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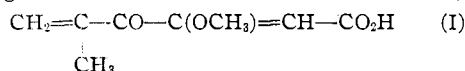
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The Synthesis of Benzene Derivatives Structurally Similar to Penicillic Acid

BY E. D. AMSTUTZ, E. A. FEHNEL¹ AND C. R. NEUMOYER²

Introduction

Penicillic acid, isolated first by Raistrick, Oxford and Smith³ from *Penicillium cyclopium* Westling, has been shown to have structure (I).



It is also known that certain acids (the carolic acid group) isolated from nutrient solutions upon which *P. charlesii* has been grown are structurally related to penicillic acid but, in spite of the presence of the α,β -unsaturated ketone⁴ system, are practically without antibiotic properties.⁵ It is thus at once apparent that there is a certain degree of antibacterial specificity associated with the penicillic acid molecule and the question immediately arises as to the extent and kind of contribution each of the component parts makes toward the antibiotic properties of the whole. The purpose of the present work was to synthesize, if possible by fairly simple methods, some compounds having the basic structural features of penicillic acid and to evaluate in terms of antibiotic effectiveness the contribution of the various groups. The present paper is a preliminary report and is concerned only with acidic materials but it is hoped that later some work on methoxyphenyl- α,β -unsaturated ketones can be reported.

Theoretical

For the purpose at hand penicillic acid has been considered to be a trisubstituted ethylene, the

(1) Roy R. Hornor Fellow in Chemistry, 1943-1944. Student Chemical Foundation Fellow, 1945-.

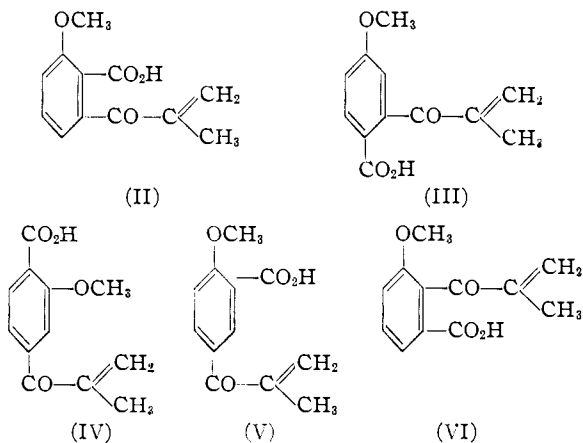
(2) The Wm. S. Merrell Co. Post-Doctorate Fellow in Organic Chemistry, 1944-.

(3) Oxford, Raistrick and Smith, *Chem. Ind.*, **61**, 22, 48 (1942).

(4) For a discussion of the unsaturated ketones see Geiger and Conn, *THIS JOURNAL*, **67**, 112 (1945).

(5) Clutterbuck, Raistrick and Reuter, *Biochem. J.*, **29**, 300, 871 (1935); **28**, 94 (1934).

substituent groups being the carboxyl, ethoxyl and methacrylyl groups. We have proceeded by substituting for the ethylene residue a benzene ring. It is apparent that in penicillic acid the methacrylyl and carboxyl groups bear to each other a relationship somewhat similar to that of ortho (or para) substituents on the benzene ring. The same is true of the carboxyl and methoxyl groups whereas the methoxyl and methacrylyl have been assigned the meta relationship. Structures (II), (III) and (IV) should then be the closest benzologs of (I).



Of almost equal interest in the present problem, however, is compound (V) in which the substituent groups do not have, with respect to each other, the penicillic acid relationship. Since (V) seemed to be more readily prepared than the others it was investigated first in the hope that certain of the methods used in its synthesis would be applicable to the rest. The diagram outlines the procedure used in the preparation of compound (V).

dehydrobromination phase we next attempted the direct synthesis from 3-methoxyphthalic anhydride by means of diisopropenyl cadmium. Krestinsky⁷ had earlier been able to prepare methyl isocrotylcarbinol from acetaldehyde and isocrotyl magnesium bromide. Although the yields were low due to the evolution of much olefin the product was reported to have the anticipated structure. We have found that isopropenyl bromide reacts vigorously with magnesium in the presence of ether to yield an organometallic compound which gives a positive test with Michler ketone. An aliquot of one preparation titrated 42% of the theoretical yield of Grignard. Some magnesium always remained when action had ceased however. The Grignard was converted to the dialkenyl cadmium in the usual way.⁶

The reaction between the supposed diisopropenyl cadmium and either phthalic anhydride or 3-methoxyphthalic anhydride afforded unsaturated, acidic products which had high neutral equivalents and high carbon contents. Experiments in which the mode of admixture of reagents was inverted gave similar results, indicating that the difficulty was due to side reactions occurring in the preparation of the organometallic intermediates. That this was actually the case was proved by carbonation of the isopropenyl Grignard reagent, when an acidic product having a neutral equivalent somewhat above that of methacrylic acid was obtained. Assuming the methacrylic to be admixed with a heptenoic acid the data indicate the presence of about 20% of the latter. That such a result should be obtained with as reactive a substance as isopropenyl bromide is not too surprising in view of the formation of *p*-phenylbenzoic acid on carbonation of phenylmagnesium bromide.⁸ The conclusion is then that in the reaction of the phthalic anhydrides with the dialkenyl cadmium compound a mixture of substances was produced. This mixture may well have contained compounds (II) and (VI) as well as ketones in which the olefinic radical is larger than propenyl. This mixture is listed in the table of bacteriological results as Mixture (II).

Because of the multiple nature of the carbonation product and the poor yield which attended its formation the use of the isopropenyl Grignard or cadmium compound did not seem suited for further investigation in this work. It is hoped however that, when conditions permit, it will be possible to return to the reaction of the vinyl type halides with magnesium.

Bacteriostatic Action

The bacteriostatic activity of the various compounds was tested by determining turbidimetrically the growth which the test organism (*S. aureus*, F.D.A. 209) showed in yeast-beef broth medium in the presence of varying amounts of

the test material. Each tube also contained 0.5% phosphate buffer which was intended to eliminate false results which might have been functions of the pH of the test material. All tests were made in duplicate and readings were made after twenty-four and forty-eight hours of growth.

TABLE I

Compound	Dilutions	
	Detectable activity at (hrs.)	No detectable activity at (hrs.)
(VIII)	4,000 (24)
(X)	4,000 (24)
(V)	12,000 (48 and 24)	16,000 (24)
Mixture (I)	4,000 (24)	4,000 (48)
Mixture (II)	24,000 (24)	32,000 (24)
Mixture (II)	24,000 (48)

The isobutyrylbenzoic acids (VIII, X, Mixture I) exhibited only slight antibacterial activity against *S. aureus*, while the methacrylylbenzoic acids (V, Mixture II) proved to be much more effective bacteriostatic agents. Mixture II, the principal constituent of which is presumably a benzolog (Compound II) of penicillic acid, was active at dilutions comparable to those at which penicillic acid is active against the same organism.

Acknowledgment.—The authors express their sincere thanks to Dr. M. G. Van Campen, Jr., and the Wm. S. Merrell Company for the bacteriological testing and for defraying a portion of the expenses of the investigation. The authors are likewise grateful to Mr. George F. Minde for his interest in some of the preliminary synthetic work.

Experimental

3-Carbomethoxy-4-hydroxyphenyl Isopropyl Ketone (VII).—Methyl *o*-anisate was prepared by methylation of methyl salicylate with methyl sulfate.⁹ The product was a colorless oil boiling at 118–123° at 4–5 mm.; yield 52%. Isobutyryl chloride from the acid¹⁰ boiled at 90–93.5°. Methyl *o*-anisate was found not to condense with isobutyryl chloride in the presence of stannic chloride in benzene as a solvent.¹¹ Seventy-eight per cent. of the ester was recovered. The use of nitrobenzene as a solvent¹² with aluminum chloride as condensing agent likewise failed to bring about reaction, the only substance recovered being *o*-anisic acid (62%).

A mixture of 54 g. (0.51 mole) of isobutyryl chloride and 83 g. (0.50 mole) of methyl *o*-anisate in 160 cc. of dry carbon disulfide was added dropwise over a thirty-minute period to a stirred and cooled mixture of 227 g. (1.7 moles) of aluminum chloride in 800 cc. of carbon disulfide. When addition was complete a further portion of 160 cc. of carbon disulfide was added through the dropping funnel and the ice bath was removed. Stirring was continued for one hour and the reaction mixture which was still evolving hydrogen chloride was allowed to stand for a period of about thirty hours with occasional stirring. The mixture was then decomposed by pouring it with vigorous stirring into 2300 g. of cracked ice. The water mixture was then extracted with a total of 2 liters of ether in small portions. The ethereal solution was washed with water (1-liter portions) and 10% sodium bicarbonate solution (1 liter total). After drying over anhydrous magnesium sulfate and dis-

(9) Wahl and Silberzweig, *Bull. soc. chim.*, (4) **11**, 30 (1912).

(10) "Organic Syntheses," Coll. Vol. 1, 2nd ed., 1941, p. 147.

(11) Method of Stadnikoff and Baryshewa, *Ber.*, **61**, 1996 (1928).

(12) Mosetti and van de Kamp, *This Journal*, **52**, 3704 (1930).

(7) Krestinsky, *Ber.*, **55**, 2754, 2762, 2770 (1922).

(8) Gilman and St. John, *This Journal*, **52**, 5017 (1930).

tilling off the low-boiling solvents, the remaining 130–160 cc. of heavy brown oil was distilled under diminished pressure to yield a forerun of 55 g. of methyl salicylate (b. p. 60–150° at 6–10 mm., characteristic odor and color with ferric chloride), 42.3 g. of heavy orange-colored oil (b. p. 150–182° at 6 mm.), and several grams of dark brown tarry residue. The second fraction readily crystallized on cooling and after recrystallization from petroleum ether melted at 97–99°; yield 23.5 g. (23%). The substance formed colorless needles giving a deep red color with ferric chloride.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.84; H, 6.35. Found: C, 64.81; H, 6.52.

The same compound was obtained by Fries rearrangement of *o*-carbomethoxyphenyl isobutyrate¹³ (b. p. 150–154.5° at 10–12 mm.). The compound was identical in every respect with that produced in the Friedel-Crafts reaction.

3-Carboxy-4-hydroxyphenyl Isopropyl Ketone (VIII).—The methyl ester (VII) (5.8 g., 0.026 mole) was saponified by refluxing two and one-half hours in a solution prepared by dissolving 5 g. of sodium hydroxide in 20 cc. of water and diluting to 100 cc. with 95% ethanol. After standing three hours the solution was acidified and extracted in the usual way with ether. Evaporation of the dried ether extract yielded 4.4 g. (81%) of crude (VIII). After two recrystallizations from water the pure compound was obtained as colorless crystals melting at 168–170° and giving a bright red color with ferric chloride.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.43; H, 5.81; neut. equiv., 208. Found: C, 63.25; H, 5.98; neut. equiv., 207, 208.

Treatment of the acid with an excess of ethereal diazomethane followed by evaporation to dryness brought about quantitative conversion of the acid to the original ester (VII), m. p. 92–96°.

3-Carbomethoxy-4-methoxyphenyl Isopropyl Ketone (IX).—To a solution of 3.6 g. (0.16 g.-atom) of sodium in 168 cc. of methanol (distilled from sodium) was added 23.5 g. (0.11 mole) of compound (VII) and the mixture was heated on a hot-plate at 50–60°. Then 27.5 g. (0.22 mole) of methyl sulfate was added slowly with constant stirring and the heating was continued until no further fading of the deep yellow color could be observed. The product was worked up by pouring into water, extracting with ether, and evaporating the dried ether solution. Since the product obtained still produced a positive test with ferric chloride the methylation was repeated twice more. The substance was thus finally obtained, after one recrystallization from petroleum ether, in the form of colorless crystals melting at 50–52° and giving no color with ferric chloride; yield, crude 24.5 g. (98%).

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.07; H, 6.83. Found: C, 65.97; H, 6.72.

3-Carboxy-4-methoxyphenyl Isopropyl Ketone (X).—The crude methyl ester (24.5 g.) was saponified in the usual way with alcoholic-aqueous caustic (32 g. of sodium hydroxide in 130 cc. of water diluted to 640 cc. with 95% ethanol). After removal of unsaponified ester and recrystallization from water there was obtained 8.6 g. (37%) of colorless crystals which melted at 97.5–99.5°.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.84; H, 6.35; neut. equiv., 222. Found: C, 64.87; H, 6.37; neut. equiv., 223, 224.

3-Carboxy-4-methoxyphenyl α -Bromoisopropyl Ketone (XI).—A solution of 8.6 g. (0.039 mole) of compound (X) in 140 cc. of glacial acetic acid was heated to 60° and 6.3 g. (0.035 mole) of bromine was added over a twenty-minute period. The solution was then maintained at temperature for another fifteen minutes by which time the color had faded to pale yellow. Upon dilution to 800 cc. with cold water a white gelatinous precipitate was thrown

down. This was dissolved in 400 cc. of ether, dried and the solution evaporated whereupon 9.8 g. (84%) of white crystals was obtained. In the crude state the substance melted at 128–135° while after one recrystallization from xylene it melted at 135–136.5°. Recovery on recrystallization was 80%. The compound gave an immediate precipitate with alcoholic silver nitrate.

Anal. Calcd. for $C_{12}H_{13}O_4Br$: Br, 26.55. Found: Br, 26.47, 26.21.

3-Carboxy-4-methoxyphenyl α -Hydroxyisopropyl Ketone (XII).—A solution of 0.5 g. of compound (XI) and 0.23 g. of potassium hydroxide in 1 cc. of 95% ethanol was heated at reflux for ten minutes. The solution was cooled, acidified with 10 cc. of 6 *N* hydrochloric acid and extracted with ether. Evaporation of the washed and dried ether solution yielded 0.3 g. of yellow solid which was recrystallized from xylene to give a colorless, crystalline product melting at 125–127°. This material gave a negative Baeyer test.

Anal. Calcd. for $C_{12}H_{14}O_5$: C, 60.48; H, 5.93; neut. equiv., 238. Found: C, 60.31; H, 6.22; neut. equiv., 237, 240.

3-Carboxy-4-methoxyphenyl Isopropenyl Ketone (V).—A mixture of 5.7 g. (0.019 mole) of the bromoketone (XI) and 6 g. (0.036 mole) of silver acetate in 240 cc. of dry benzene was refluxed in the dark for two hours. The reaction mixture was filtered while hot and reduced to a volume of 25 cc. by distillation. After cooling in an ice bath the crystalline product was removed by filtration and dried in a vacuum. The white crystalline substance (3.3 g., 79%) after recrystallization from xylene melted at 127–131° and gave a good test for unsaturation with potassium permanganate.

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65.44; H, 5.50; neut. equiv., 220. Found: C, 65.43; H, 5.57; neut. equiv., 219.

On being kept at a temperature of 110° for forty-eight hours in a hot-air oven the substance changed into an amber-colored resin which no longer reduced potassium permanganate solution and which was found to have a neutral equivalent of 223.

3-Methoxyphthalic Acid.—The reduction of 3-nitrophthalic acid to 3-aminophthalic acid hydrochloride was carried out according to the directions of Bogert and Jouard¹⁴ in yields of 75–85% (m. p. 247–262°).

3-Hydroxyphthalic acid was formed in the usual way from this amine on boiling the diazonium solution.¹⁵ On cooling the resulting clear orange-colored solution overnight some *m*-hydroxybenzoic acid (m. p. 196–201°) usually precipitated out and was removed by filtration (15% yield). The filtrate was extracted with ether until no more phenolic material could be removed, the combined ether extracts were combined, dried with magnesium sulfate, filtered and evaporated. The residue was obtained as pale orange crystals melting at 125–136°; yield 49.5, or 61.3% calculated on the basis of the amine. Recrystallization of a small sample from benzene-ethanol afforded pale yellow crystals melting at 155–159°. Pratt and Perkins¹⁶ reported a melting point of 161–163° (dec.) by rapid heating.

The crude hydroxy acid (49.5 g.) was converted to the anhydride by boiling in 400 cc. of xylene for ten minutes after which the supernatant liquid was decanted from the tar. Chilling the xylene solution in an ice-salt bath brought about the precipitation of an orange-yellow solid which was filtered off and oven-dried at 110°. The filtrate was returned to the tarry residue, boiled for another ten minutes, decanted and concentrated to 200 cc. Chilling and filtering yielded another crop which was added to the first. The total yield of pale orange crystals melting at 180–194° was 35.2 g. (87%). A small sample recrystallized again from xylene melted at 195–198°; reported¹⁶ m. p. 198–199°.

(13) Prepared in 28% yield by heating together methyl salicylate (45.6 g., 0.3 mole) and isobutyryl chloride (32.1 g., 0.3 mole) according to the method of Cox, *THIS JOURNAL*, **52**, 352 (1930).

(14) Bogert and Jouard, *ibid.*, **31**, 483 (1909).

(15) "Organic Syntheses," Coll. Vol. I, 2nd ed., 1941, p.404.

(16) Pratt and Perkins, *THIS JOURNAL*, **40**, 227 (1918).

A solution of diazomethane in ether was prepared¹⁷ from 56.5 g. of nitrosomethylurea. To 550 cc. of this solution cooled in an ice-bath 35.2 g. of crude 3-hydroxyphthalic anhydride was slowly added with vigorous stirring. After all the solid had been added and effervescence had ceased, another 100 cc. of the diazomethane solution (same concentration) was run in. The buff-colored precipitate which was then filtered off melted at 150–154° and gave only a slight pink color with ferric chloride; yield 28.3 g. (74%). Recrystallization from 300 cc. of toluene, followed by drying in an oven at 110° gave 20.8 g. of material melting at 155–158° (recorded m. p., 160–161°).¹⁸ A small sample was dissolved in boiling water, cooled and extracted with ether giving a residue, the acid, which melted at 171.5–174° (recorded¹⁸ m. p., 173–174°).

2-Carboxy-3-methoxyphenyl Isopropyl Ketone and 2-Carboxy-6-methoxyphenyl Isopropyl Ketone (Mixture I).

—To the stirred diisopropyl cadmium, prepared in 250 cc. of ether from 44 g. (0.34 mole) of isopropyl bromide, 8.8 g. (0.36 g. atom) of magnesium turnings and 29.2 g. (0.16 mole) of anhydrous cadmium chloride, was added over a period of fifteen minutes 20 g. (0.11 mole) of 3-methoxyphthalic anhydride. Stirring and cooling were continued for one hour, after which the formation of a tarry product interfered with the motion of the stirrer. After standing overnight the chilled mixture was hydrolyzed by the addition of 325 cc. of cold 10% sulfuric acid. The aqueous layer was removed and extracted several times with ether. The combined ether extracts were shaken with three 45-cc. portions of 10% potassium carbonate solution which were then combined, heated to boil off the dissolved ether, and acidified with dilute sulfuric acid. The tarry yellow precipitate was filtered off, washed well with water, and dried (yield, 17 g.). The solid was then recrystallized from 450 cc. of water yielding 8.5 g. of yellowish flaky solid which melted gradually over the range 77–130°.

Anal. Calcd. for $C_{12}H_{14}O_4 \cdot H_2O$: neut. equiv., 240. Found: neut. equiv., 237.

Recrystallization from xylene of a sample which had already undergone three recrystallizations from water gave material melting at 92–135°.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.84; H, 6.35; neut. equiv., 222. Found: C, 64.91, 65.01; H, 6.44, 6.24; neut. equiv., 223.

Bromination of Mixture (I).—One gram of the isomer mixture was dissolved in 18 cc. of glacial acetic acid and heated to 60°. While the temperature was maintained between 60 and 70°, 0.6 g. of bromine was added dropwise to the solution. The red color was discharged almost immediately. The yellow solution was then diluted to 100 cc. with water and extracted with ether. After being washed with water and dried over anhydrous magnesium sulfate the ether solution was evaporated to give a slightly yellow residue. The yield of colorless recrystallized (xylene-petroleum ether) material melting at 128–131° amounted to 0.8 g. The product was soluble with effervescence in bicarbonate solution and gave an immediate precipitate with cold alcoholic silver nitrate.

Anal. Calcd. for $C_{12}H_{12}O_4Br_2$ (one active, one inactive Br): total Br, 42.09; active Br, 21.01. Found: Total Br (Carius), 49.08; active Br (hot aq. $AgNO_3$), 25.50.

Attempted Dehydrobromination of the Dibromo Acid.—The above bromination product (0.6 g.) was stirred vigorously with an equal amount of silver acetate in 50 cc. of benzene at room temperature and in the dark. At intervals the stirring was interrupted to allow the suspended solid to settle and a drop of the clear supernatant liquid was drawn off for testing with alcoholic silver nitrate solution. After about two hours the benzene solution no longer gave a precipitate with silver nitrate, indicating the removal of all active bromine from the compound. After filtering off the silver salts, the clear benzene solution

was evaporated at room temperature, leaving a white solid residue, m. p. 62–72°. This material, which may have been an acetoxy derivative, was no longer soluble in bicarbonate, gave no precipitate with alcoholic silver nitrate and showed no sign of unsaturation on treatment with potassium permanganate in acetone.

Reactions with Isopropenyl Bromide.—Isopropenyl bromide was prepared by the method of Farrell and Bachman¹⁹ which involves the decarboxylation and dehydrobromination of α,β -dibromoisobutyric acid by heating with pyridine. A 49% yield of crude bromide was obtained using an ice-salt trap to catch vapors evolved during the reaction. On fractionation, this crude product yielded 39% of water-white halide, b. p. 48–50°. Farrell and Bachman reported 32% of crude product.

In its reaction with magnesium in the presence of ether isopropenyl bromide behaved much like any low molecular weight aliphatic bromide. In general all reactions proceeded vigorously if not too much ether was present. In the presence of larger amounts of ether the reaction appeared almost to cease. Isopropenyl bromide (30 g., 0.25 mole) was allowed to react with 7.5 g. (0.33 g. atom) of clean magnesium turnings and about 300 cc. of anhydrous ether under a nitrogen atmosphere in a liter 3-necked flask equipped with stirrer, condenser and gas inlet tube. After about thirty minutes a positive test with Michler ketone was obtained. Stirring was continued for a total reaction time of two and one-half hours after which the volume was made up to 380 cc. and a 10-cc. portion removed. This portion required 12 cc. of 0.233 *N* hydrochloric acid for neutralization, indicating a 42% yield of reagent. To the above Grignard solution was added, with efficient stirring, 11 g. (0.06 mole) of anhydrous cadmium chloride. After being stirred for thirty minutes the Michler ketone test was negative. The mixture was thereupon cooled in an ice bath and treated with 23 g. (0.16 mole) of oven-dried phthalic anhydride. The cooled mixture was stirred for one and one-half hours, after which the formation of a gummy product interfered with the motion of the stirrer. After having stood for about twelve hours the mixture was worked up in the usual way. The dried ethereal solution of the acidic reaction products deposited some phthalic acid on evaporation and the thick yellow taffy-like tar gave up still more upon extraction with chloroform; total phthalic acid recovered, 14 g. (56%). Evaporation of the chloroform solution in high vacuum yielded about 15 g. of a thick yellow oil which resisted all attempts at crystallization. It gave a positive test for unsaturation and was completely soluble in bicarbonate.

Anal. Calcd. for $HO_2C-C_6H_4COC_3H_5$: neut. equiv., 190. Found: neut. equiv., 201.

The reaction of the cadmium compound from isopropenyl bromide with 3-methoxyphthalic anhydride in ether was carried out in exactly the same fashion as above, using 20 g. (0.11 mole) of anhydride and 30 g. of isopropenyl bromide. The acidic product (12 g.), obtained by high-vacuum evaporation of the final dried ether solution, appeared as a mass of waxy yellow crystals which gave a positive Baeyer test and dissolved completely in bicarbonate.

Anal. Calcd. for $HO_2C-C_6H_3(OCH_3)COC_3H_5$: neut. equiv., 220. Found: neut. equiv., 232.

Attempts to recrystallize this material from benzene and from water were unsuccessful. All of the product was therefore taken up in 25 cc. of 10% sodium bicarbonate solution, diluted with about 50 cc. of water, cooled, acidified and extracted with ether. The waxy solid so obtained gave a neutral equivalent of 273 and melted at 70–84°. Several washings with boiling petroleum ether lowered the neutral equivalent only slightly. The final product did not contain halogen (sodium fusion), was completely soluble in bicarbonate, decolorized permanganate and decomposed with effervescence on melting, giving a substance no longer soluble in bicarbonate. This has been designated Mixture (II).

(17) "Organic Syntheses," Coll. Vol. II, 1943, p. 166.

(18) Bentley, Robinson and Weizmann, *J. Chem. Soc.*, 91, 109 (1907).

(19) Farrell and Bachman, *THIS JOURNAL*, 57, 1281 (1935).

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65.45; H, 5.46; neut. equiv., 220. Found: C, 67.44; H, 6.92; neut. equiv., 271.

In a similar run in which the ethereal solution of the cadmium alkenyl was added to the anhydride there was isolated a yellow semi-solid product of neutral equivalent 265. A similar run in which the ethereal solution of the cadmium alkenyl was added slowly to a warm (50–57°) solution of the anhydride yielded finally a small amount of product having a neutral equivalent of 244. All of these products were bicarbonate soluble and gave positive tests for olefinic unsaturation.

A Grignard reagent (prepared in ether in the usual way under nitrogen) from 6.05 g. (0.05 mole) of isopropenyl bromide and 1.3 g. (0.05 g. atom) of magnesium was carbonated by pouring onto finely crushed Dry Ice. After acidification with dilute hydrochloric acid and extraction several times with ether, the combined ether layers were extracted with saturated bicarbonate solution. The combined bicarbonate extracts were just acidified to congo red under ether with dil. sulfuric acid. The ether extracts were washed once with water, dried over anhydrous sodium sulfate and evaporated on a hot plate. After several evacuations while warm the liquid acids were titrated with standard base.

Anal. Calcd. for $C_8H_8CO_2H$: neut. equiv., 86; calcd. for $C_8H_{10}CO_2H$: neut. equiv., 127. Found: neut. equiv., 94.

Summary

Several benzene derivatives possessing the substituent groups of penicillic acid have been prepared and tested for bacteriostatic activity. The methacrylyl-methoxybenzoic acids appear to be superior to their saturated counterparts.

Methoxyphthalic anhydride has been condensed with diisopropylcadmium to yield a mixture of ketonic acids.

When pure isopropenyl bromide reacts with magnesium to produce a Grignard reagent it appears simultaneously to undergo a process which results in an enlargement of the alkenyl radical. The process appears to differ from the usual olefinic polymerization.

BETHLEHEM, PA.

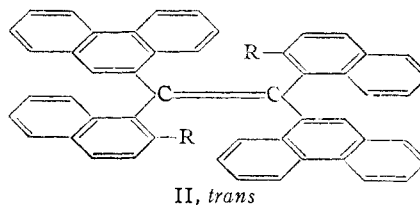
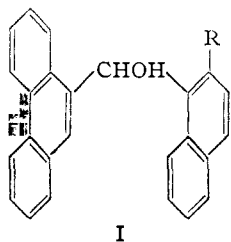
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[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE]

The Formation of Tetraarylethylenes from Diarylcarbinols

BY FELIX BERGMANN AND SHALOM ISRAELASHVILI¹

Under the influence of electrophilic reagents, such as strong acids, diaryl carbinols may be converted into ethers,² fluorenes³ or tetraaryl ethylenes.⁴ Whereas the formation of the first two products appears now to be clearly understood,^{3,5} no reasonable mechanism has as yet been formulated for the "ethylenization." We have studied this "dehydration dimerization" reaction, especially in such cases, where di-ortho substitution of one of the aryl groups in the carbinol prevents cyclization to the five-membered ring system of fluorene. Thus, (9-phenanthryl)-(2-ethoxynaphthyl-1)-carbinol (I, R = OC_2H_5) and (9-phenanthryl)-(2-methyl-naphthyl-1)-carbinol (I, R = CH_3) were converted quantitatively into the corresponding ethylenes (II) by a boiling mixture of hydrobromic and acetic acids.



As recorded earlier,³ the carbinol (I, R = H) could not be isolated, but cyclized spontaneously to 1,2,3,4,7,8-tribenzfluorene, whereas di-(9-phenanthryl)-carbinol exclusively gave the tetraaryl ethylene.⁶ No ethylenization was observed in the case of (1-naphthyl)-(2-naphthyl)- or di-(2-naphthyl)-carbinol. It is thus evident, that, with the exception of di-(1-naphthyl)carbinol,⁴ ethylenization occurs, when cyclization is impossible.

It was postulated by Magidson, that the first transformation product of a diaryl carbinol with strong acids is an ether, which is cleaved into water and two diarylmethylene radicals. These may undergo either intramolecular cyclization or intermolecular dimerization. However, benzhydrol or its ether does not cyclize to fluorene, whereas it has been found⁷ that the diphenylmethylene radical undergoes ring closure. Magidson's scheme can, therefore, not be valid under the usual reaction conditions. The following alternative hypothesis is offered:

Electrophilic reagents convert the carbinols first into diarylcarbonium ions, which cyclize directly, or, if this reaction is prohibited or slow—

(1) Part of a thesis, submitted to the Hebrew University, Jerusalem, 1945.

(2) Klinger and Lonnes, *Ber.*, **29**, 2158 (1896); Adams and Weeks, *This Journal*, **38**, 2514 (1916).

(3) For a review of the literature, see Bergmann and Israelashvili, *ibid.*, **68**, 1 (1946).

(4) Magidson, *Ber.*, **58**, 433 (1925).

(5) Hammett, "Physical Organic Chemistry," 1940, p. 300.

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