Diethyl 3-Methyl-1-(or 2)-cyano-1,2-cyclobutane Dicarboxylate.—Eight g. of powdered sodium cyanide was placed in a 200-cc. round-bottomed flask containing a solution of 20 g. of diethyl α,α'-dibromo-β-methyl adipate in 15 cc. of absolute alcohol. The mixture was heated under reflux on the steam-bath for twenty-four hours. It was then cooled and filtered by means of suction to remove solid inorganic substances (sodium bromide and excess sodium cyanide). The solid material was washed with ether and the washings were added to the filtrate, which after the removal of the ether and alcohol boiled at 140 to 143° at 3 mm. The yield of diethyl 3-methyl-1-(or 2)-cyano-1,2-cyclobutane dicarboxylate was 8 g. or 63% of the theoretical; d_4^{20} 1.08854; n_D^{21} 1.44735.

Anal. Calcd. for $C_{12}H_{17}O_4N$: C, 60.2; H, 7.2. Found: C, 59.7; H, 7.2.

Hydrolysis of the Cyano Ester.—The cyano ester was hydrolyzed by treatment with hot barium hydroxide (20%) according to the method of Perkin.[2] From 8 g. of the ester was obtained 8.5 g. of the barium salt of the tricarboxylic acid; this corresponds to a yield of 67% of the theoretical.

Anal. Calcd. for $C_{16}H_{14}O_{12}Ba_3$: Ba, 50.8. Found: Ba, 50.9.

Summary

Diethyl α,α'-dibromo-β-methyl adipate has been converted by treatment with sodium cyanide in absolute alcohol into diethyl 3-methyl-1-(or 2)-cyano-1,2-cyclobutane dicarboxylate. The latter has been hydrolyzed to the corresponding cyclobutanetricarboxylic acid, which has been isolated in the form of its neutral barium salt.

The diphenyl and di-β-naphthyl esters of α,α'-dibromo-adipic acid have been prepared. Attempts at ring closure were unsuccessful with these esters.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE OKLAHOMA AGRICULTURAL AND MECHANICAL COLLEGE]

THE SYNTHESIS OF SOME NEW COMPOUNDS RELATED TO APOCYNIN AND APOCYNOL[1]

BY HENRY P. HOWELLS, B. H. LITTLE AND H. P. ANDERSEN

RECEIVED JULY 19, 1930 PUBLISHED OCTOBER 6, 1930

The syntheses described herein were undertaken originally with the aim of securing intermediates for a study of the effect of length of side chain upon the physiological properties of certain unstudied phenolic bodies related to guaiacol. In choosing the method of preparation for such intermediates as the acyl substituted guaiacols, the findings of Finnemore[2] on methods of obtaining acetovanillone appeared to answer our immediate problem. His work[3] suggested also new lines of thought that made the

---

[2] Perkin, *J. Chem. Soc.*, **65**, 580 (1894).

[1] This communication is an abstract of portions of theses submitted by B. H. Little and H. P. Andersen in partial fulfilment of the requirements for the degree of Master of Science at the Oklahoma Agricultural and Mechanical College.

[2] Finnemore, *J. Chem. Soc.*, **93**, 1520 (1908).

[3] Finnemore[2] pointed out that apocynol or α-(4-hydroxy-3-methoxyphenyl)-methyl carbinol and its demethylated product possessed certain structural similarities to epinephrine, and stated that these products were still under investigation since the

synthesis of our products seem even more interesting in a study of the relation of structure to physiological action.

Apocynin, a constituent of the extract from Canadian Hemp (*Apocynum cannabinum*) used in medicine mainly as a cardiac stimulant and a diuretic, was shown by Finnemore[4] to be identical with acetovanillone or (4-hydroxy-3-methoxyphenyl) methyl ketone. In order to obtain the latter substance in sufficient amounts for further study, a new synthesis[2] was devised in which apocynol, resulting from the hydrolysis of the product obtained by the action of vanillin benzoate with the Grignard reagent, was oxidized with a chromic acid mixture. The carbinol could not be obtained directly by reacting vanillin with methylmagnesium iodide. In the present work this reaction also failed to go when other alkylmagnesium halides were used with vanillin.

It was hoped that the above method for obtaining the benzoate of apocynol could be adapted here in the preparation of its ethyl, *n*-propyl, *n*-butyl and *n*-amyl homologs, which might serve as starting materials. These compounds would yield the desired homologs of apocynol and apocynin when subjected to suitable oxidation and hydrolytic changes. Such changes have been carried out with greatest success in the case of the *n*-butyl derivatives by modifying the work of Finnemore for similar transformations. The various modifications will be described in detail later, but two of the more important changes should be pointed out here. First, it was found essential to use molecular quantities in reacting vanillin benzoate with the Grignard reagent to form the α-(4-benzoxy-3-methoxyphenyl)-*n*-alkyl carbinols. This was accomplished through the use of the titration method of Gilman[5] and co-workers for determining R-Mg-X in the reagent. Second, alcoholic potassium hydroxide was used to hydrolyze the benzoate esters in place of aqueous potassium hydroxide as used by Finnemore in forming apocynol. The factor which necessitated this change was no doubt due to the decreased solubility in water of the higher molecular weight esters. Absolute alcohol possessed a marked advantage over water as a solvent in diminishing greatly the time required for the reaction and the degree of decomposition of the hydrolyzed product in the hot alkaline solution. Since the *n*-butyl members of the above groups of compounds were much more easily prepared than the *n*-propyl and *n*-amyl members of each series, and since the five carbon side chain appeared to be of sufficient length for representative pharmacological testing, only the work with the *n*-butyl compounds has been described in detail in this paper.

physiological properties promised to be of interest. Through private communication it was learned that he did not extend this work.

[4] Finnemore, *J. Chem. Soc.*, 93, 1513 (1908).

[5] Gilman, Zoellner and Dickey, This Journal, 51, 1576 (1929).

The faint vanillin-like odor of apocynin noted by Finnemore[2] suggested to us at the start that the present study might lead to some interesting observations of the relation between chemical constitution and odor. It was observed also that Nomura and co-workers had made in recent years a series of studies with homologs of zingerone and related compounds with the view of unraveling the relation between their chemical constitution and pungency. In one of the earlier papers[6] it was found that 4-hydroxy-3-methoxyphenylbutane, possessed a pungent taste similar to zingerone. Thus it appeared that the presence of the carbonyl group in the side chain of zingerone is not essential, although it did seem to produce some effect on the taste. In view of the latter fact, the isomeric ketones which are prepared in the progress of this work may be of additional value in a study of the effect on taste or odor produced by the shifting of the carbonyl group in the side chain. The work has not been sufficiently advanced to draw conclusions but the odor and taste of certain products described herein at least indicate that some interesting correlations along this line may be possible.

Experimental

Benzoate of Vanillin.—The method used by Popovici[7] for the preparation of this compound was modified as follows. To a solution of 50 g. of vanillin in 125 cc. of 10% sodium hydroxide there was added rapidly and with vigorous shaking 46 cc. of benzoyl chloride, cooling intermittently so as to allow the benzoate ester to crystallize out in small white globules. Excess benzoyl chloride was decomposed by addition of 50 cc. of 10% sodium hydroxide and shaking well. The precipitate was collected, washed with 2 *N* ammonium hydroxide followed by slightly warmed water, dried and crystallized from 75% alcohol, when it appeared as colorless, monoclinic needles, m. p. 77° (corr.); yield, about 78%. Popovici reported the m. p. as 78° and Wörner[8] gave 75°.

α-(4-Benzoxy-3-methoxyphenyl)-*n*-butyl carbinol, $C_6H_3(OCOC_6H_5)(OCH_3)(CHOHC_4H_9)$.—This compound was prepared by a method somewhat similar to that used by Finnemore[2] for obtaining the simpler methyl carbinol by the action of the Grignard reagent upon the benzoate of vanillin. The present Grignard reagent was prepared essentially by the method recommended recently by Gilman[5] and co-workers, using 37 g. of *n*-butyl iodide, 4.8 g. of magnesium, a small crystal of iodine and 10 cc. of anhydrous ether in a closed system. The titration method of Gilman and co-workers for estimating *n*-butylmagnesium iodide showed the yield of reagent to be about 70% in most of the runs. The diluted Grignard reagent was cooled with an ice-bath and to it was added dropwise with constant stirring 35 g. of vanillin benzoate dissolved in slightly warmed anhydrous ether. The mixture was stirred for three hours and then boiled gently for half an hour, after which it was cooled and decomposed with cracked ice and 2 *N* sulfuric acid. The ether layer was washed with a saturated sodium bisulfite solution, 1.0% sodium hydroxide, and water in the order named. The ether solution was saturated with carbon dioxide. dried over anhydrous sodium sulfate, filtered and evaporated under diminished pressure on a water-bath. A colorless oil remained which solidified largely upon cooling. The oily solid was washed with ligroin (b. p. 90–120°)

---

[6] Nomura and Hotta, *Sci. Repts. Tôhoku Imp. Univ.*, **14**, 119 (1925).

[7] Popovici, *Ber.*, **40**, 3504 (1907).

[8] Wörner, *ibid.*, **29**, 139 (1896).

and crystallized from 75% alcohol, when it appeared as colorless monoclinic needles, m. p. 109.3° (corr.); yield, about 48%.

Anal. Calcd. for $C_{19}H_{22}O_4$: C, 72.61; H, 7.06. Found: C, 73.05; H, 7.20.

The compound was soluble in alcohol, acetone, ether and glacial acetic acid, but insoluble in water. The crystals dissolved in concentrated sulfuric acid to give a red color, but dilute alcoholic ferric chloride gave no change.

α-(4-Hydroxy-3-methoxyphenyl)-*n*-butyl carbinol, $C_6H_3(OH)(OCH_3)(CHOHC_4H_9)$, was obtained by the hydrolysis of the above benzoate ester through a modification of the method used by Finnemore[2] for preparing the simpler homolog, apocynol. A solution of 3 g. of the benzoate in 50 cc. of 10% alcoholic potassium hydroxide was refluxed for thirty minutes. The alcohol was evaporated off under suction and the residue was dissolved in water. The solution was saturated with carbon dioxide and the precipitate which settled out was taken up in ether. The ether solution was dried over anhydrous sodium sulfate and then evaporated to a brown solid residue mixed with some oily impurity. The oil was insoluble in boiling ligroin (b. p. 90–120°) but the solid material dissolved and separated out upon cooling as colorless monoclinic crystals, m. p. 81.5° (corr.); yield, about 10%.

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.57; H, 8.57. Found: C, 68.10; H, 8.82.

The crystals dissolved in concentrated sulfuric acid to give a red color, and in dilute alcoholic ferric chloride to form a blue color. The product was soluble in alcohol, acetone, chloroform, ethyl acetate and dilute sodium hydroxide. The product possessed a very faint clove-like odor.

(4-Benzoxy-3-methoxyphenyl)-*n*-butyl ketone, $C_6H_3(OCOC_6H_5)(OCH_3)(COC_4H_9)$.—The corresponding carbinol was oxidized to the ketone derivative in essentially the same manner as described by Bogert and Howells[9] for the oxidation of acyl hydroquinones to the corresponding quinones. A solution of 10 g. of the carbinol in 50 cc. of warm glacial acetic acid was added slowly (ten minutes) to a mixture of 10 g. of potassium dichromate, 10 cc. of concentrated sulfuric acid and 100 cc. of water, while the solution was stirred vigorously. This stirring was continued for about ten minutes after all of the carbinol had been added, during which time the temperature was brought to about 85°, and then cooled. The mixture was diluted with an equal volume of water and, after a short period of standing, the precipitate was filtered off, washed well with water and dried. Recrystallized from alcohol, it gave colorless, shiny triclinic crystals, m. p. 88.1° (corr.) yield, about 92%.

Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.08; H, 6.39. Found: C, 72.87; H, 6.42.

The product was soluble in ether, acetone and chloroform, but insoluble in dilute sodium hydroxide. The crystals dissolved in concentrated sulfuric acid to give a yellow color. The product possessed no particular odor.

The phenylhydrazone when crystallized from alcohol gave colorless triclinic crystals, m. p. 163° (corr.); yield, about 46.5%. The crystals dissolved in concentrated sulfuric acid to give a yellow color. Nitrogen was determined by Milbauer's[10] modification of the Kjeldahl method.

Anal. Calcd. for $C_{25}H_{26}O_3N_2$: N, 6.96. Found: N, 6.94.

(4-Hydroxy-3-methoxyphenyl)-*n*-butyl ketone, $C_6H_3(OH)(OCH_3)(COC_4H_9)$, was obtained by the hydrolysis of the above benzoate ester, using the same method already described for the corresponding carbinol derivative. The solid residue which remained after evaporating off the ether was recrystallized from 25% alcohol. A mixture of color-

---

[9] Bogert and Howells, THIS JOURNAL, **52**, 837 (1930).

[10] Milbauer, *Z. anal. Chem.*, **42**, 725 (1903).

less monoclinic and triclinic crystals seemed to separate out, m. p. 62.9° (corr.); yield, about 90%.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.23; H, 7.69. Found: C, 68.95; H, 7.68.

The ketone did not possess the faint vanillin odor characteristic of the lower homolog, acetovanillone (apocynin), but it did carry a very faint pleasant odor. The product was soluble in alcohol, acetone, chloroform, ethyl acetate, hot benzene and toluene, and slightly soluble in hot water. The crystals dissolved in concentrated sulfuric acid to give a yellow color, and in dilute alcoholic ferric chloride to form a greenish-yellow color. The ketone was apparently decomposed by boiling 50% sulfuric acid with the evolution of products having a faint guaiacol odor mixed with a penetrating odor characteristic of some of the lower fatty aldehydes. The remaining solution turned a greenish-yellow color unlike the red color noted by Finnemore[2] in the case of apocynin.

Attempts were made to prepare the phenylhydrazone, β-naphthylhydrazone and *p*-nitrophenylhydrazone, but the products were all oils which were too difficult to purify. The semicarbazone seemed to form, but physical examination and color reaction pointed to it as being the starting material.

The diphenyl urethan was formed from diphenylcarbamine chloride in the usual manner. The product gave fluffy needles from alcohol, m. p. 121.5–123° (corr.); yield, about 52%.

Anal. Calcd. for $C_{25}H_{25}O_4N$: N, 3.47. Found: N, 3.30.

Comparative Yields of Carbinols from Vanillin Benzoate with Some Grignard Reagents.—In view of the findings of Gilman[5] and co-workers, that the even-numbered halides give yields of Grignard reagents higher than the preceding halides that have an odd number of carbon atoms and furthermore a gradual drop in yield results in a given series with the ascent of that series to halides of higher molecular weight, it might be expected that *n*-butylmagnesium bromide would give a better yield of the carbinol than that from *n*-propyl- or *n*-amylmagnesium bromide in the usual mode of synthesis. However, the relative yields obtained in this work cannot be accounted for in this way, since the titration method of Gilman and coworkers was used in correcting for molecular proportions of reagents. It was also found that *n*-butyl iodide gave better results than *n*-butyl bromide when used in the synthesis of the carbinol, although we had predicted greater success with the bromide, since the above workers found that with a given alkyl group the lower yields are with iodide and the higher with the bromide. Perhaps *n*-butylmagnesium bromide is too active and not only attacks the aldehyde part of vanillin benzoate but also reacts with the phenyl ester group giving rise to oily by-products. Recent work[11] on the relative reactivities of some Grignard reagents indicates butylmagnesium bromide to be much more reactive than the iodide. Further work is being done in this connection to determine the relative merits of R-Mg-I and R-Mg-Br in reactions of the above type.

α-(4-Benzoxy-3-methoxyphenyl)-*n*-propyl carbinol, $C_6H_3(OCOC_6H_5)(OCH_3)$-$(CHOHC_3H_7)$, was obtained by essentially the same method that was described for the

---

[11] Gilman, Heck and St. John, *Rec. trav. chim.*, **49**, 212 (1930).

n-butyl homolog. Colorless monoclinic crystals formed upon recrystallization from alcohol, m. p. 111.3° (corr.); yield, about 31.5%.

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 72.00; H, 6.67. Found: C, 71.61; H, 6.90.

The crystals were soluble in ether, chloroform and glacial acetic acid, but insoluble in water. The product dissolved in concentrated sulfuric acid to give a red color. The compound possessed a faint pleasant odor.

(4-Benzoxy-3-methoxyphenyl)-*n*-propyl ketone, $C_6H_3(OCOC_6H_5)(OCH_3)(COC_3H_7)$.—The above carbinol was oxidized readily by the method already described for the *n*-butyl homolog. Colorless triclinic crystals were obtained from alcohol, m. p. 79° (corr.); yield, about 51.5%.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.48; H, 6.04. Found: C, 71.82; H, 6.00.

The crystals were soluble in ether, acetone and chloroform, but insoluble in dilute alkali. The product dissolved in concentrated sulfuric acid to give a yellow color.

The phenylhydrazone when crystallized from alcohol gave colorless triclinic crystals, m. p. 175.5° (corr.). The crystals dissolved in concentrated sulfuric acid to give a yellow color.

Anal. Calcd. for $C_{24}H_{24}O_3N_2$: N, 7.22. Found: N, 7.12.

α-(4-Benzoxy-3-methoxyphenyl)-*n*-amyl carbinol, $C_6H_3(OCOC_6H_5)(OCH_3)(CHOHC_5H_{11})$, was also obtained by essentially the same method as described for its *n*-butyl homolog. The crude product was an oil mixed with about an equal amount of solid material, which was finally purified after considerable difficulty. Most of the oil was eliminated by pressing the crude product on a porous plate and allowing it to stand for several hours in a refrigerator. The mixture had a pleasant pungent odor along with a marked odor resembling that of valeric acid. The product was finally washed with ligroin and recrystallized from alcohol as colorless monoclinic crystals, m. p. 95.6° (corr.). The yield varied widely and usually resulted a bit below 10%, although one run seemed to give close to a 48% yield of a product which melted only a few degrees from the correct melting point.

Anal. Calcd. for $C_{20}H_{24}O_4$: C, 73.17; H, 7.32. Found: C, 72.91; H, 7.95.

The crystals were soluble in ether, chloroform, acetic acid and ethyl acetate, but insoluble in water. The product dissolved in concentrated sulfuric acid to give a red color.

The carbinol was oxidized with a chromic acid mixture for producing the ketone derivatives but the small amount of liquid product could not be sufficiently purified for complete identification. The small quantity of oil was apparently changed readily to the phenylhydrazone in the usual manner. The product after one crystallization from 75% alcohol gave colorless crystals, m. p. 134.6° (corr.). The crystals dissolved in concentrated sulfuric acid to give a yellow color.

Anal. Calcd. for $C_{26}H_{28}O_3N_2$: N, 6.73. Found: N, 6.65.

Summary

1. Some new derivatives of the *n*-propyl, *n*-butyl and *n*-amyl homologs of apocynol and apocynin have been prepared and described. The *n*-butyl derivatives are apparently the most readily obtained of the series and thus have been studied in detail to give the *n*-butyl homologs of apocynol and apocynin, which appear to be of interest in a study of the relation between structure and physiological action.

2. Tests on the comparative yields of the carbinols from vanillin benzoate and the Grignard reagent seem to indicate that R-Mg-I reagents are

superior to the R-Mg-Br type. Further work is being planned to determine the relative merits of the iodides and bromides in reactions of the above type.

STILLWATER, OKLAHOMA

[CONTRIBUTION NO. 61 FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

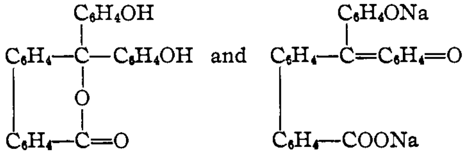
STUDIES IN THE DIPHENIC ACID AND PHTHALIC ACID SERIES. IV

BY H. W. UNDERWOOD, JR., AND G. E. BARKER[1]

RECEIVED JULY 19, 1930 PUBLISHED OCTOBER 6, 1930

I. The Structure of Phenoldiphenein

Phenoldiphenein dissolves in sodium hydroxide solution with the development of a light yellow color.[2] The apparently anomalous behavior of this compound makes it desirable to obtain evidence regarding its structure. The arrangement of the groups in phenolphthalein has been established by the isolation of *p,p'*-dihydroxybenzophenone and benzoic acid from the melt obtained by the fusion of the phthalein with potassium hydroxide. The analysis of the potassium salt of phenolphthalein and the preparation of a dimethyl ether show the presence of two acidic hydrogen atoms and two hydroxyl groups. An account of the application of these procedures to phenoldiphenein is given in this paper. The results of our experiments show that phenoldiphenein and its sodium salt are represented by the formulas



$$\begin{array}{lcl} \qquad C_6H_4OH & & \qquad C_6H_4ONa \\ C_6H_4{-}\overset{|}{\underset{|}{C}}{-}C_6H_4OH & \text{and} & C_6H_4{-}\overset{|}{C}{=}C_6H_4{=}O \\ | \qquad \overset{|}{\underset{|}{O}} & & | \\ C_6H_4{-}C{=}O & & C_6H_4{-}COONa \end{array}$$

Apparently the groups in diphenic anhydride give a light yellow instead of a red color to the sodium salt of the phenol condensation product.

Discussion of Experiments

All of the temperatures given are uncorrected.

Fusions of Phenolphthalein, Phenoldiphenein and the Fluorenone-phenol Condensation Product with Potassium Hydroxide.—A procedure which gave satisfactory results with phenolphthalein was first developed, and this was applied to phenoldiphenein and the fluorenone–phenol condensation product.

---

[1] Some of the experimental results described in this paper are taken from a thesis submitted to the Faculty of the Massachusetts Institute of Technology by G. E. Barker in partial fulfilment of the requirements for the degree of Bachelor of Science.

[2] Underwood and Kochmann, THIS JOURNAL, **45**, 3071 (1923); **46**, 2069 (1924).