of the product is not kinetically well defined although, with careful control, it may be isolated before the yellow chromophore has developed. The second stage occurs at a considerably slower rate and, because the third stage is exceedingly slow, yields a product which is fairly well defined. By employing a trace of moisture and a progressively increasing temperature, a trichloride has been formed with the elimination of nine molecules of hydrogen chloride. This trichloride reacted rapidly with fuchsin-aldehyde reagent, compared to a slow reaction (after ten minutes) with the dichloride.

(3) The above observations provide a reasonable basis for a preliminary assignment of structures to the repeating units of the products, *provided there has been no change in ring structure during the chlorination reaction.* If the (9:3) trichloride is an aldehyde and has been formed without alteration in ring form, all ten hydrogen atoms of the repeating unit are accounted for. Of the nine hydrogen atoms eliminated as hydrogen chloride, six represent the oxidation of the carbinol groups of carbon atoms 2, 3 and 6 to carbonyl groups, while the remaining three, on carbon atoms 1, 4 and 5, are substituted by chlorine.

Acknowledgment.—The authors wish to acknowledge the support given to this study by Sharples Chemicals, Inc. Appreciation is also expressed for the contributions of other workers on this problem, who have been mentioned in the footnotes.

Summary

The chlorination of starch with elementary liquid chlorine has been accomplished. The reaction is kept under control by the use of a sufficient excess of liquid chlorine to reduce the activity of the hydrogen chloride formed, which otherwise leads to a destructive carbonization reaction. The reaction is characterized by a pronounced induction period, an unusual series of color changes in the product, and a reluctance to react beyond the dichloride stage. Both oxidation and substitution occur, and as many as nine of the ten hydrogen atoms per glucose unit have been eliminated as hydrogen chloride.

Besides forming potentially useful reactive derivatives of starch, the reaction appears to be capable of shedding additional light on the nature and structure of starch.

MANHATTAN, KANSAS RECEIVED NOVEMBER 29, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, FACULTY OF ENGINEERING, KYÔTO UNIVERSITY]

The Preparations of Synthetic Estrogens. III.[1] A New Isomer of 3-*p*-Anisyl-3,4-hexanediol

BY KEIITI SISIDO AND HITOSI NOZAKI

For the preparation of diethylstilbestrol Kuwada, Sasagawa and Nisikawa,[2] Wessely, Kerschbaum, Kleedorfer, Prillinger and Zajic[3] as well as Fieser and Christiansen[4] have used 3-*p*-anisyl-4-hexanone (III) as the intermediate. It is known that the ketone (III) can be prepared by the dehydration of 3-*p*-anisyl-3,4-hexanediol (II).[2,5] In the course of the investigation to find a route to this estrogen from simple compounds we have developed new methods for the synthesis of the hexanediol (II) starting either from *p*-methoxyacetophenone or from *p*-methoxybutyrophenone and have discovered that the diol (II) thus prepared is a new diastereomeric isomer.

Oxidation of *p*-methoxyacetophenone with selenium dioxide gives *p*-anisylglyoxal (I) according to Karrer and Segesser[6] as well as to Anley and Robinson.[7] As the yields reported in both of these papers are very poor, we have repeated the reaction in a modified procedure[8] and were able to obtain satisfactory result. It is to be noted that Kaplan[9] has pointed out accidentally low yields in the reaction with selenium dioxide depending on the kind of oxide used. This same reason may account for the unsuccessful results of these investigators.[6,7] Meanwhile Kipnis, Soloway and Ornfelt[10] have described a similar preparation of *p*-ethoxyphenylglyoxal in 41% yield.

As the result of the Grignard reaction of *p*-anisylglyoxal (I) and ethylmagnesium iodide[11] 3-*p*-anisyl-3,4-hexanediol (II) is to be expected. The reaction product whose analytical data agreed with the theoretical value of this diol (II) melted at 99–100° and gave a monoacetate of m. p. 121° by a treatment with acetic anhydride and pyridine. The formation of the monoacetate may show that one of the two hydroxyl groups is tertiary, which is difficult to be acetylated.

The same diol (II) was also obtained by means of another synthesis using *p*-methoxybutyrophe-

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[1] Previous paper: Sisido and Nozaki, THIS JOURNAL, **70**, 778 (1948).

[2] Kuwada, Sasagawa and Nisikawa, *J. Pharm. Soc., Japan*, **60**, 224 (1940) (in German).

[3] Wessely, Kerschbaum, Kleedorfer, Prillinger and Zajic, *Monatsh.*, **73**, 127 (1940).

[4] Fieser and Christiansen, U. S. Patent 2,248,019, July 1, 1941.

[5] Ruggli and Businger, *Helv. Chim. Acta*, **24**, 1112 (1941).

[6] Karrer and Segesser, *ibid.*, **18**, 273 (1935).

[7] Anley and Robinson, *J. Chem. Soc.*, 369 (1937).

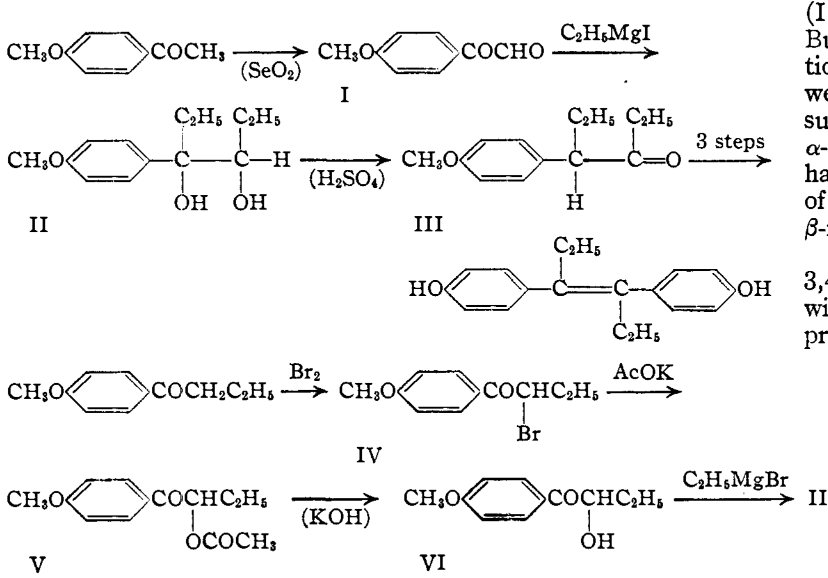
[8] *Cf.* Arnold and Fuson, THIS JOURNAL, **58**, 1295 (1936).

[9] Kaplan, *ibid.*, **63**, 2654 (1941).

[10] Kipnis, Soloway and Ornfelt, *ibid.*, **69**, 1231 (1947).

[11] *Cf.* Madelung and Oberwegner, *Ber.*, **65**, 931 (1932), for the reaction between phenylglyoxal and phenylmagnesium bromide.

none. The ketone was brominated and the product (IV) was treated with potassium acetate. Saponification of the resulting α-acetoxy-*p*-methoxybutyrophenone (V) yielded *p*-anisoylethylcarbinol (VI). The Grignard reaction of this α-ketol (VI) with ethylmagnesium bromide resulted in 3-*p*-anisyl-3,4-hexanediol (II), m. p. 99–100°, which gave on acetylation the monoacetate, m. p. 121°. The diol (II) and its acetate were found to be identical with the compounds prepared above from *p*-anisylglyoxal (I) and ethylmagnesium iodide.



The structure of the hexanediol (II) was ascertained by the oxidation with lead tetraacetate, which gave *p*-methoxypropiophenone in a good yield.

Kuwada, Sasagawa and Nisikawa[2] and later Ruggli and Businger[5] have prepared 3-*p*-anisyl-3,4-hexanediol (II) by the action of *p*-anisylmagnesium bromide upon propionoin and described the melting point as 83–84° and 180–181°, respectively. The monoacetate of this hexanediol (II) prepared by the former authors was described as melting at 101–102°. Thus, in any case, the melting points of our compounds are completely different from the corresponding ones of these authors. At our request, Dr. Kuwada and Mr. Sasagawa of the Takeda Pharmaceutical Industries Co., Osaka, carried out the mixed melting point determinations of our compounds with their corresponding ones and observed the depression in both cases. As they have confirmed, in this occasion, the correctness of their melting points, it seems to us that the melting point of Ruggli and Businger[5] is an error, probably a misprint: 80–81° instead of 180–181°.

Since 3-*p*-anisyl-3,4-hexanediol (II) has two asymmetric carbon atoms at 3- and 4-positions, respectively, there should exist a pair of diastereomeric isomers. The differences in the melting points above mentioned must be attributed to this stereoisomerism. The exclusive formation of one of these isomers in each of the syntheses is not surprising in view of the analogous facts found in the literature.[12,13] These peculiarities have been interpreted by the hypothesis of the intramolecular asymmetric induction.[14] According to the nomenclature adopted in such cases, the hexanediol (II) known in the literature should be termed α-compound and the diastereomeric isomer prepared by us β-compound. The steric configurations of these diastereomeric hexanediols (II) have not been established. But considering the investigations of McKenzie, *et al.*,[12e,h] as well as of Roger,[12f,g] we may assume, by the analogy, that the α-form of the hexanediol (II) has the asymmetric carbon atoms of different signs and that the β-isomer those of same signs.

The behavior of 3-*p*-anisyl-3,4-hexanediol (II) when treated with acetic anhydride in the presence of a small quantity of acetyl bromide is worth being described. Recently we have discovered that the tertiary hydroxyl groups, which are said to be acetylated with difficulty, can be esterified conveniently by means of a mixture of acetic anhydride and a trace of acetyl bromide.[15] As the ordinary acetylation of the hexanediol yielded only the monoacetate as described above, we have tried to apply this treatment. Anomalies were encountered, however, in this case, yielding at the first stage of the reaction the monoacetate but on further reaction leading to the elimination of acetic acid to produce 3-*p*-anisyl-4-hexanone (III).[16] Of course, this hexanone (III) can be prepared by the dehydration of the β-form of 3-*p*-anisyl-3,4-hexanediol (II) with 35% sulfuric acid according to the known procedure which was applied in the case of the α-isomer.[2,5]

Diethylstilbestrol can be prepared in good yields from our 3-*p*-anisyl-4-hexanone (III) by

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(12) For the Grignard reaction of acyloins or α-ketoalcohols see: (a) Tiffeneau and Lévy. *Bull. soc. chim.*, [4] **41**, 1351 (1927): (b) Tiffeneau and Lévy. *ibid.*, [4] **45**, 196 (1929): (c) McKenzie. Luis, Tiffeneau and Lévy, *ibid.*, [4] **45**, 414 (1929); (d) Tiffeneau, Lévy and Ditz, *ibid.*. [5] **2**, 1848 (1935); (e) McKenzie and Wren, *J. Chem. Soc.*. **97**, 473 (1910): (f) Roger, *Helv. Chim. Acta*. **12**, 1060 (1929); (g) Roger, *J. Chem. Soc.*. 1048 (1937): 108 (1939); (h) McKenzie and Wood, *ibid.*. 1536 (1939): (i) Partridge. *ibid.*. 1201 (1939).

(13) For the Grignard reaction of glyoxal derivatives see: (a) Wren and Still, *ibid.*, **103**, 1770 (1913); (b) Buck and Ide, THIS JOURNAL, **54**, 820 (1926); (c) Fischer and Taube, *Ber.*, **59**, 851. 857 (1926): (d) Ramart-Lucas and Salmon-Legagneur, *Bull. soc. chim.*, [4] **45**, 718 (1929); (e) see also ref. 12a.

(14) Kayser, *Ann. Chim.*. [11] **6**, 145 (1936): see also ref. 12h.

(15) The detail will be published before long.

(16) *Cf.* Parry. *J. Chem. Soc.*, **99**, 1172 (1911).

the essentially same procedures shown in the literature.[2,3,4]

Experimental[17]

p-Anisylglyoxal[18] (I).—To a solution of 22 g. of freshly prepared selenium dioxide[19] in 120 cc. of 95% alcohol at 55–60° 30 g. of p-methoxyacetophenone was added all at once. The resulting mixture was stirred and refluxed during five hours and allowed to stand. The hot alcoholic solution was separated from the precipitated selenium by decantation and evaporated. When about 100 cc. of alcohol had passed over, 50 cc. of benzene was added to the residue and the mixture again distilled to remove the water contaminated in the reaction product. This procedure was repeated until the distillate was no longer turbid. At this stage, the residue was distilled under reduced pressure. A fraction which came over at 115–130° and 4 mm. was collected and redistilled. Most of it distilled at 125–127° and 6 mm. The substance formed yellowish solid at room temperature and its vapor had a deep yellow color; yield about 22 g.

Since anisylglyoxal is very hygroscopic and, when exposed in air, changes readily into the colorless hydrate, it is troublesome to purify it by means of recrystallization or to determine its melting point. On the other hand, since the hydrate, which may conveniently be obtained by the crystallization from water, loses water even at about 75° and yields a yellow semi-solid mass, the accurate melting point is very difficult to determine, but the whole melts at about 110–114°. The fact that nothing has been described in the literature[6,7] concerning the melting point of p-anisylglyoxal as well as its hydrate may be due to such circumstances.

It is to be added that a crystalline substance melting at 177–179° was isolated from the distillate which came over at 125–150° and 5 mm. This was identified to be p-anisic acid by a mixed melting point.

Because of the close proximity of the boiling points of p-anisylglyoxal (I) and p-methoxyacetophenone the glyoxal derivative above obtained may be suspected to contain a small quantity of the unchanged material but this offers only little obstacle in the following reaction.

β-3-p-Anisyl-3,4-hexanediol*[20] **(II) from p-Anisylglyoxal (I).**—A solution of 20 g. of freshly distilled dry p-anisylglyoxal (I) in 80 cc. of absolute ether was added dropwise to a Grignard reagent prepared from 9 g. of magnesium, 57 g. of ethyl iodide and 150 cc. of ether. The reaction temperature was kept below 15° by means of an ice-bath. After the addition was completed, the mixture was stirred and refluxed for additional three hours and allowed to stand overnight. The product was poured into an iced solution of ammonium chloride. The whole was distilled to remove ether on a water-bath and extracted with hot benzene. The benzene extract was washed with warm water and evaporated. The residue was dissolved in hot ligroin and allowed to cool. Thus was obtained 10 g. of colorless needles, m. p. 98–99°. Recrystallizations from ligroin gave a pure sample which melted at 99–100°.

Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.39; H, 9.41.

A mixture of this hexanediol, m. p. 99–100°, with the diastereometric α-isomer, m. p. 83–84°, prepared by Kuwada, Sasagawa and Nisikawa[2] from propionoin and p-anisylmagnesium bromide, melted at 66–68.5°.

α-Bromo-p-methoxybutyrophenone* (IV).—To a solution of 36 g. of p-methoxybutyrophenone in 108 cc. of glacial acetic acid 35 g. of bromine was added under stirring in the course of two hours, during which time the reaction temperature was maintained at 10–20°. After additional fifteen minutes of stirring at the same temperature bromine was consumed almost completely. The contents were then poured into ice-water and the crystals separated were collected, washed with water, sodium thiosulfate solution and finally with water and dried. There was obtained about 50 g. of white crystals, which gave a pure substance, m. p. 54–54.5°, after one recrystallization from ligroin.

Anal. Calcd. for $C_{11}H_{13}O_2Br$: C, 51.38; H, 5.10. Found: C, 51.22; H, 5.23.

α-Acetoxy-p-methoxybutyrophenone* (V).—A mixture of 70 g. of the bromo ketone (IV), 40 g. of potassium acetate and 350 cc. of methanol was refluxed under stirring for three hours, the solvent distilled off and the residue was treated with water. The product was extracted with ethyl acetate, the combined extracts were washed with water, dried and distilled to remove the solvent. When the residue was dissolved in hot ligroin and allowed to cool, 33 g. of colorless needles, m. p. 63°, was obtained.

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.32; H, 6.68.

p-Anisoylethylcarbinol* (VI).—Twenty-three grams of the α-acetoxy ketone (V) was added to 120 cc. of 10% alcoholic potash and the mixture allowed to stand overnight at room temperature. The product was poured into water, acidified with acetic acid and extracted with benzene. The extract was washed with water, dried and the solvent distilled off under reduced pressure. The residue weighed 18 g. and formed a yellow liquid, which was subjected immediately to the following Grignard reaction. When the crude α-ketol was distilled under reduced pressure, most of it came over at 157–159° and 7 mm.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.58; H, 7.13.

β-3-p-Anisyl-3,4-hexanediol* (II) from the Carbinol (VI).—To a Grignard reagent prepared from 8.8 g. of ethyl bromide, 2 g. of magnesium and 25 cc. of ether a solution of 3 g. of the α-ketol (VI) in 15 cc. of ether was added with stirring during ten minutes and the mixture was refluxed for additional thirty minutes. When the product was treated in the usual way, 3 g. of colorless prisms, m. p. 97–98°, were obtained. Recrystallizations from ligroin gave a pure material which melted at 99–100° and showed no depression when admixed with the diol prepared from p-anisylglyoxal and ethylmagnesium iodide.

Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.50; H, 9.21.

Monoacetate* of β-3-p-Anisyl-3,4-hexanediol.—A solution of 1.0 g. of the β-hexanediol (II) in 10 cc. of pyridine and 10 cc. of acetic anhydride was refluxed for five minutes and allowed to stand overnight. The reaction product was poured into cold water and the resulting crystals were collected, washed with dilute hydrochloric acid and water, dried and recrystallized from ligroin. Thus were obtained colorless needles, m. p. 121°, whose analytical figures suggested that the substance was a monoacetate of the anisylhexanediol.

Anal. Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.18; H, 8.69.

A mixture of this β-monoacetate with the α-isomer, m. p. 101–102°,[2] melted at 88–89°.

Oxidation of β-3-p-Anisyl-3,4-hexanediol (II) with Lead Tetraacetate.—To a solution of 1.1 g. of the β-diol compound (II) in 30 cc. of benzene and 5 drops of glacial acetic acid was added 3 g. of lead tetraacetate in small portions. During this time the whole was heated at 55–65°. The reaction mixture was stirred at 55–70° for additional one and a half hours, added with a small quantity of ethylene glycol to remove the excess of the oxidizing agent and poured into water. The benzene layer was separated, dried and evaporated. The oily residue was dissolved in alcohol, added to aqueous solution of semicarbazide hydrochloride and sodium acetate and allowed to stand

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(17) Microanalyses by Miss Kenko Ogawa of our Laboratory.

(18) We treated p-methoxyacetophenone following partly the procedure of "Organic Syntheses," **15**, 67 (1935), in which the preparation of phenylglyoxal from acetophenone was described.

(19) Selenium dioxide was prepared, according to Kaplan (ref. 9), by oxidizing crude selenium with nitric acid and purified immediately by the sublimation.

(20) *, Asterisk means new compound.

overnight. The reaction product isolated by the usual procedure formed colorless plates, m. p. 172–173°, after recrystallization from ligroin, yield, 0.8 g. This did not show any depression in a mixed melting point with a known specimen of *p*-methoxypropiophenone semicarbazone.

Anal. Calcd. for $C_{11}H_{15}O_2N_3$: C, 59.71; H, 6.83. Found: C, 60.03; H, 7.23.

3-*p*-Anisyl-4-hexanone (III).—Ten grams of β-3-*p*-anisyl-3,4-hexanediol (II) was added in small portions to 200 g. of 35% sulfuric acid. The mixture was stirred for forty minutes at 95–98°. After cooling, the product was extracted with benzene and this benzene solution washed with water, dried over anhydrous sodium sulfate and evaporated. When the residue was distilled under reduced pressure, 7.5 g. of colorless oil came over at 117–125° and 6 mm. By treating 0.5 g. of this distillate with semicarbazide sulfate in dilute alcohol there was obtained 0.4 g. of the semicarbazone,[3] m. p. 130–131°, after recrystallizations from ligroin and then from benzene.

Anal. Calcd. for $C_{14}H_{21}O_2N_3$: C, 63.85; H, 8.04. Found: C, 63.76; H, 8.22.

The oxime[2] of the dehydration product formed colorless plates, m. p. 113°.

Anal. Calcd. for $C_{13}H_{19}O_2N$: C, 70.55; H, 8.66. Found: C, 70.09; H, 8.19.

The Reaction of β-3-*p*-Anisyl-3,4-hexanediol (II) with a Mixture of Acetic Anhydride and Acetyl Bromide.—To a suspension of 3 g. of the β-hexanediol (II) in 30 cc. of acetic anhydride was added under stirring 5 drops of acetyl bromide. The reaction temperature rose spontaneously from 10 to 18° after fifteen minutes and all of the diol crystals went into solution. When the solution was stirred at 15° during additional fifteen minutes, a good quantity of long needles separated again. A small portion of this solid substance was taken out, pressed on a porous tile and recrystallized from ligroin. The product melted at 120–121° and was identified by the mixed melting point with the monoacetate of β-3-*p*-anisyl-3,4-hexanediol. If the reaction mixture was allowed to react further at the same temperature, the solids dissolved for the second time and a clear solution was obtained after five hours of stirring. At this stage, the solution was poured into ice-water added with several drops of pyridine. The oily product was extracted with benzene and the benzene solution washed with dilute hydrochloric acid, water, dilute sodium carbonate solution and finally with water, dried over anhydrous sodium sulfate and evaporated. The residue formed yellowish liquid and did not solidify in spite of several attempts. When 0.5 g. of the product was treated with semicarbazide in dilute alcohol, 0.5 g. of colorless plates, m. p. 128–130°, were obtained and found to be identical with the semicarbazone of 3-*p*-anisyl-4-hexanone (III) by a mixed melting point.

Attempted acetylation of the monoacetate of 3-*p*-anisyl-3,4-hexanediol with a mixture of acetic anhydride and acetyl bromide leads also to the formation of 3-*p*-anisyl-4-hexanone (III) as a result of the elimination of acetic acid.

***trans*-3,4-Di-*p*-anisyl-3-hexene.**—Starting from 4 g. of 3-*p*-anisyl-4-hexanone (III) above obtained, we prepared through 3,4-di-*p*-anisyl-3-hexanol *trans*-3,4-di-*p*-anisyl-3-hexene, m. p. 123–124° (mixed melting point!), according to the synthetical method of Kuwada,[2] Wessely[3] or Fieser[4] and respective collaborators; yield, 2 g.

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.08; H, 8.01. Found: C, 80.56; H, 8.38.

Summary

1. *p*-Anisylglyoxal was obtained in good yields by the oxidation of *p*-methoxyacetophenone with selenium dioxide.

2. A new diastereomeric isomer of 3-*p*-anisyl-3,4-hexanediol resulted in the Grignard reaction of *p*-anisylglyoxal and ethylmagnesium iodide or of *p*-anisoylethylcarbinol and ethylmagnesium bromide.

3. Diethylstilbestrol was prepared also from this new *p*-anisylhexanediol in good yields.

KYÔTO, JAPAN RECEIVED[21] FEBRUARY 25, 1948

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[21] Original manuscript received April 29, 1947.

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Antitubercular Compounds. bis-(Aminoaryl)-cyclopropane Derivatives. 1-(2-Amino-4-thiazolyl)-2-(4-aminophenyl)-cyclopropane

BY DIETER G. MARKEES[1] AND ALFRED BURGER

On the basis of the correlation of the activity of DDT and similar chlorinated insecticides with the distribution coefficient of their "inhalation anesthetic" group,[2] the tuberculostatic activity of several compounds containing *p*-aminophenyl in place of *p*-chlorophenyl groups has been studied.[3,4,5,6] In the table of Läuger, Martin and Müller,[2] bis-*p*-chlorophenyl derivatives of cyclopropane were given an equally high insecticidal rating as the corresponding trichloroethane derivatives. Although these chlorinated cyclopropane derivatives were purely speculative[7] we decided to synthesize analogous bis-*p*-aminoaryl compounds for comparison with various bis-*p*-aminoaryl sulfones of proved chemotherapeutic value. The excellent pharmacological properties of Promizole (I)[8] suggested that we begin with a study of one of its cyclopropane analogs (II). A synthesis of II is recorded in this paper. An investigation of the bis-1,1- and -1,2-(4-aminophenyl)-cyclopropane series will be reported soon.

The starting material for the preparation of the diamine II was 2-phenylcyclopropanecarboxylic acid (III)[9] of which two stereoisomeric forms had been obtained by Burger and Yost.[10] Nitration of the lower-melting more abundant isomer yielded two mononitro derivatives. The chief product

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[1] Charles C. Haskell Post-Doctorate Fellow.

[2] Läuger, Martin and Müller, *Helv. Chim. Acta*, **27**, 892 (1944).

[3] Burger, Graef and Bailey, THIS JOURNAL, **68**, 1725 (1946).

[4] Graef and Burger, *ibid.*, **68**, 2400 (1946).

[5] Kirkwood and Phillips, *ibid.*, **69**, 934 (1947).

[6] Kirkwood, Phillips and McCoy, *ibid.*, **68**, 2405 (1946).

[7] Mylius and Koechlin, *Helv. Chim. Acta*, **29**, 405 (1946).

[8] Bambas, THIS JOURNAL, **67**, 671 (1945).

[9] Buchner and Geronimus, *Ber.*, **36**, 3782 (1903).

[10] Burger and Yost, THIS JOURNAL, **70**, 2198 (1948).