Experimental[8]

Microcrystalline Racemic Calcium Pantothenate (M. p. 170–172°)

A. From the Amorphous Product.—Eleven grams of amorphous ether-precipitated material[4] was dissolved in 50 ml. of methyl Cellosolve by warming on the steam-bath. After standing for six weeks at room temperature the solution was found to contain a finely divided white solid which appeared as very small needles when examined under the microscope. The product was filtered, washed with fresh solvent and dried *in vacuo* at 100° for seven hours; m. p. 166–168°. Recrystallization from methyl Cellosolve (10 ml. per g.) raised the melting point to 170–172°.

Anal. Calcd. for $C_{18}H_{32}N_2O_{10}Ca$: C, 45.37; H, 6.77; Ca, 8.41; N, 5.88. Found: C, 45.50, 45.25; H, 7.01, 6.71; Ca, 8.38, 8.21; N, 5.69; microbiological assay,[9] 50.3% activity.[6] Further recrystallizations from methyl Cellosolve did not change the melting point.

B. From Calcium, β-Alanine and Pantolactone.—To 250 ml. of anhydrous methanol was added 10.10 g. (0.252 mole) of distilled calcium metal,[10] and the mixture was warmed gently until the reaction became vigorous. When the evolution of hydrogen had ceased, the resulting suspension of calcium methoxide was cooled to room temperature and 44.9 g. (0.504 mole) of finely divided β-alanine[11] was added. The resulting mixture was stirred mechanically until a clear solution was obtained (about thirty minutes). A solution of 69.0 g. (0.530 mole) of racemic pantolactone (b. p. 119–122.5° (12.5 mm.)) in 500 ml. of methyl Cellosolve was then added and the methanol was distilled off *in vacuo*. The residual methyl Cellosolve solution was seeded with the crystals described in the preceding paragraph. After standing one month at room temperature, the product was filtered, washed with fresh solvent and dried *in vacuo* at 100°. The yield was 93 g. (77.5%); m. p. 166–169°. Recrystallization from methyl Cellosolve raised the melting point to 170–172°.

Microcrystalline Racemic Calcium Pantothenate (m. p. 187–189°)

A. From the 170–172° Melting Product.—Three grams of the above described microcrystalline salt was dissolved in 10 ml. of dry methanol at room temperature and seeded with crystalline calcium (+)-pantothenate.[1] On standing at room temperature, well defined colorless needles crystallized from the solution. After standing for eleven days the resulting thick slurry of the methanol solvate was filtered, washed with methanol and dried to constant weight *in vacuo* at 100°; m. p. 185–187°. After recrystallization from methanol (5 ml. per g.) it melted at 187–189°.

Anal. Calcd. for $C_{18}H_{32}N_2O_{10}Ca$: C, 45.37; H, 6.77; Ca, 8.41; N, 5.88. Found: C, 45.51; H, 6.58; Ca, 8.59; N, 6.07; microbiological assay, 52.8% activity. Further recrystallizations from methanol did not change the melting point.

B. From Calcium, β-Alanine and Pantolactone.—The methanol solution was prepared by the same method as that described above using 50.10 g. (1.25 mole) of calcium, 222.8 g. (2.50 mole) of β-alanine, 328.5 g. (2.525 mole) of racemic pantolactone (m. p. 84–85°)[12] and 2.5 liters of dry methanol. The solution was seeded with some of the crystals described in the preceding paragraph. After standing for six weeks at room temperature the resulting slurry was filtered, washed with methanol and dried *in vacuo* at 100° for eight hours. The yield was 419 g. (70%); m. p. 180–184°.

Anal. Calcd. for $C_{18}H_{32}N_2O_{10}Ca$: Ca, 8.41. Found: Ca, 8.39; microbiological assay, 47.2% activity.

The time required for the above recrystallizations may be shortened considerably by operation at slightly elevated temperatures (30–40°). Cooling to 0° was found to inhibit the crystallization completely.

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(13) Original manuscript received May 24, 1945.

(8) Melting points on calcium pantothenate depend somewhat upon the rate of heating. Those reported in this paper were taken on finely powdered samples in Pyrex capillary tubes with the bath temperature increased at about 2° per minute.

(9) Strong, Feeney and Earle, *Ind. Eng. Chem., Anal. Ed.*, **13**, 566 (1941).

(10) Obtained from the Electro Metallurgical Company, 30 E. 42nd St., New York, N. Y.

(11) Ford, THIS JOURNAL, **67**, 876 (1945).

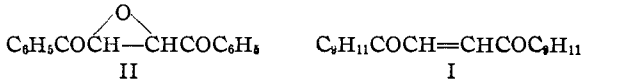
(12) Pure racemic pantolactone melts at 90–91°. See Ford, THIS JOURNAL, **66**, 20 (1944).

Coupling of Aryl Methyl Ketones by the Action of Sodium Hypohalite Solutions

BY REYNOLD C. FUSON AND ROBERT JOHNSON

When it was discovered that the diiodo derivatives of highly hindered aryl methyl ketones could be made by treating the ketones with limited amounts of sodium hypoiodite[1] an attempt was made to prepare the corresponding chloro iodo ketones by subjecting the monochloro ketones to the action of the hypoiodite. When the reaction was tried with α-chloroacetomesitylene, however, it was found to take a different course. Treatment with sodium hypochlorite or hypobromite converted the ketone to a halogen-free compound which proved to be the coupling product, *sym*-dimesitoylethylene (I). Both this compound and the ethane made from it by reduction had properties which corresponded to those reported by Conant and Lutz.[2]

It was found that acetophenone could be coupled in a similar manner. The product in this case, however, was the oxide (II) of the expected olefin, *sym*-dibenzoylethylene. The oxide had been made earlier by Lutz and Wilder.[3] Its structure was confirmed by synthesis. It was made by the action of phenylglyoxal on phenacyl bromide.[4]



II I

Experimental

α-Chloroacetomesitylene and Sodium Hypoiodite.—Twenty grams of iodine dissolved in aqueous potassium iodide solution was added slowly, with stirring, to a mixture of 5 g. of α-chloroacetomesitylene, 100 ml. of 10% sodium hydroxide solution, 150 ml. of water and 70 ml. of dioxane. The addition was complete in thirty minutes. The product obtained by ether extraction was recrystallized from methanol and then from ethanol. The product melted at 173–174.5° and was shown by the mixed melting point method to be identical with the *sym*-di-(2,4,6-trimethylbenzoyl)-ethylene previously prepared by Conant and Lutz.[2] By use of the method of these authors the ethylene was reduced to the ethane melting at 136–137.5°.

By using sodium hypochlorite and α-chloroacetomesitylene a similar result was obtained. The yield of the ethyl-

(1) Johnson and Fuson, THIS JOURNAL, **57**, 919 (1935).

(2) Conant and Lutz, *ibid.*, **45**, 1303 (1923).

(3) Lutz and Wilder, *ibid.*, **56**, 1987 (1934).

(4) Bodforss, *Ber.*, **51**, 192 (1918); Kleucker, *ibid.*, **55B**, 1634 (1922).

ene from 10 g. of chloro ketone was 1 g. melting at 173–174.5°. The synthesis was carried out in two ways.

(a) From Phenylglyoxal and Phenacyl Bromide.—One gram of phenylglyoxal was added rapidly, with vigorous stirring, to a mixture of 20 ml. of 10% sodium hydroxide solution, 15 ml. of dioxane and 3 g. of phenacyl bromide. After being stirred for fifteen minutes the mixture was shaken with ether. Evaporation of the ether gave a small quantity of solid which upon purification by recrystallization from ethanol, proved to be *sym*-dibenzoylethylene oxide.

(b) From *sym*-Dibenzoylethylene.—A mixture of *sym*-dibenzoylethylene, dioxane, 10% sodium hydroxide solution and sodium hypochlorite solution was shaken for a short period of time. An appreciable quantity of the oxide was removed by ether extraction.

Acetophenone and Sodium Hypoiodite.—A mixture of 20 g. of acetophenone, 30 ml. of dioxane and 200 ml. of 10% sodium hydroxide solution was stirred vigorously in the cold during the addition of 50 g. of iodine in aqueous potassium iodide solution. The addition was completed in one to two hours. The reaction mixture was extracted with benzene, and the residue obtained by distilling the benzene was freed from iodoform by steam distillation. From the residue by recrystallization from ethanol was obtained a small amount of a compound melting at 128–129°.[3]

Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.11; H, 4.76. Found: C, 76.0; H, 5.0.

It has been reported[5] that *sym*-dibenzoylethylene forms in 58–71% yields when phenacyl chloride is treated with aqueous potassium hydroxide. Attempts to use this method to make the mesityl analog, however, were unavailing. Treatment of α-chloroacetomesitylene in dioxane with 10% aqueous sodium hydroxide solution, alcoholic potassium hydroxide solution or sodium ethoxide failed to yield any *sym*-dimesitoylethylene.

(5) Bogoslov, *J. Gen. Chem. U. S. S. R.*, **14**, 993 (1944); *C. A.*, **39**, 600 (1945).

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Effect of Phenylacetic Acid Derivatives on the Types of Penicillin Produced by Penicillium Chrysogenum Q176

BY K. HIGUCHI, F. G. JARVIS, W. H. PETERSON AND M. J. JOHNSON

Because of recent emphasis on the differences in *in vivo* behavior among the various penicillins, data on the relative amounts of the penicillins produced by *P. chrysogenum* Q176 under various conditions become of interest. Some of our recent pertinent data are therefore summarized in Table I. The assay used to differentiate the penicillins is a microbiological procedure involving the use of four organisms, which will be published elsewhere. On known mixtures of three penicillins (G, X and K), the assay has given an average error of 10% in the estimation of the quantity of one component. Yields in the table are expressed as *S. aureus* units.

The following conclusions may be drawn from the table: (1) The penicillin produced in the absence of phenylacetic acid derivatives is largely K. Although the remainder has been calculated as G, its amount is too small to permit confidence in the result. (2) In the presence of corn steep liquor, which is known to contain phenylacetic acid derivatives, the proportion of G produced increases. The production of G is greatest early in the fermentation. (3) In the presence of added phenylacetic acid derivatives there is a great increase in the proportion of G. (4) The addition of a phenylacetic acid derivative always results in an increase in unit yield (and a larger increase in molar yield). (5) The addition of *p*-hydroxyphenylacetic acid results in the production of significant amounts of penicillin X, but phenylacetic

TABLE I

EFFECT OF PHENYLACETIC ACID DERIVATIVES ON PENICILLIN PRODUCTION

Run no.[a]	Compound added[c]	Age of fermentation, hr.	Total penicillin, u./ml.	Composition of penicillin, % G.	X[b]	K
1	None	42	94	13	...	87
		66	233	14	...	87
		75	264	12	...	88
	β-Phenylethylamine	42	117	91	...	9
		66	272	76	...	24
		90	435	66	...	34
	Phenylacetic acid[d]	42	169	88	...	12
		66	333	79	...	21
		75	387	74	...	26
	Phenylacetamide	42	119	91	...	9
		66	194	69	...	31
		90	384	57	...	43
2	None	60	161	44	3	53
		108	569	29	1	70
	β-Phenylethylamine	60	267	93	2	5
		108	726	78	5	17
	Phenylacetamide[d]	60	335	103	1	− 4
		108	616	78	2	20
	Phenylacetic acid[d]	60	448	109	3	−12
		108	673	76	−1	25
	p-Hydroxyphenylacetic acid	60	195	57	18	25
		108	422	42	11	47
	p-Hydroxyphenylacetic acid[d]	60	209	39	26	35
		108	462	34	10	56
3	None	49	638	30	...	70
4	Phenylacetic acid[e]	24	216	35	...	65
		60	1000	67	...	33
		72	1045	77	...	23

[a] Runs 1 and 2 were carried out in 500-ml. Erlenmeyer flasks containing 85 ml. (run 1) or 100 ml. (run 2) of medium. The medium used in run 1 consisted of the following constituents in grams per liter: lactose 22.5; glucose 7.5; ammonium lactate 7.1; potassium dihydrogen phosphate 2.0; magnesium sulfate 0.25; ferrous sulfate 0.20; copper sulfate 0.005; zinc sulfate 0.02; aluminum chloride 0.00027; potassium dichromate 0.000053. The medium used in run 2 contained the following constituents in grams per liter: corn steep liquor solids 30; lactose 30; calcium carbonate 10. Runs 3 and 4 were carried out in aerated and agitated tanks. The volume of medium used was 220 liters. The medium used in run 3 contained in grams per liter: steep liquor solids 40; lactose 40; calcium carbonate, 10; sodium sulfate 1.0. The medium used in run 4 was the same as that in run 3 except that the steep liquor concentration was 20 g. per liter. [b] When the differential assay results were calculated as a mixture of G and K only, no figure is given for X. [c] The compounds were added at a level of 0.5 g. per liter, and were added before sterilization unless otherwise stated. [d] The compound was added twenty-four hours after inoculation. [e] The phenylacetic acid was added in 6 equal portions, at 0, 12, 24, 36, 48 and 60 hours.