a pinch of sodium methylate was added was refluxed for one-half hour. On cooling, 16 g. of the ester precipitated. After recrystallization from methanol, the product melted at 122–123°.

Anal. Calcd. for $C_{14}H_{14}O_3$: sapn. equiv., 244. Found: sapn. equiv., 245.

2-Hydroxy-1-naphthalenepropio-N,N′-diphenylamidine.—One hundred grams of (I) was refluxed with 125 g. of aniline. Ammonia came off rapidly at first, then more and more slowly. After eight hours 86% of the theoretical ammonia had been driven off. The mixture was cooled and stirred into 400 cc. of ethanol and allowed to stand overnight. The product, which was removed by filtration and washed with ethanol weighed 123 g. and melted at 147°. After recrystallization from xylene, it melted at 150–151°.

Anal. Calcd. for $C_{25}H_{22}ON_2$: N, 7.64. Found: N, 7.87.

It has been discovered in preliminary tests that the 2-hydroxy-1-naphthalenepropionic acid is moderately effective as a root growth promoter when applied to chrysanthemum cuttings and is of some value as a spray material to reduce premature apple drop. It is hoped that this publication will stimulate investigation by others in various fields of possible utility.

Acknowledgment.—The author is indebted to Miss Marion Treiber for assistance in preparing a number of the amides tabulated above.

Summary

1. A new reaction is described in which α-(ω-cyanoethyl)-β-naphthol is obtained in excellent yield from acrylonitrile and β-naphthol.
2. Derivatives prepared from α-(ω-cyanoethyl)-β-naphthol include 2-hydroxy-1-naphthalenepropionic acid, its methyl ester, various amides and the N,N′-diphenylamidine.

AKRON, OHIO RECEIVED NOVEMBER 26, 1947

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

A New Synthesis of Atranol (2,6-Dihydroxy-4-methylbenzaldehyde) and the Corresponding Cinnamic Acid

BY ROGER ADAMS AND JEAN MATHIEU

In experiments designed to prepare products suitable for the synthesis of natural tetrahydrocannabinol,[1] techniques for certain reactions were developed which may be of general interest. A new synthesis of atranol was also discovered. The compounds desired are 2,6-dihydroxy-4-*n*-amylcinnamic acid and its ester. This preliminary work, however, has involved the synthesis of the corresponding 4-methyl derivatives, since orcinol is a much more readily accessible substance than olivetol (3,5-dihydroxy-*n*-amylbenzene).

Orcinol dimethyl ether can be formylated (I) in the position between the methoxyls by treating lithium orcinol dimethyl ether with methylformanilide.[1b] Demethylation of this product was attained only after an exhaustive study of different reagents. Anhydrous aluminum bromide proved successful and a 70% yield of 2,6-dihydroxy-4-methylbenzaldehyde (II) resulted. This product is known as atranol. It was first isolated by degradation of atranorin, a product occurring in various lichens, and its structure was determined by oxidation to *p*-orsellinic acid.[2] It has been synthesized by Pfau in low yields by the introduction of an aldehyde group into ethyl 2,4-dihydroxy-6-methylbenzoate (orcinol carboxylic ester), followed by saponification and decarboxylation.[3] The new method offers a much simpler and more satisfactory procedure. Anhydrous aluminum chloride under similar conditions gives primarily resins, although in very small runs (0.1 g.), a 30% yield of atranol could be isolated. With benzene as a solvent, aluminum chloride causes demethylation of only one methoxyl with formation of 2-hydroxy-6-methoxy-4-methylbenzaldehyde (atranol monomethyl ether). This compound has been described by Asahina,[4] who found it in the pyrolysate of stictinic acid and synthesized it from atranol.

Although atranol dimethyl ether (I) condenses with malonic acid in presence of piperidine with formation of an almost quantitative yield of the corresponding cinnamic acid,[1b] the unmethylated product, atranol(II), did not react similarly under the same conditions. The conversion of substituted aromatic aldehydes to the cinnamic acids by the Knoevenagel reaction has been exhaustively studied. In general the yields are excellent but previous investigators have noted the abnormally low yields of products when *o*- or *p*-hydroxybenzaldehydes were subjected to condensation under conditions entirely suitable to other substituted benzaldehydes.[5] The conditions found most satisfactory for the condensation of salicylaldehyde with malonic acid[5b] were (a) the use of a small amount of pyridine as catalyst resulting in a yield of 51% of 3-carboxycoumarin or (b) heating at 80° followed by twenty-four hours at room temperature in presence of trace amounts of a variety of tertiary bases such as lutidine, quinoline, etc. (methylacridine[1c] proved to be the best) resulting in a 66–77% yield of product. An explanation of the difficulty in the condensation of *o*- and *p*-hydroxybenzaldehydes was suggested by

(1) (a) Adams, McPhee, Carlin and Wicks, THIS JOURNAL, **65**, 356 (1943); (b) Adams and Carlin, *ibid.*, **65**, 360 (1943).

(2) Pfau, *Helv. Chim. Acta*, **9**, 650 (1926).

(3) Pfau, *ibid.*, **16**, 282 (1933).

(4) Asahina, *Ber.*, **66**, 943 (1933).

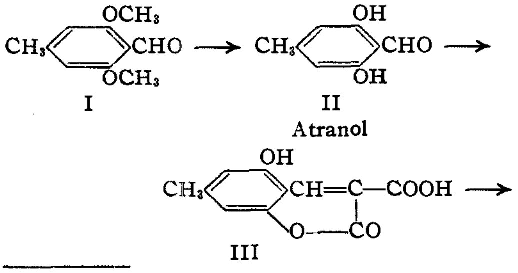
(5) (a) Dutt, *J. Indian Chem. Soc.*, **1**, 297 (1925); **9**, 309 (1932); (b) Kurien and Pandja, *ibid.*, **11**, 823 (1934); (c) *Proc. Indian Acad. Sci.*, **1A**, 440 (1935).

Vorsatz,[6] who pointed out that at the temperatures usually employed the *o*- and *p*-hydroxycinnamic acids readily decarboxylated with subsequent polymerization of the corresponding styrenes. He was able to overcome this side reaction by keeping the reactants at a relatively low temperature for a period of many days. He also observed that replacing the piperidine by aniline greatly accelerated the reactions. Thus, protocatechuic aldehyde, and 2,3,4-trihydroxybenzaldehyde condensed in better than 80% yield. In this investigation, the usual procedure with atranol and malonic acid failed but that described by Vorsatz using pyridine and aniline proceeded very satisfactorily to give a 75% yield of 3-carboxy-5-hydroxy-7-methylcoumarin (III). Aniline thus appears to be a catalyst of general utility for *o*- and *p*-hydroxybenzaldehyde condensations. Whether the mechanism involves intermediate formation of a Schiff base is now under investigation.

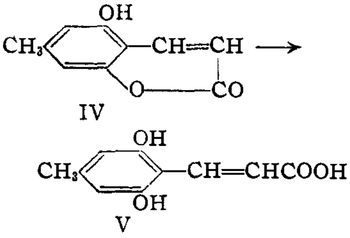
Sastry and Seshadri[7] have described the decarboxylation of 3,8-dicarboxy-5-hydroxy-7-methylcoumarin and report the formation of 8-carboxy-5-hydroxy-7-methylcoumarin. Since the melting point of their product is identical with that of the 3-carboxy derivative obtained in this research and prepared by an unequivocal method, it is probable that in the decarboxylation of the 3,8-dicarboxy derivative the 8-carboxyl group has been lost and that the product reported by Sastry and Seshadri is the 3-isomer.

The decarboxylation of 3-carboxy-5-hydroxy-7-methylcoumarin could not be accomplished with quinoline and copper and only a low yield of impure product resulted when the metal alone was used. It was discovered that aqueous sodium bisulfite was an excellent reagent for this purpose and 75–90% yields of 5-hydroxy-7-methylcoumarin (IV) was readily obtained. Presumably the coumarin is opened and carbon dioxide is lost without transforming the *cis*-cinnamic acid intermediate to the *trans* form. Sodium sulfite could not be used in place of sodium bisulfite.

The 5-hydroxy-7-methylcoumarin was hydrated to the *trans*-2,6-dihydroxy-4-methylcinnamic acid (V) in 65–85% yields by means of aqueous sodium sulfite. In the esterification of the acid produced, difficulties were encountered and only diazomethane gave satisfactory results.



I II Atranol III



IV V *trans*

Experimental

2,6-Dimethoxy-4-methylbenzaldehyde (Atranol Dimethyl Ether).—Modifications of Adams and Carlin's method[1b] were introduced to avoid special apparatus and to increase the yield. In a 200-ml. round-bottom flask provided with a dropping funnel, a mechanical stirrer and a reflux condenser fitted with a calcium chloride tube was placed 2.5 g. of lithium hammered to paper thickness under a layer of paraffin oil. The lithium was washed twice with anhydrous ether by decantation and covered with 100 ml. of anhydrous ether. The stirrer was started, 5 g. of *n*-butyl chloride was added all at once and the flask warmed gently to start the reaction. The reflux was maintained by dropwise addition of 15 g. of *n*-butyl chloride. Stirring was continued for about two hours when the lithium disappeared almost completely.

After addition dropwise of 25 g. of orcinol dimethyl ether, the stirrer was stopped and the flask placed in an oil-bath at 50° for eight hours. The oil-bath was removed, the stirrer started and a mixture of 25 g. of N-methylformanilide and 25 ml. of anhydrous ether introduced dropwise. At the end of the addition the mixture was heated for one more hour at 50°.

The product was poured over a mixture of 100 g. of crushed ice and 300 ml. of 3 *N* hydrochloric acid and extracted twice with ether (200 ml., 100 ml., 100 ml.). The combined ether extracts were washed with *N* hydrochloric acid, 10% aqueous sodium bicarbonate, water and dried over anhydrous sodium sulfate.

The ether was distilled and the residue was dissolved in 100 ml. of boiling cyclohexane. On cooling the aldehyde crystallizes in white needles and was filtered, washed twice with a little cyclohexane and finally with petroleum ether (b. p. 60–100°). The product was pure enough for the next step. From the mother liquor, a little more product was obtained but had to be crystallized from cyclohexane to be of acceptable purity. The yield in ten runs was between 12–16 g. (45–55%).

The melting point after crystallization from cyclohexane was 91–92° (Adams and Carlin,[1b] 91–92°).

2,6-Dihydroxy-4-methylbenzaldehyde (Atranol).—To a solution of 5 g. of atranol dimethyl ether in 250 ml. of carbon disulfide in a 500-ml. round-bottom flask fitted with a mechanical stirrer, 22 g. of aluminum bromide (3 moles per mole of aldehyde) in 250 ml. of carbon disulfide was added quickly with stirring. The addition complex precipitated as a red gum. After stirring for one hour the carbon disulfide was decanted into a separatory funnel and 100 g. of crushed ice, 150 ml. of 3 *N* hydrochloric acid and 200 ml. of ether was added to the residual gum in the flask and stirred until it was completely dissolved (one to two hours). The carbon disulfide in the separatory funnel was washed with 50 ml. of 3 *N* hydrochloric acid, the carbon disulfide layer discarded and the acid layer added to the mixture in the flask. The ether layer was removed and the aqueous layer extracted with two 200-ml. portions of ether.

The combined ether solutions were extracted with three 50-ml. portions of *N* aqueous sodium hydroxide. The atranol was precipitated from the alkaline solution by addition of 15 ml. of concentrated hydrochloric acid. The product was filtered, washed with a little water and crystallized from 125 ml. of boiling water (Norit). Yield, (average of twelve runs), 2.9 g. (70%) of slightly yellow product of adequate purity for the next step.

---

[6] Vorsatz, *J. prakt. Chem.*, **145**, 265 (1936).

[7] Sastry and Seshadri, *Proc. Indian Acad.*, **12A**, 498 (1940).

The product can be purified by crystallization from water, or toluene, and sublimation. It forms white crystals which start shrinking at 117° and melt at 123°; Pfau[3] reports m. p. 121° for his synthetic product and m. p. 124° for that obtained by degradation.

Anal. Calcd. for $C_8H_8O_3$: C, 63.15; H, 5.30. Found: C, 63.58; H, 5.40.

It was found that when working with larger runs, the yield was not as satisfactory. The conditions described were the best observed after careful study of many catalysts and solvents, modification of temperature and time.

Aluminum chloride, under similar conditions, gave only resins. In 0.1 g. runs, a yield of 30% could be obtained with this reagent.

2-Hydroxy-6-methoxy-4-methylbenzaldehyde (Atranol Monomethyl Ether).—A solution of 10 g. of atranol dimethyl ether in 200 ml. of benzene and 10 g. of aluminum chloride was placed in a 250-ml. round-bottom flask and stirred mechanically at room temperature. The complex, a dark liquid, formed in about ten minutes and the mixture was then heated for ten minutes at 85° without stirring.

The product was poured onto a mixture of 100 g. of crushed ice and 100 ml. of 3 *N* hydrochloric acid. The precipitate was not filtered but 250 ml. of 3 *N* aqueous sodium hydroxide was added which took it into solution. The alkaline solution was washed with ether, acidified and extracted twice with ether. The combined ether extracts were washed with 10% aqueous sodium bicarbonate, water and dried over anhydrous sodium sulfate. The residue from the ether was distilled under reduced pressure; b. p. 110–112° (1 mm.); yield, 7.4 g. (80%). After purification from toluene, it has a m. p. of 82–83°; Asahina[4] reports a m. p. of 78°.

Anal. Calcd. for $C_9H_{10}O_3$: C, 65.05; H, 6.06. Found: C, 65.64; H, 6.24.

2-Hydroxy-6-methoxy-4-methylbenzaldoxime.—The oxime was prepared in the usual way and purified from ethanol, m. p. 150–151°.

Anal. Calcd. for $C_9H_{11}O_3N$: C, 59.66; H, 6.12. Found: C, 59.72; H, 6.06.

3-Carboxy-5-hydroxy-7-methylcoumarin.—A mixture of 10 g. of atranol, 15 g. of malonic acid (2 moles per mole of aldehyde), 20 ml. of pyridine and 0.4 g. of aniline was heated in an open flask on an oil-bath at 55°. After about four hours, the product crystallized as a yellow mass.

It was heated one more hour and decomposed by trituration with 200 ml. of *N* hydrochloric acid. The product was filtered with suction, dissolved in 200 ml. of *N* hydrochloric acid, and precipitated by addition of 20 ml. of concentrated hydrochloric acid. The yield was 11 g. (75%) of yellowish product of satisfactory purity for the next step. It may be purified by crystallization from acetophenone, m. p. 270–271°.

Anal. Calcd. for $C_{11}H_8O_5$: C, 60.00; H, 3.66. Found: C, 60.00; H, 3.80.

Aniline was the only catalyst used which resulted in a satisfactory yield of the desired product; pyridine, piperidine, pyridine with piperidine, pyridine with methylaniline, ammonia in alcohol, acetic acid and sulfuric acids failed as catalysts.

5-Hydroxy-7-methylcoumarin.—A mixture of 5 g. of 3-carboxy-5-hydroxy-7-methylcoumarin and 60 ml. of a 25% aqueous solution of sodium bisulfite was placed in a 250-ml., round-bottom flask fitted with a mechanical stirrer and a dropping funnel. The flask was warmed with a bare flame until the solution was complete, the mixture stirred for about five minutes and then boiled for about thirty seconds. To the solution 50 ml. of a 50% aqueous solution of potassium hydroxide was then introduced and at the end of the addition the solution was boiled for ten seconds.

The flask was cooled in a freezing mixture, and concentrated hydrochloric acid (about 40 ml.) was added dropwise which resulted in formation of an abundant white precipitate. After one hour in the freezing mixture, the product was filtered with suction, washed twice with water and dried. The yield was 3.0 to 3.5 g. (75–90%). The product was of satisfactory purity for the next step. It may be purified by crystallization from a 50% mixture of dioxane and water. The melting point was 215–216° identical with that reported by Sastry and Seshadri[7] for 8-carboxy-5-hydroxy-7-methylcoumarin. It is believed probable that Sastry and Seshadri had in hand the 3-carboxy derivative.

Anal. Calcd. for $C_{10}H_8O_3$: C, 68.18; H, 4.57. Found: C, 68.67; H, 4.99.

Decarboxylation by means of copper gave only a 10% yield of the same product. The use of quinoline–copper failed completely.

2,6-Dihydroxy-4-methyl-*trans*-cinnamic Acid.—A mixture of 8 g. of 5-hydroxy-7-methylcoumarin and 60 ml. of a 25% aqueous solution of sodium sulfite in a 250-ml. round-bottom flask fitted with a mechanical stirrer and a dropping funnel was heated and stirred. When complete solution had taken place, the mixture was brought to boiling and the flask placed for one hour and a half in an oil-bath at 100° without stirring.

The stirrer was started again and 30 ml. of a 50% aqueous solution of potassium hydroxide was added dropwise after which the mixture was brought to boiling for about fifteen seconds. Upon cooling in a freezing mixture and dropwise addition of concentrated hydrochloric acid (about 30 ml.) an abundant white precipitate formed. The yield was 7 to 8.5 g. (65–85%) of product of satisfactory purity for the next step. The product may be purified by crystallization from glacial acetic acid, m. p. 200° with evolution of carbon dioxide.

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 62.10; H, 5.40.

Methyl 2,6-Dihydroxy-4-methyl-*trans*-cinnamate.—A current of diazomethane, prepared by heating a solution of diazomethane in ether, was passed into a stirred solution of 6 g. of 2,6-dihydroxy-4-methyl-*trans*-cinnamic acid in 200 ml. of dried ether. The esterification was followed by dipping blue litmus first in the ether solution and "revealed" by dipping in water (one test per minute). After about twenty minutes the esterification was complete and 100 ml. of a 10% aqueous solution of sodium bicarbonate was added all at once to decompose the excess of diazomethane.

The liquid was placed in a separatory funnel and washed with *N* hydrochloric acid, 10% aqueous sodium bicarbonate, water and dried over anhydrous sodium sulfate. The yield was 6 g. (95%). It was purified by crystallization from 40 ml. of a mixture of water and ethanol (2:1), m. p. 184–185°.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.82; H, 5.98.

The usual method of esterification with methanol and sulfuric acid, hydrogen chloride or *p*-toluenesulfonic acid was unsatisfactory. The use of silver oxide and methyl iodide also failed.

Summary

1. The preparation of 2,6-dimethoxy-4-methylbenzaldehyde has been simplified. By demethylation with aluminum bromide, 2,6-dihydroxy-4-methylbenzaldehyde, atranol, is produced.

2. Atranol condenses with malonic acid in presence of pyridine and aniline to give 3-carboxy-5-hydroxy-7-methylcoumarin.

3. Aqueous sodium bisulfite readily causes decarboxylation of 3-carboxy-5-hydroxy-7-methylcoumarin to 5-hydroxy-7-methylcoumarin.

4. For hydration of the coumarin, aqueous sodium sulfite is satisfactory and 2,6-dihydroxy-4-methyl-*trans*-cinnamic acid results. The acid can be esterified with diazomethane.

URBANA, ILLINOIS

RECEIVED MARCH 8, 1948