

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

AN ATTEMPTED SYNTHESIS OF A TRICYCLIC SYSTEM
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The intricate sociological and political problems as well as the chemical aspects serve to give to morphine a position that is unique among organic compounds. With the collaboration of the Committee on the Study of Drug Addiction sponsored by the Rockefeller Foundation the author undertook the investigation of some synthetic methods which might possibly lead to a synthesis of at least a portion of the morphine skeleton. It may be stated at once that the projected program was not completed, but the results are now recorded because the author is temporarily engaged in other problems.

In view of the complex structure of morphine, any attempt at a final synthesis is desirably preceded by a series of preliminary syntheses each devoted to only a portion of the whole molecule. The object of such procedure is to determine not only whether or not the anticipated reactions are feasible experimentally, but the optimum conditions for each stage in the process. There are three homocyclic and two heterocyclic systems in the molecule, one of these containing a nitrogen bridge. Naturally occurring examples of the latter are rare, and are in general difficult to synthesize, and although the homocyclic systems present difficulties, it was felt that the crux of the synthesis lay in the availability of the nitrogen ring system.

It has been the object of the present work to synthesize the simplest example of such a structure, and the adjoining example (I) was chosen with this in mind, especially in view of the fact that a portion of the Robinson morphine structure is here represented.^{2,3} Two possible syntheses suggested themselves and the preliminary stages were conveniently carried on concurrently, especially in view of the fact that the now readily available ethyl α -cyano- β -phenylacrylate is the obvious starting point in both procedures.

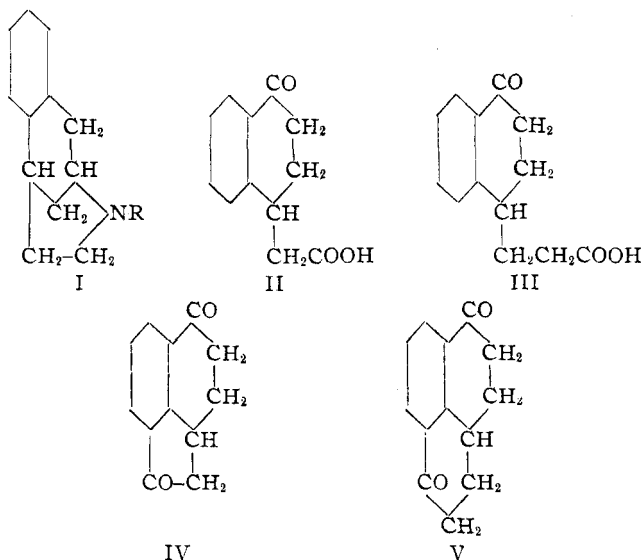
In the one series β -phenyladipic acid was synthesized from phenylsuccinic acid by the well-known stages involving the reduction of the ester to the glycol, converting this first into the dibromide, then into the dicyanide and ultimately hydrolyzing the latter. The yields in several of the stages were excessively poor so that the small amount of 1-keto-1,2,3,4-tetrahydronaphthalene-4-acetic acid (II) ultimately obtained by

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² Cahn and Robinson, *J. Chem. Soc.*, 909 (1926).

³ It is of considerable interest that the alkaloids of *Sinomenium acutum*, and particularly sinomenine, have been assigned constitutions closely related to morphine by Goto and by Kondo and their collaborators, *cf.*, *e. g.*, *Ann.*, **470**, 224 (1929).

ring closure of the acyl chloride with aluminum chloride was neither sufficient for further syntheses nor was it obtained in a satisfactory state of purity. In view of the fact that a small quantity of a tricyclic diketone (IV) was isolated from the Friedel-Crafts reaction product, it is almost certain that the acidic fraction is a mixture of the two possible keto acids, although von Braun, Bayer and Cassel⁴ in an analogous case succeeded in isolating only the six-membered ring compound.



In the second series the synthesis of γ -phenylpimelic acid from β -phenylglutaric acid by an analogous series of reactions proceeded somewhat more satisfactorily although much remains to be desired in the matter of yields. Furthermore, ring closure by means of the Friedel-Crafts reaction proceeded smoothly enough and purification of the resulting product, namely, 1-keto-1,2,3,4-tetrahydronaphthalene-4-propionic acid (III) presented no difficulties. There can be no question in this case of ambiguity of structure, a statement which also applies to the synthesis of hydrind-1-one-3-acetic acid, which was *inter alia* prepared from β -phenylglutaric acid by the same general method. The easy accessibility of the latter keto acid is conducive to its further study and the author hopes to place on record such an investigation in the near future.

As in the previous case a neutral product was obtained during the Friedel-Crafts reaction, examination of which proved it to be the tricyclic diketone (V). The two examples are of some theoretical interest because of the fact that in general it is rare that two carbonyl groups will enter the benzene ring except under drastic experimental conditions.

⁴ Von Braun, Bayer and Cassel, *Ber.*, 60, 2602 (1927).

The present observations are undoubtedly due to the particularly suitable orientation of the reacting groups.

Experimental Part

Phenylsuccinic Acid.—The procedure of Baker and Lapworth⁵ for the preparation of phenylsuccinic acid is somewhat inadequate when large quantities are desired. The direct addition product of hydrogen cyanide and ethyl α -cyano- β -phenylacrylate⁶ does not always crystallize. It is therefore extracted with ether from the acidified solution, the ether solution is thoroughly washed with water and the solvent distilled, the last small amount under reduced pressure. The residual addition product from 600 g. of unsaturated ester is heated overnight on a steam cone in a 5-liter round-bottomed flask with a mixture of 1200 cc. of concentrated hydrochloric acid and 800 cc. of water and then heated under reflux until hydrolysis and decarbonylation are complete. The mixture is then evaporated over a large Bunsen burner until unpleasant bumping commences, diluted to 4 liters with hot water, treated with norit and filtered hot. The mixture is rapidly cooled with vigorous stirring and when crystallization is complete the acid is filtered off on a large Büchner funnel, washed with iced water, drained as thoroughly as possible and then washed with about 800 cc. of benzene in small portions. The latter treatment serves to remove a greenish fluorescent material which is difficult to remove otherwise. The yield is 375 to 395 g. A further 20 g. may be obtained from the mother liquor and washings but the product is difficult to purify. As thus obtained the acid was used for the preparation of the ethyl ester, esterification being quantitatively effected by an adaptation of the continuous alcohol-carbon tetrachloride process recommended by Clarke and Davis⁷ for the preparation of ethyl oxalate. The pure ester is a viscous liquid boiling at 175° (16 mm.).

β -Phenylglutaric Acid.—The preparation of β -phenylglutaric acid from the addition product of ethyl sodiomalonate in absolute alcohol to ethyl α -cyano- β -phenylacrylate by hydrolysis and decarboxylation was satisfactorily accomplished only by vigorous boiling with 48% hydrobromic acid.⁸ The use of concentrated hydrochloric acid and of sulfuric acid of various concentrations was never satisfactory. In the former case boiling for ten days did not effect complete hydrolysis. A typical preparation is the following. A solution of 5 g. of sodium in 150 cc. of absolute⁹ alcohol is treated with 170 g. of dry

⁵ Baker and Lapworth, "Organic Syntheses," John Wiley and Sons, Inc., New York, 1928, Vol. VIII, p. 88.

⁶ α -Cyano- β -phenylacrylic acid may be esterified in 90% yield as follows. The acid (346 g.), absolute alcohol (690 cc.) and sulfuric acid (45 cc.) are heated under reflux for eleven to twelve hours (optimum yield). The mixture is cooled in ice, and the crystalline ester filtered off and washed with cold alcohol (290–300 g.). The mother liquor is evaporated somewhat and yields a second crop (100–110 g.) of less pure product, but sufficiently pure for the preparation of phenylsuccinic acid.

⁷ Clarke and Davis, "Organic Syntheses," John Wiley and Sons, Inc., New York, 1922, Vol. II, p. 23.

⁸ Avery and Bouton, *Am. Chem. J.*, 20, 510 (1898).

⁹ Smith, *J. Chem. Soc.*, 1288 (1927), has provided a general technique which suffices to remove the last traces of water from commercial "absolute" alcohol when the most exacting requirements are to be met. Instead of ethyl succinate, the less expensive ethyl phthalate (27.5 g.) is added to a liter of "absolute" alcohol in which 7 g. of sodium has been dissolved. The mixture is heated under reflux for about an hour and then distilled, taking precautions to exclude atmospheric moisture throughout the entire procedure.

ethyl malonate. The still warm mixture is treated with 200 g. of ethyl- α -cyano- β -phenylacrylate (dried in a vacuum desiccator) in one portion, heated gently under reflux for twenty minutes, cooled, acidified to Congo red and the addition product extracted with ether and thoroughly washed with water. (It has been noted repeatedly that about 15 to 21% of the theoretical quantity of sodium is amply sufficient and in fact the yield is always better than if a whole mole be used. It may also be pointed out that ethyl cyanoacetate seems to add to the unsaturated ester with equal facility but the resultant ester is much more resistant to hydrolysis, presumably because of the consumption of a mole of acid during the hydrolysis of the additional cyano group.) The oily addition product freed as far as possible from ether is heated with 350 cc. of 48% hydrobromic acid (a larger proportion of 40% acid is not as satisfactory and requires longer boiling) gently at first and vigorously after about an hour. Hydrolysis is generally complete in twenty-four to thirty hours. The mixture is diluted to one liter with hot water, boiled for some time with a generous portion of norite, filtered and cooled. The acid is filtered off, washed with cold water and with benzene (yield, 170–180 g.). Further purification by recrystallization from water is tedious and never yields an acid in compact well-formed crystals. However, if it is dissolved in one and one-half times its volume of boiling ethyl acetate and while still hot treated with an equal weight of benzene, slow cooling yields hard stout glistening prisms melting sharply at 140–141°. ¹⁰ The recovery is well over 80%, and in the preparation of large quantities the yield of pure acid varies between 75 and 85% when the various mother liquors are worked over.

Continuous esterification by means of alcohol-carbon tetrachloride yields the pure ethyl ester quantitatively as a colorless semi-viscous liquid boiling at 188° (18 mm.).

2-Phenylbutane-1,4-diol.—Seventy grams of sodium is introduced into a 3-liter round-bottomed flask immersed in cold water, fitted with a stirrer, reflux condenser protected by a drying tube, and a dropping funnel. A solution of 62.5 g. of ethyl phenylsuccinate in 800 cc. of absolute alcohol⁹ is added at the maximum rate just so that the reaction does not get out of control. When all has been added and the vigor of the reaction has subsided somewhat, the cooling water is gradually heated to boiling and the stirrer is started. In the course of about two hours the sodium has dissolved. The mixture is treated with 400 cc. of water and 800 cc. of solvent is distilled off through a short column. The remaining small amount of alcohol is removed at a water pump and the glycol then extracted from the cooled residue with a mixture of equal quantities of ether and benzene. Three successive extractions with liberal quantities of solvent suffice and when a series of runs are made the volume of solvent can be greatly reduced by using the later extracts from one run for the first extraction of the next. The solvent from the combined and cautiously washed extracts is distilled off and the residue distilled. The crude glycol is collected at 150–180° (4 mm.) and the yield from 625 g. of ester is 210 to 220 g. As thus prepared it has been used for the subsequent preparation of the dibromide. Redistillation through a short column yields a viscous colorless oil of faint but pleasant odor reminiscent of rose, b. p. 165° (4 mm.). Attempts to obtain the glycol crystalline failed. On chilling, it set to a solid glass at –10°.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.29; H, 8.43. Found: C, 72.61; H, 8.39.

A characteristic derivative is the *bis*-phenylurethan obtained in the usual way. After two recrystallizations from alcohol, in which it is sparingly soluble when cold, it melted sharply at 113°.

Anal. Calcd. for $C_{24}H_{24}O_4N_2$: N, 6.93; Found: N, 7.03.

2-Phenyl-1,4-dibromobutane.—A mixture of 200 g. of the crude glycol and 100 cc. of acetic anhydride was saturated with a stream of dry hydrogen bromide. The heated

¹⁰ All melting points are corrected.

mixture was allowed to cool to room temperature and after twenty-four hours was again saturated with hydrogen bromide and finally heated on a steam-bath for several hours. The cooled product was copiously diluted with ether, thoroughly washed with water and with sodium bicarbonate solution, dried over calcium chloride, the solvent removed and the residue distilled under reduced pressure. The yield of a mobile heavy product boiling at 173–175° (16 mm.) varies from 275 to 295 g. The dibromide loses hydrogen bromide readily and in the course of several days turns dark and turbid. Further purification to a stable colorless product was not attempted.

β -Phenyladipic Acid.—A solution of 110 g. of sodium cyanide in 100 cc. of water and 500 cc. of alcohol was treated with 292 g. of the above dibromide and heated under reflux for twelve hours, during which time the heavy oil gradually dissolved and sodium bromide separated. The dark mixture was filtered through a layer of charcoal and the residue washed with alcohol. The alcohol in the filtrate was distilled off and the mixture extracted with ether–benzene. The solvent from the washed and dried solution was removed and the residue distilled under reduced pressure. An appreciable low-boiling fraction was discarded. The higher-boiling fraction (100 g.) was obtained at 190–200° (4 mm.) and hydrolyzed without further purification by an excess of aqueous alcoholic potassium hydroxide. Removal of the solvent, extraction of an appreciable amount of unsaponifiable product, and final acidification yielded to ether extraction a colorless oily acid which on cooling set to a semi-solid mass. Benzene was added and the colorless crystals filtered off and washed with the same solvent, in which the acid is practically insoluble; yield, 35 g. One recrystallization from ether–benzene yielded well-formed rhombic plates of β -phenyladipic acid, m. p. 146°. The acid is readily soluble in acetone, ether or alcohol, but practically insoluble even in hot water.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.86; H, 6.31. Found: C, 65.53; H, 6.28.

1-Keto-1,2,3,4-tetrahydronaphthalene-4-acetic Acid. II.—A mixture of 35 g. of β -phenyladipic acid and 100 g. of phosphorus pentachloride, which liquefied in a short time, was heated for three hours on a steam cone and then freed of volatile fractions at a water pump. The residue was diluted with 300 cc. of carbon disulfide and treated with 26 g. of anhydrous aluminum chloride in small portions. The mixture was gently warmed for fifteen minutes, then cooled and the supernatant layer of carbon disulfide decanted. The dark residue was decomposed with ice and dilute hydrochloric acid, and the reaction products extracted with ether. The ether solution was thoroughly washed with water and then the acid products were removed by shaking with several successive portions of aqueous sodium bicarbonate.

There remained in the ethereal solution a small amount of a neutral substance which was obtained as an oil on removal of the ether. In the course of several days it crystallized for the greater part. The adhering oil was largely removed on a porous plate and the still somewhat yellow resinous mass recrystallized from a large volume of petroleum ether–benzene (90:10). The substance was thus obtained in minute needles (yield, about 0.5 g.) melting at 149°. Its mode of preparation together with its physical properties and analyses show the substance to be 4,9-diketo-1,2,3,4-tetrahydroacenaphthene, IV.

Anal. Calcd. for $C_{12}H_{10}O_2$: C, 77.42; H, 5.38. Found: C, 77.62; H, 5.24.

The acidic products present in the sodium bicarbonate extract from the ethereal solution were recovered by acidification and extraction with ether. Attempts to obtain either the free acid or the methyl ester in a state of homogeneity were unsuccessful. In view of the isolation of the above diketone it is quite certain that there is present a mixture of the two theoretically possible isomers.

3-Phenylpentane-1,5-diol.—Using the same technique and the same molecular proportions as with the lower homolog, this glycol was obtained in a 60% yield based on

the crude product distilling at 175–185° (5 mm.). Redistillation yielded a colorless viscous oil of faintly pleasant odor boiling at 174° (4 mm.).

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.33; H, 8.89. Found: C, 73.44; H, 8.80.

Recrystallization of the *bis-phenylurethan*, prepared in the usual way, first from alcohol and then from benzene yielded stout well-defined prisms melting at 112–113°.

Anal. Calcd. for $C_{26}H_{26}O_4N_2$: N, 6.70. Found: N, 6.76.

3-Phenyl-1,5-dibromopentane.—Of the various procedures that were tried to convert the glycol into the dibromide, only the acetic anhydride–hydrogen bromide method gave encouraging results. Following the details given for the lower homolog, from 160 g. of the glycol there was obtained 230 g. of crude dibromide, b. p. 177–182° (16 mm.), the greater portion distilling at 180°. As thus obtained it loses hydrogen bromide readily, and in the course of several days darkens appreciably. It was characterized by conversion to *3-phenyl-1,5-diphenoxypentane*, the conversion being readily effected by heating for several hours with an excess of aqueous alcoholic sodium phenate. Removal of solvents and steam distillation to remove some volatile oily impurities yielded a viscous product which crystallized in the course of several days. After pressing out on porous tile it was twice recrystallized from benzene–petroleum ether and was thus obtained in stout prisms, m. p. 72°, sparingly soluble in alcohol.

Anal. Calcd. for $C_{23}H_{24}O_2$: C, 83.13; H, 7.23. Found: C, 82.91; H, 7.12.

It may be mentioned here that several attempts to obtain the lower homolog in an analogous way yielded only uncrystallizable oils. There appears to be a much greater tendency for the elimination of hydrogen bromide due to the greater stability of the conjugated system thus produced.

γ -Phenylpimelic Acid.—The conversion of the above dibromide to the dicyanide and subsequent hydrolysis to the acid proceeded with much better yields than in the preparation of β -phenyladipic acid. From 264 g. of the dibromide and 95 g. of sodium cyanide in aqueous alcohol there was obtained 156 g. of crude dinitrile, b. p. 200–215° (4 mm.). It was at once converted into the acid by hydrolysis with excess potassium hydroxide in dilute alcohol. Removal of the solvent and extraction of the alkaline liquid with several portions of ether to remove a small amount of unsaponified product and subsequent acidification and extraction with ether yielded, after drying and evaporation of the solvent, a colorless viscous oil which crystallized readily in contact with benzene. The yield of product, m. p. 83–84°, after filtering and washing with benzene, was 132 g. A further small amount was recovered from the mother liquor. Recrystallization from ether–benzene yielded stellate aggregates of fine needles melting at 84°. Recrystallization from water is difficult on account of the low melting point but stout prisms can be obtained in the course of several months. The acid is only very sparingly soluble in cold water and but slightly when hot.

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.10; H, 6.78. Found: C, 65.89; H, 6.78.

1-Keto-1,2,3,4-tetrahydronaphthalene-4-propionic acid, III.—Without modification this keto acid was obtained from γ -phenylpimelic acid by the procedure above outlined for the lower homolog. From 94.4 g. of the acid, 84 g. of phosphorus pentachloride, 60 g. of aluminum chloride, and 300 cc. of carbon disulfide, there was obtained 48 g. (53%) of slightly colored crystalline acid melting at 105–106°. It is readily soluble in benzene and sparingly in ether, and was easily recrystallized by cautious addition of ether to a concentrated solution in benzene. As thus obtained it consisted of large colorless plates melting sharply at 108–109°.

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.56; H, 6.42. Found: C, 71.54; H, 6.27.

The methyl ester was prepared in the usual way as a colorless viscous oil after distillation, but it could not be induced to crystallize.

Hexahydrobenznaphthene- α,α' -dione, V.—Corresponding to the diketo compound obtained from β -phenyladipic acid there was obtained, in the ethereal extract from the preparation of the ketonaphthalenepropionic acid, a neutral product after the removal of the acids by extraction with sodium bicarbonate solution. The dried ether solution on evaporation yielded a pale brown oil which crystallized on cooling. Filtration and cautious washing with ether, in which the compound is sparingly soluble, and recrystallization from a concentrated solution in benzene by the cautious addition of ether, gave colorless stout prisms (5 g.) which melted sharply at 111° .

Anal. Calcd. for $C_{13}H_{12}O_2$: C, 78.00; H, 6.00. Found: C, 77.55; H, 5.82.

Characterization by the preparation of the dioxime in alkaline solution with excess hydroxylamine yielded the desired substance in minute needles from acetone, m. p. $253\text{--}254^\circ$ with darkening. The dioxime is readily soluble in hot acetone but only sparingly so in hot alcohol or acetic acid.

Anal. Calcd. for $C_{13}H_{14}ON_2$: N, 12.17. Found: N, 11.55.

Hydrind-1-one-3-acetic Acid.—In the course of a preliminary investigation this compound was obtained in unsatisfactory yield by treating β -phenylglutaric anhydride¹¹ dissolved in nitrobenzene with finely powdered aluminum chloride. The procedure which was ultimately found to give satisfactory and consistent yields was analogous to that used in the preparation of the corresponding tetralone derivatives.

A mixture of 208 g. of β -phenylglutaric acid and 420 g. of phosphorus pentachloride was gently warmed on a steam cone until reaction was complete. The phosphorus oxychloride and excess pentachloride were removed in vacuo at 100° and the cooled residue treated with 200 cc. of carbon disulfide. The addition of 140 g. of powdered aluminum chloride in small portions induced a vigorous elimination of hydrogen chloride. When reaction was complete the carbon disulfide was removed at a water pump and the dark tarry residue decomposed with ice and hydrochloric acid. The crystalline product was filtered off, thoroughly washed with cold water, freed of neutral products by solution in sodium bicarbonate and reprecipitation (yield, 178 g.). Small quantities may be recrystallized from hot water, in which it is sparingly soluble, and it is then obtained in large colorless rhombic plates melting at 155° . Larger quantities may be recrystallized from benzene-petroleum ether.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.48; H, 5.26. Found: C, 69.43; H, 5.26.

Methyl Hydrind-1-one-3-acetate.—The crude acid (190 g.) dissolved in 700 cc. of absolute methanol was heated under reflux for fifteen hours with 15 cc. of concentrated sulfuric acid. Addition of water, extraction with ether-benzene, thorough washing, finally with aqueous sodium bicarbonate and removal of solvent, yielded a dark oil which was distilled under reduced pressure. The fraction boiling at $175\text{--}180^\circ$ (18 mm.) weighed 130 g. and solidified completely on cooling. Recrystallized from benzene-petroleum ether it consisted of large rhombic plates melting sharply at 54° .

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.59; H, 5.88. Found: C, 69.96; H, 5.86.

Addendum

In view of the low yields that were obtained in the preparation of the phenyl-glycols it was necessary to submit the method of reduction to a thorough examination to ascertain its validity. It had been observed that the toluene method described by Marvel and Tanenbaum,¹² which

¹¹ Adams and Noller, "Organic Syntheses," John Wiley and Sons, Inc., New York, 1925, Vol. V, p. 17.

¹² Marvel and Tanenbaum, *THIS JOURNAL*, **44**, 2648 (1922).

gave rather good yields in the case of δ -phenoxybutyl alcohol, did not improve the yields perceptibly when applied to the preparation of the phenyl-glycols. It has indeed been found that even in the preparation of the phenoxy-alcohol yields as good as previously recorded may be obtained by reducing ethyl γ -phenoxybutyrate (104 g.) with sodium (70 g.) in large pieces and absolute alcohol (650 cc.). At first the mixture is cooled to keep the reaction under control and then heated on a steam cone to dissolve the sodium completely. No stirring whatever is necessary. The alcohol is isolated in the usual way.

In one experiment where the ester contained considerable quantities of γ -phenoxybutyronitrile there was isolated also δ -phenoxybutylamine and a solid substance remained in the distillation flask which on recrystallization from benzene consisted of colorless needles and melted sharply at $94-95^\circ$. Analysis proved it to be α -phenoxybutyr- δ -phenoxybutylamide, $C_6H_5OCH_2CH_2CH_2CONHCH_2CH_2CH_2CH_2OC_6H_5$.

Anal. Calcd. for $C_{20}H_{27}O_3N$: C, 73.40; H, 7.65; N, 4.28. Found: C, 73.40; H, 7.78; N, 4.27.

ϵ -Phenoxyamyl Alcohol, $C_6H_5OCH_2CH_2CH_2CH_2CH_2OH$.—Ethyl δ -phenoxyvalerate (108 g.) in alcohol (800 cc.) was reduced as above described with sodium (70 g.). The alcohol isolated in the usual way was obtained as a colorless rather viscous oil, b. p. $164-166^\circ$ (17 mm.), which on cooling in ice solidified completely. At room temperature it remelted, yield, 75%. It was characterized by the preparation of the phenylurethan, which was obtained in stout prisms melting at $93-94^\circ$.¹³

In conclusion it may be pointed out that ethyl sebacate when reduced by the same molecular proportions of sodium gave 1,10-dihydroxydecane in 77% yield.

Summary

1. An attempt, thus far unsuccessful, has been made to effect the synthesis of a portion of the morphine nucleus.
2. The preparation of some intermediates, notably, β -phenyladipic and γ -phenylpimelic acids, is described.
3. Two unusual cases of the easy introduction of two carbonyl groups into the benzene ring by means of the Friedel-Crafts reaction have been discovered.
4. A note regarding the reduction of esters with sodium is appended.

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¹³ Von Braun, Deutsch and Schmatloch, *Ber.*, **45**, 1250 (1912).