <sub>20</sub> O <sub>2</sub> Cl <sub>2</sub>		Cl, 16.3	Cl, 16.5
7	s	sls			C <sub>26</sub> H <sub>20</sub> O <sub>2</sub> F <sub>2</sub>		F, 9.4	F, 9.4

<sup>a</sup> Almost all of the pinacol precipitated from the solution when the reaction mixture was hydrolyzed.

<sup>b</sup> The pinacol holds acetone of crystallization in the ratio of 3 pinacol:2 acetone; these crystals melt at 95°. The solvent is lost at 60° under reduced pressure and can also be eliminated by dissolving the pinacol in ether and evaporating the ether in a current of air.

<sup>c</sup> The pinacol crystallizes from acetone with solvent of crystallization; the solvent is lost when the crystals are exposed to air.

started in this manner several days of shaking were sometimes necessary before the reaction began. About a dozen glass beads was added to the mixture, the bottle was stoppered and then shaken mechanically for four or five days. The deep blue solution of the disodium derivative was then shaken for fifteen minutes while it was subjected to one to two atmospheres pressure of carbon dioxide; in five minutes the solution was pale yellow in color, showing that carbonation was complete. The solution was decanted from the excess of sodium and was treated with alcohol until all suspended particles of sodium were destroyed; about 300 cc. of water was added with stirring and in short time the sodium salt of the diphenylbenzilic acid precipitated. The sodium salt was filtered off and was converted to the free acid by digestion with 5% hydrochloric acid for twenty-four hours; yield, 15 g. (88%). By this method we have prepared about 150 g. of diphenylbenzilic acid.

**Methyl Ester of 4,4'-Diphenylbenzilic Acid.**—Esterification of the acid by a mixture of methanol and hydrogen chloride was unsuccessful; the product was an oil which did not crystallize. Excellent results were obtained by the use of diazomethane. The ester was obtained in clusters of colorless needles by recrystallization from a mixture of benzene and petroleum ether; yield, 89%; m. p. 130.5-131.5°. Methyl diphenylbenzilate is very soluble in hot benzene, soluble in cold benzene and slightly soluble in petroleum ether.

*Anal.* Calcd. for C<sub>27</sub>H<sub>22</sub>O<sub>3</sub>: C, 82.2; H, 5.6. Found: C, 82.2; H, 5.6.

**Rearrangement of the Pinacols.**—Rearrangement was usually attempted by refluxing the pinacol with a mixture of acetyl chloride, acetic acid and benzene.<sup>4</sup> In two cases, *as*-4,4'-diphenylbenzopinacol and *as*-3,3'-dimethyl-4'',4'''-diphenylbenzopinacol, after the acetyl chloride treatment the mixture was heated with the more powerful reagent iodine in acetic acid<sup>8</sup> in order to complete the rearrangement; in the case of *as*-4,4'-dichlorobenzopinacol and *as*-4,4'-difluorobenzopinacol only the iodine and acetic acid treatment was employed.

The mixtures of pinacolones were cleaved into triaryl-methanes and acids by alcoholic potassium hydroxide; for the concentrated alkali solutions methanol was used as the solvent. The conditions employed for rearrangement and scission and the yields of triaryl-methanes and acids are given in Table IV.

**Analyses of Acid Mixtures.**—The extent of migration undergone by each group in the pinacol was determined by analysis of the acid mixtures. In the mixtures containing anisic acid or phenetic acid the proportion of these acids was estimated by making a methoxyl or ethoxyl determination. The results of different runs checked each other closely.

The mixtures of benzoic acid and *p*-phenylbenzoic acid and of *m*-toluic acid and *p*-phenylbenzoic acid were separated in virtue of the slight solubility of *p*-phenylbenzoic acid in water (0.02 g./100 cc.). *p*-Chlorobenzoic acid was separated from benzoic acid by digestion of the mixture of acids with cold benzene; the latter dissolves

(8) Gomberg and Bachmann, THIS JOURNAL, 49, 237 (1927).

TABLE IV  
 REARRANGEMENT OF PINACOLS

<i>as</i> -benzopinacol	Wt. samples, g.	Rearr. time, days	Alc. cc.	Scission KOH, g.	Time, days	Yield of methanes		Yield of acids	
						g.	%	g.	%
3,3'-Dimethyl-4'',4'''-dimethoxy- <sup>a</sup>	1.00	2	100	25	2	0.70	102	0.305	97
	0.45	3	50	3	2	.35	112	.145	98
4,4'-Dimethyl-4'',4'''-dimethoxy- <sup>a</sup>	1.00	5	100	25 <sup>b</sup>	3	.70	102	.305	96
	2.00	3	100	25	3	1.35	99	.620	97
4,4'-Diethoxy- <sup>a</sup>	0.45	3	50	3	2	0.33	104	.120	89
	2.00	4	50	12	2 <sup>c</sup>	1.44	103	.530	89
4,4'-Diphenyl- <sup>d</sup>	0.53	1	100 <sup>e</sup>	10	3	0.37	104	.150	93
	2.00	1	100	10	3	1.43	104	.560	88
	2.00	1	100	10	3	1.45	105	.580	92
3,3'-Dimethyl-4'',4'''-diphenyl- <sup>f</sup>	1.00	1	100	6	2	0.65	96	.270	91
	2.00	1	100	6	1	1.43	104	.585	93
4,4'-Dichloro- <sup>g</sup>	2.00	0.02	100	25	1	1.44	103	.590	93
	3.00	.02	100	25	1	2.08	102	.880	95
4,4'-Difluoro- <sup>h</sup>	2.00	.3	100	25	1	1.34	97	.605	99
	2.00	.3	100	25	1	1.35	97	.590	96

<sup>a</sup> Rearranged by heating with 40 cc. of acetyl chloride, 20 cc. of acetic acid and 80 cc. of benzene. <sup>b</sup> Two days with 6% potassium hydroxide gave 40% cleavage; an additional one and one-half days with 15% alkali gave a total of 75% cleavage; 25% potassium hydroxide gave complete scission in three days. <sup>c</sup> Further heating with 25% potassium hydroxide gave no more acid. <sup>d</sup> Heated with 40 cc. of acetyl chloride and 20 cc. of acetic acid; after one day the excess of acetyl chloride was distilled off, 10 cc. of acetic acid and 0.05 g. of iodine was added and the mixture was refluxed for one-half hour. The acetyl chloride treatment alone gave only 35% rearrangement in one day and 50% in two days. <sup>e</sup> Ten cc. of benzene was added to the mixture in order to dissolve the mixture of pinacolones. <sup>f</sup> Treatment as in (d). <sup>g</sup> Refluxed with 50 cc. of acetic acid and 0.05 g. of iodine. <sup>h</sup> Treatment as in (g). Heating with the standard acetyl chloride mixture for four days effected only 10% rearrangement.

benzoic acid to a much greater extent than it does *p*-chlorobenzoic acid. A 0.565-g. sample of a mixture of the two acids was shaken with 17 cc. of benzene and filtered; the residue of *p*-chlorobenzoic acid after being washed with 3 cc. of benzene weighed 0.245 g. A synthetic mixture of similar proportions when treated in the same manner showed that 0.05 g. of *p*-chlorobenzoic acid was dissolved by the benzene; this correction was applied to the weight of acid isolated. The proportion of *p*-fluorobenzoic acid in admixture with benzoic acid was determined by fusing the mixture with sodium peroxide and making a determination of the fluoride radical.<sup>9</sup>

**2,2 - Di - *p* - fluorophenyl - 1,2 - diphenylethanone - 1,** (FC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>(C<sub>6</sub>H<sub>5</sub>)CCOC<sub>6</sub>H<sub>5</sub>.—This pinacolone was readily isolated in a pure state from the mixture obtained by rearrangement of *as*-4,4'-difluorobenzopinacol. By recrystallization from propanol the compound was obtained as colorless cubes; m. p. 121.5–122.5°.

*Anal.* Calcd. for C<sub>26</sub>H<sub>18</sub>OF<sub>2</sub>: F, 9.9. Found: F, 9.7.

**4,4'-Difluorotriphenylmethane.**—This compound was isolated from the mixture of triarylmethanes produced by cleavage of the pinacolones. It was also obtained by scission of the pure 2,2-di-*p* fluorophenyl-1,2-diphenyl-

ethanone-1 and also by reduction of 4,4'-difluorotriphenylcarbinol which was synthesized by interaction of *p*-fluorophenylmagnesium bromide and methyl benzoate. 4,4'-Difluorotriphenylmethane crystallizes in colorless prisms from propanol; m. p. 55–56°.

*Anal.* Calcd. for C<sub>19</sub>H<sub>14</sub>F<sub>2</sub>: F, 13.6. Found: F, 13.6.

### Summary

Seven new unsymmetrical aromatic pinacols of the type RR(OH)CC(OH)R'R' have been synthesized.

The pinacols have been rearranged to pinacolones and a comparison of the migration aptitudes of the phenyl, *p*-biphenyl, *p*-chlorophenyl, phenetyl, anisyl, *p*-fluorophenyl, *p*-tolyl and *m*-tolyl groups in unsymmetrical pinacolones has been obtained.

It has been found that there is no simple relationship between the values of the migration aptitudes of groups in symmetrical pinacols and the values which hold in unsymmetrical pinacols.

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(9) Willard and Winter, *Ind. Eng. Chem., Anal. Ed.*, **5**, 7 (1933).