Although this compound is an indicator similar to Benzoyl Auramine G,[8] the color change from yellow to blue is not so sharp. The *p*H range is 4.0–5.2.

Anal. Calcd. for $C_{28}H_{33}N_3O$: N, 10.12. Found: N, 10.01, 9.95.

Solid Salts of Amines.—In working with the alkyl anilines used, it was found convenient to prepare solid derivatives by the use of 3,5-dinitrobenzoic acid. The salt of dimethylaniline has been prepared previously by the same method.[9]

0.002 mole of the dialkylaniline and 0.004 mole of the 3,5-dinitrobenzoic acid (0.002 mole with monobutylaniline) were dissolved in a few cc. of absolute alcohol and allowed to crystallize overnight. The salt was then recrystallized from absolute alcohol with char treatment. All the four salts crystallized as hexagonal prisms (see Table I).

TABLE I

3,5-Dinitrobenzoic acid salt of	M. p., °C., corr.	Nitrogen, % Calcd.	Nitrogen, % Found		Neut. equivalent Calcd.	Neut. equivalent Found
Diethylaniline	120	12.22	12.33	12.41	286.6	280
Di-*n*-propylaniline	118	11.65	11.84	11.90	300.5	294
Di-*n*-butylaniline	104	11.14	11.14	11.34	314.5	308
n-Butylaniline	98.5	11.63	11.40	11.49	361.3	352

Summary

In a study of the ketonimine dyes:

1. Di-*n*-butyldiaminodiphenylmethane, tetra-*n*-butyldiaminodiphenylmethane and tetra-*n*-propyldiaminodiphenylmethane have been synthesized. The picrates of the latter two are also given.
2. 4-Di-*n*-propylaminobenzoic acid has been made.
3. 4-Aminobenzophenonephenylimide and its hydrochloride have been prepared.
4. 4-Aminobenzophenonimine, 4-dimethylaminobenzophenonimine and 4-diethylaminobenzophenonimine have been made and characterized as their solid 3,5-dinitrobenzoic acid salts.
5. Benzoyl ethyl auramine was made, and its properties as an indicator are described.
6. The solid derivatives of diethyl-, di-*n*-propyl-, di-*n*-butyl- and *n*-butyl-aniline with 3,5-dinitrobenzoic acid have been prepared and characterized.

WASHINGTON, D. C. RECEIVED JUNE 2, 1936

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[8] J. T. Scanlan and J. D. Reid, *Ind. Eng. Chem., Anal. Ed.*, **7**, 125 (1935).

[9] C. A. Buehler, E. J. Currier and R. Lawrence, *ibid.*, **5**, 277 (1933).

[CONTRIBUTION FROM THE PEDIATRIC RESEARCH LABORATORY OF THE JEWISH HOSPITAL OF BROOKLYN]

Synthesis of Derivatives of Symmetrical Diphenylethane Related to Materials Occurring Naturally. I. Synthesis of the Ring System Proposed for Calciferol

BY SAMUEL NATELSON AND SIDNEY P. GOTTFRIED

A general and flexible method for the synthesis of compounds related to the naturally occurring derivatives of diphenylethane, which include compounds as widely distributed in nature as alkaloids, sterols, bile acids, sex hormones, toad poisons and cardiac aglycones[1] should be of value for the synthesis of degradation products and ultimately for the synthesis of some of the naturally occurring materials themselves.

This report offers a new route to this biologically important series which is capable of wide variation. As an example of its application, a compound having the ring system proposed for calciferol was synthesized in good yield. The formulas proposed by Windaus,[2] Heilbron,[3] Lettré[4] and Müller[5] assume that the phenanthrene ring is open to give a hydrogenated diphenylethane structure to calciferol and tachysterol.

As can be seen from the accompanying flow sheet, the starting materials for this synthesis are the readily available phthalic anhydride and phenylacetic acid.

Phthalic anhydride and phenylacetic acid condense in good yield to form benzal-phthalide (I).[6] The relationship of benzal-phthalide to the naturally occurring materials was recognized and this material and its derivatives were then built up to

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[1] L. F. Fieser, "Chemistry of Natural Products Related to Phenanthrene," Reinhold Publishing Co., New York City, 1936; L. F. Small, "Chemistry of the Opium Alkaloids," U. S. Treasury Dept., Supplement No. 103, 1932. These two monographs offer an inspiring and complete review of the literature on this subject.

[2] Windaus and Thiele, *Ann.*, **521**, 160 (1935).

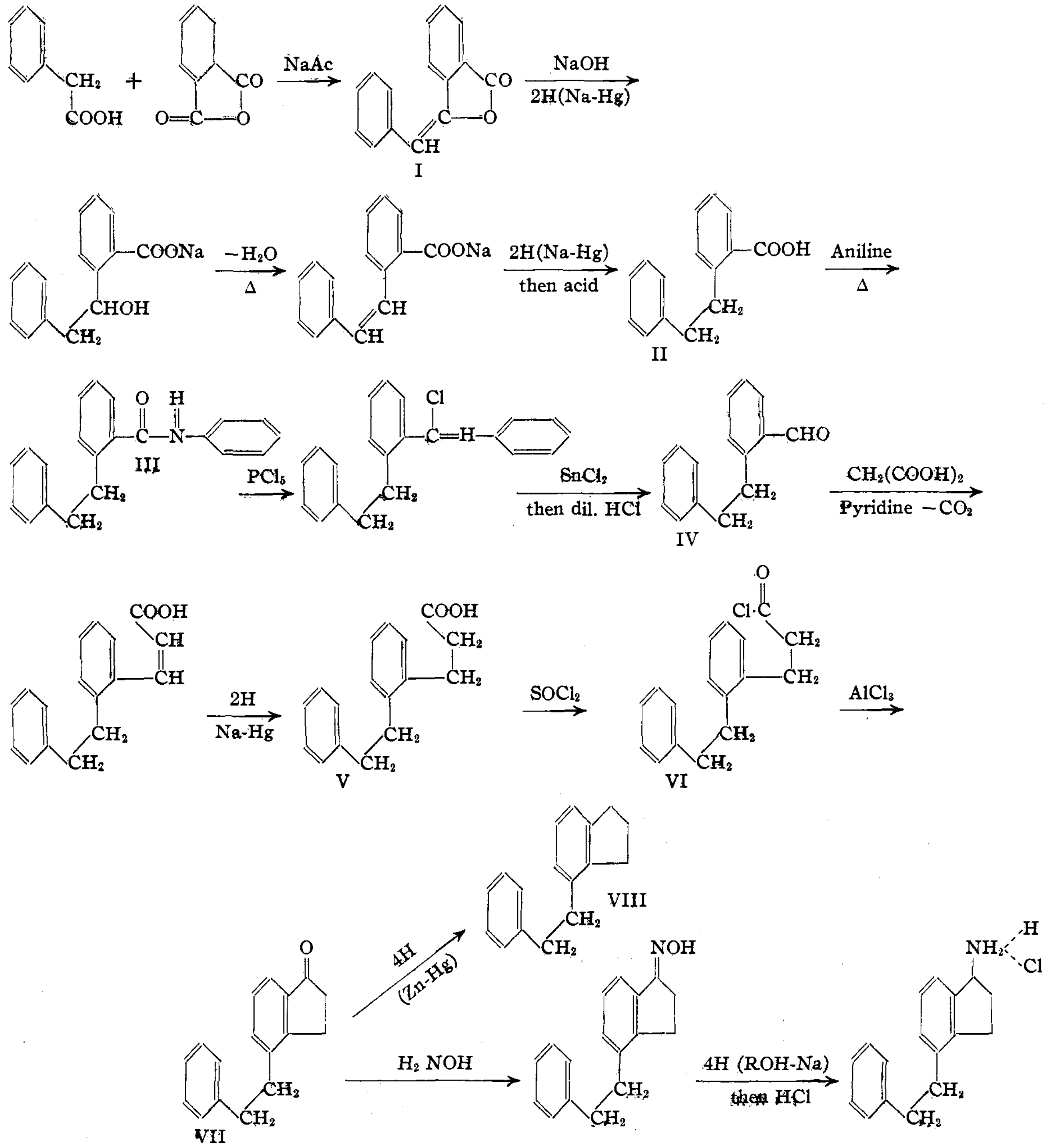
[3] Heilbron and Spring, *Chem. Ind.*, **54**, 795 (1935).

[4] Lettré, *Ann.*, **511**, 280 (1934).

[5] Müller, *Z. physiol. Chem.*, **233**, 223 (1935).

[6] "Organic Syntheses," Vol. XIII, 1933, p. 10; Gabriel, *Ber.*, **18**, 3470 (1885).

FLOW SHEET



form 4-β-phenethylindane (VIII), the structure proposed for the calciferol nucleus. This was accomplished by converting benzal-phthalide to o-β-phenethylbenzoic acid (II) by a reduction, dehydration and further reduction applying and improving the method of Gabriel.[7] The acid was then reduced to the corresponding aldehyde (IV) applying the general procedure of Sonn and Müller. Before this procedure was resorted to, several different methods of reduction had been tried, but all had been abandoned either because of poor yield or inability to be applied to large quantities. The following procedures were found to be inapplicable for preparing the aldehyde from the acid: catalytic reduction of the acid chloride, distillation of the calcium salt of the acid with calcium formate, reduction of the ester with sodium and butyl alcohol followed by chromate oxidation, reduction of the amide electrolytically and with so-

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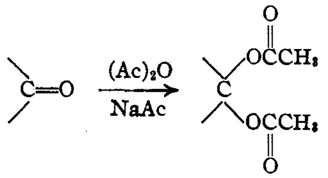
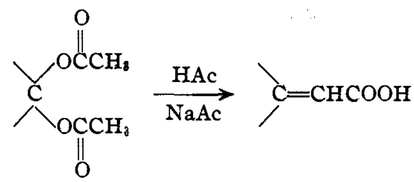
[7] Gabriel and Posner, *Ber.*, **27**, 2506 (1894).

dium amalgam, reduction of the anhydride (mixed) of this acid (II) and acetic acid.

When the Perkin reaction was applied to ortho-β-phenethylbenzaldehyde to form the substituted cinnamic acid, the main product of the reaction was found to be the substituted benzylidine diacetate, although some o-β-phenethylcinnamic acid was formed.



o-β-Phenethylbenzylidine diacetate when heated with sodium acetate in the presence of glacial acetic acid yielded the o-β-phenethylcinnamic acid. This would seem to be in line with the old Nef theory as to the mechanism of the Perkin reaction.[8]



Because of the poor yields obtained from the Perkin reaction when applied to o-β-phenethylbenzaldehyde (IV), this aldehyde was condensed quantitatively with malonic acid in the presence of small amounts of pyridine as a sort of modified Knoevenagel reaction. The reaction between malonic acid and the aldehyde in the presence of traces of pyridine is so satisfactory that it could be used to determine the percentage of aldehyde in a sample, by titrating the water-insoluble acid produced.

The o-β-phenethylcinnamic acid was then reduced to o-β-phenethylhydrocinnamic acid (V). This acid was then cyclized by treatment of its acid chloride (VI) with aluminum chloride in the presence of petroleum ether. The 4-β-phenethylindanone-1 formed was then reduced by the Clemmensen reduction to 4-β-phenethylindane, the ring system for the proposed structure for calciferol (vitamin D_2) and tachysterol. The formula of (VIII) is written in such a way as to indicate the close relationship to the cholane nucleus.

The over-all yield was good, 230 g. of benzal-phthalide yielding from 34–45 g. of the final product. As can be seen from the experimental part of this paper, the yields can be almost doubled if o-β-phenethylbenzoic acid is converted to its anilide (III) from its acid chloride by the action of thionyl chloride. The danger of using this method is that the whole yield can be ruined if traces of mercury, from earlier treatment, are present.

It is noteworthy that the ketone group in 4-β-phenethylindanone-1 is in the same position as the ketone group in androsterone and is in a favorable position for the addition of side chains in the synthesis of compounds related to sterols and bile acids.

It is apparent that by the use of substituted derivatives of phenylacetic acid and phthalic anhydride, various derivatives may be prepared. For example, 6-nitro-3-methoxyphenylacetic acid is being employed in an attempt to bring about a phenanthrene ring closure by the Pschorr method and at the same time prepare a cyclopentenophenanthrene derivative with an hydroxyl group in the same position as for cholesterol or androsterone. The close relationship between the alkaloids and sterols can be emphasized in that benzal-phthalide is closely related to benzylisoquinoline. This observation has suggested an attempt at a new method for the synthesis of benzyl isoquinoline alkaloids.

At the present time a mild reduction of calciferol and its degradation to a product which might be synthesized by this method has been undertaken to test the structure proposed for the antirachitic irradiation product produced from ergosterol.

Experimental

Benzal-phthalide.—Benzal-phthalide was prepared by the method of Weiss[6] using double the quantities specified. The yield of once crystallized material, m. p. 98–99°, is 77–84%. Care should be taken not to allow the temperature to rise above 240° for any length of time, for the yield may be completely destroyed.

Benzyl-phthalide.—Two hundred and thirty grams of benzal-phthalide is dissolved by heating with a solution of 60 g. of potassium hydroxide in 100 cc. of water. Benzal-phthalide is insoluble in hot dilute alkali. The dark red solution is then diluted to 1.5 liters with water and poured onto sodium amalgam, prepared by adding 2100 g. of mercury to 70 g. of molten sodium under mineral oil, with stirring. The solution is vigorously stirred until the color completely disappears, about four to six hours, depending upon the efficiency of the stirrer. The material is then transferred to a large separatory funnel and the mercury is drawn off. Ether is added and the mixture is shaken to remove traces of mineral oil. The lower layer is removed and acidified. The benzyl-phthalide comes down as an oil and then crystallizes in heavy colorless crystals which are

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(8) Nef, *Ann.*, **298**, 277 (1897).

filtered off, m. p. 61° (recrystallized from dilute alcohol); b. p. 190–200° (5 mm.); yield quantitative.

***o*-Carboxystilbene.**—The still moist benzyl-phthalide, from the above preparation, is dissolved in 400 cc. of 95% alcohol with warming; 60 g. of potassium hydroxide is added and the whole is gradually heated in a sand-bath, in a liter flask, until all the alcohol is removed and the light brown residue begins to foam, the temperature is raised to 180° and kept there until the foaming ceases and the whole material solidifies (two to four hours). The solid while still warm is dissolved in 1.5 liters of water. If this acid is desired, the solution is washed with ether, acidified, filtered and dried to give *o*-carboxystilbene. The yield is almost quantitative (210 g.); m. p. 160° (recrystallized from dilute alcohol).

***o*-β-Phenethylbenzoic Acid.**—The 1.5 liters of solution containing the dissolved sodium salt of *o*-carboxystilbene is added to an amalgam of 70 g. of sodium in 2100 g. of mercury. The mixture is stirred vigorously until a large part of the amalgam reacts. As the reaction proceeds, the solution becomes warm and remains warm until reduction is complete when it goes back to room temperature (four to six hours). The solution is transferred to a separatory funnel, the mercury separated and then washed with ether. All traces of colloidally suspended mercury must be removed if the acid is to be converted to the acid chloride. The solution is therefore filtered through two thicknesses of filter paper with suction, acidified and then either allowed to stand overnight or cooled with crushed ice to complete the crystallization of the acid. The acid is filtered off and dried at 60°; yield 210–211 g.; m. p. 130° (recrystallized from alcohol).

Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.64; H, 6.19. Found: C, 79.30; H, 6.27.

Acid Chloride of *o*-β-Phenethylbenzoic Acid.—Two hundred and ten grams of dried, mercury-free *o*-β-phenethylbenzoic acid is placed in a flask fitted with a reflux condenser; 400 cc. of thionyl chloride is slowly added through the top of the condenser. This large excess of thionyl chloride is necessary before the reaction will proceed to completion. The excess over the amount consumed is recovered on distillation at the end of the reaction. The acid slowly reacts and dissolves. When addition is complete a calcium chloride tube is placed on top of the condenser and refluxing is continued for one hour on a water-bath. The excess thionyl chloride is recovered under mild vacuum on a water-bath and the residue is distilled, preferably for so large a volume at less than 10 mm. The pale yellow distillate crystallizes when scratched after cooling; yield 190 g.; m. p. 50–55°; b. p. 202° (20 mm.), 180° (5 mm.).

Anal. Calcd. for $C_{15}H_{13}O_2Cl$: Cl, 14.52. Found: Cl, 14.39.

If traces of mercury are present, large amounts of hydrogen chloride are given off and the material turns black and resinifies on attempted distillation. The ability of the smallest traces of mercury to split out large amounts of hydrogen chloride has been pointed out already.[9]

Ethyl Ester of *o*-β-Phenethylbenzoic Acid.—Two hundred and ten grams of *o*-β-phenethylbenzoic acid was added to 500 cc. of absolute alcohol which had been saturated with dry hydrogen chloride. Dry hydrogen chloride was passed through the cooled mixture for one hour when a large part of the acid dissolves. The mixture is then refluxed gently, in the hood, for two hours when a heavy pale yellow oily lower layer is formed. The alcohol is distilled off and the residue is vacuum distilled on a glycerol bath. The yield of pure ester, pale yellow oil, which slowly hydrolyzes in air, is 210–220 g.; b. p. 205° (18 mm.); sp. gr. 1.063 (25°); $n^{29}\text{D}$ 1.5528.

Anal. Calcd. for $C_{17}H_{18}O_1$: C, 80.31; H, 7.09. Found: C, 79.99; H, 7.01.

When 64 g. of this ester is reduced with 40 g. of sodium in 400 cc. of anhydrous normal butyl alcohol with 150 cc. of toluene, 30 g. of a pale yellow liquid of b. p. 170–195° (20 mm.) is obtained. On fractional distillation this is separated into two fractions b. p. 177° (20 mm.) and 195° (20 mm.). On careful study neither of these seemed to be the alcohol. It is intended to make a detailed study of this reduction.

Mixed Anhydride of *o*-β-Phenethylbenzoic Acid and Acetic Acid.—Ten grams of *o*-β-phenethylbenzoyl chloride, 3 g. of sodium acetate and 8 g. of acetic anhydride are heated together for six hours at 180°. Water is added and the solution is neutralized with dilute sodium carbonate. The precipitate was filtered off and recrystallized from alcohol in which it is very soluble hot and insoluble cold; heavy colorless prisms which are rather inert but hydrolyze slowly on boiling in water. On hydrolysis by boiling in alkali and then acidification, *o*-β-phenethylbenzoic acid and acetic acid are obtained; m. p. 95°.

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.12; H, 5.97. Found: C, 76.21; H, 6.03.

***o*-β-Phenethylbenzanilide. Method 1.**—Two hundred and ten grams of dry *o*-β-phenethylbenzoic acid is placed in a liter, three-necked flask, fitted with thermometer, dropping funnel and bent tube leading to a receiver; 96 g. of aniline is added and the material is slowly heated in a sand-bath to 250° when about one-half the aniline distils over with some water. The melt is kept at 250° while 125 g. of aniline is added through the dropping funnel at such a rate that the temperature never drops below 240°. Aniline continues to distil through the bent tube into the receiver carrying the water formed in the reaction with it. After all the aniline has been added (three to four hours) the temperature is kept at 240° until all the aniline distils off. The melt is poured into an aluminum dish and allowed to solidify. The solid is ground to a fine powder in a mortar, washed with dilute hydrochloric acid, transferred back to the original flask and extracted with two hot 400-cc. portions of sodium carbonate solution containing 50 g. of sodium carbonate in each portion. The residue is filtered off, washed with water and recrystallized from hot alcohol, in which it is very soluble hot and difficultly soluble cold. On acidification, the combined sodium carbonate washings yielded 75 g. of the original acid. Hence the percentage yield should be based on 135 g. of the acid; yield 125 g. of the anilide, needle-like crystals slightly colored by this method; m. p. 137°.

Anal. Calcd. for $C_{21}H_{19}ON$: C, 83.72; H, 6.31; N, 4.64. Found: C, 84.22; H, 6.18; N, 4.58.

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(9) Natelson, *Ind. Eng. Chem.*, **25**, 1391 (1933).

Method 2.—One hundred and ninety grams of the pure crystalline acid chloride is ground in a porcelain dish with 180 g. of aniline. The mixture becomes warm and forms a homogeneous melt. When the reaction has ceased the mixture is heated further on a water-bath for thirty minutes at 90°. On cooling the mass solidifies and is washed with dilute hydrochloric acid and then warm dilute sodium carbonate. On recrystallization from alcohol colorless needles are obtained, m. p. 137°, yield 200 g.

o-β-Phenethylbenzaldehyde.—Three hundred grams of anhydrous stannous chloride, prepared by heating the hydrate over a small flame in a porcelain dish in the hood until all water has been removed and the material solidifies, is dissolved in one liter of anhydrous ether by passing a rapid stream of dry hydrogen chloride through the ether. Two layers form, the heavy oily lower layer contains the dissolved tin. Sonn and Müller in the preparation of this complex for reduction purposes dried their tin salt in a desiccator.[10] This does not dry the tin completely and accounts for inconsistent yields as reported by subsequent investigators. Evidence that their tin was never dry is evinced by the fact that their tin solution was homogeneous. This happens every time moisture gets into the reaction. If dry, the tin solution always separates into two layers before addition of the material to be reduced.

One hundred and twenty grams of recrystallized and dried *o*-β-phenethylbenzanilide is mixed with 110 g. of phosphorus pentachloride in a 500-cc. Claisen flask. The mixture is warmed in a water-bath until the mixture begins to liquefy. The flask is removed from the water-bath and shaken as the reaction proceeds slowly, until the mixture is all liquid except for the lumps of excess phosphorus pentachloride. The phosphorus oxychloride is removed under vacuum over a water-bath and the residue is dissolved from the excess phosphorus pentachloride by two 200-cc. portions of anhydrous ether. The ether washings are added to the stannous chloride solution and allowed to stand overnight. A vigorous reaction immediately ensues and the lower layer turns red, the tin complex of the aldehyde anil crystallizing out in yellow plates. The complex is filtered off from the heavy oily mixture and washed with ether, until the red color has been washed out; yield 138 g., yellow crystals, dec. 213°.

Anal. Calcd. for $C_{21}H_{20}NCl_3Sn$: N, 2.77. Found: N, 3.00.

To the crystals of the tin complex is added 50 cc. of 10% hydrochloric acid and steam is passed through the mixture in a steam distillation outfit. A pale yellow oil separates at the top of the solution and a small amount of the material steam distils over. The distillate and residue are combined and extracted with ether. The ether is dried over anhydrous sodium sulfate, filtered and the ether is evaporated off; yield 60 g. of a pale yellow oil; sp. gr. 1.089; $n^{29}D$ 1.5827.

Anal. Calcd. for $C_{15}H_{14}O$: C, 85.71; H, 6.67. Found: C, 86.00; H, 6.51.

Phenylhydrazone of o-β-phenethylbenzaldehyde was prepared by heating 1 g. of the aldehyde with a few drops of phenylhydrazine in 5 cc. of alcohol, adding water and recrystallizing from 80% alcohol; colorless feathery needles which turn brown on standing, m. p. 95°.

Anal. Calcd. for $C_{21}H_{20}N_2$: N, 9.33. Found: N, 9.02.

This aldehyde forms a sodium bisulfite derivative on long shaking with a saturated solution of sodium bisulfite.

o-β-Phenethylcinnamic Acid.—Sixty grams of *o*-β-phenethylbenzaldehyde is added to 35 g. of malonic acid in a 600-cc. flask fitted with a calcium chloride tube; 6 g. of pyridine is added and the mixture is warmed on a water-bath at 90° for two hours. The material separates into two layers and the lower layer slowly dissolves as carbon dioxide slowly is given off. At the end of two hours the material crystallizes on shaking or cooling. The material is dissolved in 40 g. of sodium carbonate dissolved in 500 cc. of warm water. If *o*-β-phenethylhydrocinnamic acid is desired the solution is reduced directly. If *o*-β-phenethylcinnamic acid is desired the solution is extracted with ether, to remove pyridine and impurities, acidified, filtered and dried. Drying has to be finished in a desiccator for this acid holds the last traces of water tenaciously; yield 71–72 g.; m. p. 149–150° (from dilute alcohol).

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.95; H, 6.34. Found: C, 80.31; H, 6.47.

o-β-Phenethylhydrocinnamic Acid.—The solution in sodium carbonate of *o*-β-phenethylcinnamic acid is poured directly onto sodium amalgam, prepared by dissolving 24 g. of sodium in 620 g. of mercury, and vigorously stirred until the solution has come back to room temperature and most of the amalgam has been decomposed (four to six hours). The mixture is transferred to a separatory funnel, the mercury separated, and the solution washed with ether. The aqueous layer is separated and filtered through a double suction filter. Since the next step is the conversion to the acid chloride, every trace of suspended mercury must be scrupulously removed even if it is necessary to filter several times. The solution is acidified, allowed to stand for several hours, filtered, washed with water and dried; yield 72 g.; colorless thick crystals; m. p. 110–111° (recrystallized from dilute alcohol).

Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.30; H, 7.08. Found: C, 80.11; H, 7.20.

Perkin Reaction on o-β-Phenethylbenzaldehyde

1. **With Sodium Acetate.**—Ten grams of the aldehyde, 2.5 g. of sodium acetate and 8 g. of acetic anhydride heated together for sixteen hours at 180–200° yields on extraction with sodium carbonate solution and acidification, 0.5 g. of *o*-β-phenethylcinnamic acid, m. p. 149–150° (from dilute alcohol), 1.0 g. of *o*-β-phenethylbenzylidine diacetate and 8 g. of unchanged aldehyde (average of several experiments).

2. **With Potassium Acetate.**—Ten grams of the aldehyde, 3 g. of potassium acetate and 8 g. of acetic anhydride heated together for six hours yield 1 g. of *o*-β-phenethylcinnamic acid, m. p. 149–150°, 8.6 g. of *o*-β-phenethylbenzylidine diacetate and practically no aldehyde. *o*-β-Phenethylbenzylidine diacetate melts at 85°.

Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.08; H, 6.41. Found: C, 73.51; H, 6.24.

3. **Conversion of the Diacetate to o-β-Phenethylcinnamic Acid.**—Eighteen grams of *o*-β-phenethylbenzylidine diacetate, 33 g. of acetic acid and 28 g. of sodium acetate heated at 200° for ten hours yields 10 g. of *o*-β-phenethyl-

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[10] Sonn and Müller, *Ber.*, **52**, 1927 (1919).

cinnamic acid, m. p. 149–150° (from dilute alcohol). The acids obtained from the Perkin reaction all reduced quantitatively to *o*-*β*-phenethylhydrocinnamic acid, m. p. 110–111°.

***o*-*β*-Phenethylhydrocinnamoyl Chloride.**—To 70 g. of *o*-*β*-phenethylhydrocinnamic acid is added 140 cc. of thionyl chloride. The mixture is refluxed for one hour and the excess thionyl chloride is removed on a water-bath. Vacuum is applied and everything that can be removed up to 100° at 10 mm. is removed. The material is transferred quantitatively with the aid of a small amount of ether to a 300-cc. distilling flask, which is sealed off at the top and connected by means of a wide side-arm to an inner seal in a 125-cc. receiving flask. The ether is evaporated off from the outfit under vacuum on a water-bath and the receiver is connected to a high vacuum produced by a mercury vapor pump backed by an oil pump. The traps are cooled with alcohol–solid carbon dioxide mixture while the receiver is cooled by an ordinary ice and salt-bath. The pressure is measured on a McLeod gage. The distilling flask is heated in a dibutyl phthalate bath. The temperature was determined by placing a thermometer in the bath. The acid chloride comes over as an almost colorless, pale yellow, mobile liquid at a bath temperature of 155–165° (slow heating) at a pressure of 0.002–0.004 mm.; yield 57 g. On heating with sodium hydroxide solution the acid chloride dissolves and on precipitation regenerates *o*-*β*-phenethylhydrocinnamic acid; m. p. 110°; b. p. 155–165° (0.002–4 mm.); sp. gr. 1.015; $n^{29}\text{D}$ 1.5664.

Anal. Calcd. for $C_{17}H_{17}OCl$: Cl, 13.27. Found: Cl, 13.20.

4-*β*-Phenethylindanone-1.—Fifty-seven grams of *o*-*β*-phenethylhydrocinnamoyl chloride is dissolved in 200 cc. of redistilled, over sulfuric acid, anhydrous petroleum ether, b. p. 45–65°, 57 g. of fresh anhydrous aluminum chloride is covered with 50 cc. of petroleum ether and the petroleum ether solution of the acid chloride is added, refluxing the solution on the water-bath. Refluxing is continued for one-half hour after the final addition. Almost all the color goes from the petroleum ether layer to the aluminum chloride which now becomes a deep brown. The mixture is cooled, decomposed with crushed ice and dilute hydrochloric acid and extracted with two 250-cc. portions of ether. The combined extracts are dried with anhydrous sodium sulfate, and the mixture of petroleum ether and diethyl ether is evaporated off. The residue is extracted with hot sodium carbonate solution to recover unchanged acid, dissolved in ether, washed with water, dried with anhydrous sodium sulfate and evaporated. The residue is then distilled under high vacuum as for the acid chloride. A pale yellow viscous oil comes over up to 160° at 0.0003 mm. A better vacuum could be maintained in the absence of the acid fumes; yield 42 g. of a viscous oil which gelled at room temperature but would not crystallize. It softens to a mobile liquid just below 38° and its melting point is probably in that vicinity. On standing for several months, during which time this compound was prepared numerous times in order to attempt to obtain it crystalline, the material partly resinified. The material as first obtained is of a high degree of purity as shown by analysis and in that it gave an 88% yield of oxime and a 92% yield of hydrocarbon on reduction.

Anal. Calcd. for $C_{17}H_{16}O$: C, 86.40; H, 6.80. Found: C, 86.08; H, 6.98.

4-*β*-Phenethylindanoxime-1.—Four grams of 4-*β*-phenethylindanone-1 is dissolved in 50 cc. of alcohol. To this mixture is added 1.6 g. of hydroxylamine sulfate dissolved in 6 cc. of water. Two drops of phenolphthalein solution are added and 10% potassium hydroxide solution is added drop by drop from a pipet until the solution is just alkaline. The mixture is refluxed and drops of alkali are added from time to time to keep the solution just alkaline. At the end of one hour the barely alkaline solution is allowed to cool, when flat glistening plates of the oxime crystallize out. If rapidly cooled the oxime comes out as needles, m. p. 135° (from alcohol in which it is very soluble hot and insoluble cold).

Anal. Calcd. for $C_{17}H_{17}ON$: N, 5.56; C, 81.31; H, 6.77. Found: N, 5.49; C, 81.40; H, 6.44.

4-*β*-Phenethylindanamine-1.—Three grams of 4-*β*-phenethylindanoxime-1 is dissolved in 100 cc. of absolute alcohol, 3 g. of sodium is added in small bits and the solution is refluxed under a condenser with a calcium chloride tube for one hour, the sodium dissolving. The solution is cooled and neutralized with concd. hydrochloric acid, 50 cc. of water is added and the alcohol is evaporated off. Some of the hydrochloride of the amine crystallizes from the aqueous solution at this point. The whole mixture is made alkaline with 10% sodium hydroxide and the amine is extracted with 50 cc. of benzene in two portions. The benzene solution is dried with anhydrous sodium sulfate and filtered. The dry benzene solution is saturated with dry hydrogen chloride and then evaporated to 10 cc. on a steam-bath; 75 cc. of anhydrous petroleum ether is added and the hydrochloride of the amine comes out in fine crystals. The crystals are filtered and washed with a 3 to 1 mixture of petroleum ether and benzene; yield 2.8 g.; m. p. 192°.

Anal. Calcd. for $C_{17}H_{21}NCl$: N, 5.12; Cl, 12.98. Found: N, 5.16; Cl, 12.96.

4-*β*-Phenethylindane.—Into a two-liter flask fitted with a reflux condenser, 300 g. of zinc dust is added and 4 g. of mercuric chloride dissolved in 25 cc. of hot water. The solution is slowly added to the zinc dust and thoroughly shaken and warmed.

Forty grams of 4-*β*-phenethylindanone-1 is dissolved in 500 cc. of alcohol which is added to the zinc dust from the top of the condenser; 400 cc. of concd. hydrochloric acid is added from the top of the condenser drop by drop refluxing the alcohol until all the hydrochloric acid has been added and a large amount of the zinc has dissolved (four hours). The condenser is turned down and the alcohol is distilled off. Care must be taken not to go too far, for the hydrocarbon which comes out as a colorless oil has a tendency to steam distil to some extent. The oil which separates at the surface of the residue is taken up in ether, dried with anhydrous sodium sulfate, filtered and the ether is evaporated off. The oil which remains is distilled under high vacuum to a colorless mobile liquid, b. p. 115–120° (0.0001 mm.); sp. gr. 1.020 (25°); $n^{29}\text{D}$ 1.5640; yield 34 g.

Anal. Calcd. for $C_{17}H_{18}$: C, 91.89; H, 8.11. Found: C, 91.31; H, 8.10.

The authors are indebted to Dr. B. Kramer and Albert E. Sobel for their advice and encouragement during the course of this investigation.

Summary

1. A new route to derivatives of diphenylethane related to materials occurring naturally is demonstrated.

2. 4-β-Phenethylindane is synthesized as representing the ring system for the proposed structure for calciferol and tachysterol.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

A Modification of the Clemmensen Method of Reduction[1]

BY ELMORE L. MARTIN

While a great many compounds containing the carbonyl group can be reduced by the method of Clemmensen,[2] the results sometimes leave much to be desired. Substances which neither dissolve appreciably in the acid mixture nor melt at the boiling temperature usually present difficulties and a number of readily available β-aroylpropionic acids which are of use in the synthesis of polynuclear hydrocarbons are of this type. Thus Fieser and Peters[3] observed that β-3-acenaphthoylpropionic acid is but little affected by prolonged boiling with hydrochloric acid and amalgamated zinc, Haworth and Mavin[4] found β-1-methyl-4-naphthoylpropionic acid to be unusually resistant to reduction, and Cook and Hewett[5] were unable to reduce β-1-pyrenoylpropionic acid by any of the usual modifications in the original procedure of Clemmensen. Although the addition of a miscible solvent such as alcohol, acetic acid, or dioxane facilitates the reduction of certain ketonic compounds (ketocholanic acids, hydrindones), this leads in the above cases only to resinification. The keto acid appears to undergo polymolecular reduction or condensation at the surface of the metal with the formation of a gummy, insoluble coating which obstructs the normal functioning of the zinc.

It was found by Fieser and Peters[3] and by Haworth and Mavin[4] that the reduction of the above two keto acids can be accomplished by the use of the lower-melting esters, but the yield in the first case was only 40% and the process was tedious. After repeating Fieser and Peters' experiments with the same results it was found that when toluene was added in quantity sufficient to retain the ester in a clear surface layer the yield of the pure reduction product rose to 60% and the process was greatly simplified. The surface of the metal remained clean and bright throughout the reaction and the product was easily isolated from the toluene layer. Attempts to reduce free β-3-acenaphthoylpropionic acid in the presence of toluene were successful only when a small amount of acetic acid was used to provide the required, slight concentration of the keto acid in the aqueous layer. The toluene probably is beneficial partly because it keeps the otherwise undissolved material out of contact with the metal and partly because in the two-phase system the reduction occurs at such a high dilution that polymolecular reactions are largely inhibited.[6]

Various fellow workers engaged in synthetic experiments in this Laboratory kindly coöperated in testing the toluene method, and the yields of purified products, usually checked in two or more experiments, are summarized in Table I. The author is indebted to Mr. C. K. Bradsher, Mr. J. T. Dunn, Mrs. L. F. Fieser, Dr. E. B. Hershberg, Mr. H. L. Holmes, Mr. W. C. Lothrop, Dr. M. S. Newman and Mr. C. C. Price for permission to report their results. The β-aroylpropionic acids investigated were invariably reduced more satisfactorily in the presence of toluene than without it, and two acids could be reduced in this way but not by the usual procedure. With β-1-pyrenoylpropionic acid, however, the results were negative both with and without toluene. The modification seems definitely advantageous with compounds containing methoxyl groups, for the difficulties frequently experienced are at least mini-

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(1) Paper prepared by L. F. Fieser.

(2) Clemmensen, (a) *Ber.*, **46**, 1838 (1913); (b) **47**, 51, 681 (1914).

(3) Fieser and Peters, THIS JOURNAL, **54**, 4374 (1932).

(4) Haworth and Mavin, *J. Chem. Soc.*, 2720 (1932).

(5) Cook and Hewett, *ibid.*, 398 (1933).

(6) Lewis, Ramage and Robinson [*ibid.*, 1414 (1935)] used anisole in two Clemmensen reductions but gave no results by the usual procedure for comparison.