side; methyl tetrabenzoyl-β-D-glucopyranoside shows $+28.8°$ in 1:9 dioxane–methanol (c 0.27).

Acknowledgment.—We wish to thank Miss Paula M. Parisius for analytical determination incident to this research.

BETHESDA, MARYLAND

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

Preparation and Reactions of *o*-Hydroxycinnamic Acids and Esters

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The superiority of aniline–pyridine as a solvent and catalyst combination for the condensation of malonic acid with *o*- and *p*-hydroxybenzaldehydes has been demonstrated. The use of aqueous sodium bisulfite for the decarboxylation of 3-carboxycoumarins has been shown to be of general application. Although methyl *o*-hydroxycinnamate condenses with isoprene to form a pyrone in low yield, *o*-hydroxy- and 2,6-dihydroxycinnamic acids and the methyl ester of the latter do not react with isoprene under conditions similar to those which are effective with the analogous compounds having methoxy in place of hydroxy groups. When the hydroxy groups are protected with acetal linkages, either prepared from ethyl vinyl ether or dihydropyran, the addition of isoprene does not occur.

The low reactivity of *o*-hydroxycinnamic acid or ester with isoprene in the Diels–Alder reaction has been observed by previous investigators[2] in the field of natural products. An attempt has now been made to determine, if possible, conditions which might bring about the desired addition more satisfactorily and to observe the reactivity when the phenolic group or groups are blocked with acetal formation. A detailed study of the use of aniline[3] as a catalyst in obtaining *o*- and *p*-hydroxycinnamic acids has been made.

o-Hydroxycinnamic acid and 2,6-dihydroxycinnamic acid were selected as type compounds. Abnormally low yields were reported when *o*- and *p*-hydroxybenzaldehydes were condensed with malonic acid in the presence of pyridine–piperidine, whereas other aromatic aldehydes condensed very satisfactorily. Aniline[3] was found to be superior to piperidine in the condensation of 2,6-dihydroxy-4-methylbenzaldehyde with malonic acid to produce 3-carboxy-5-hydroxy-7-methylcoumarin (75% yield). The use of aniline was therefore applied to a similar condensation with various hydroxybenzaldehydes. The results which are listed in Table I indicate the high yields of products. *m*-Hydroxybenzaldehyde was included to demonstrate that aniline is not limited in its catalytic effect merely to the *o*- and *p*-hydroxy compounds.

The reactions proceeded without significant side reactions when the temperature was below approximately 55°. In the case of vanillin increasing the temperature 10° reduced the yield from 86 to 71%. In those compounds without an *o*-hydroxy group where cyclization could not occur, very little difficulty was encountered in obtaining the corresponding cinnamic acids under various conditions.

TABLE I

THE REACTION OF ALDEHYDES WITH MALONIC ACID

A, 3-carboxycoumarin, m.p. 187–189° (cor.); B, 3-hydroxycinnamic acid, m.p. 191° (cor.); C, 4-hydroxycinnamic acid, m.p. 210–211° (cor.) (dec.); D, 4-hydroxy-3-methoxycinnamic acid, m.p. 168.5–169.5° (cor.); E, 3-carboxy-7-hydroxycoumarin, m.p. 262° (cor.) (dec.); F, 3,4-dihydroxycinnamic acid, m.p. 194° (cor.) (dec.); G, 3-carboxy-5-hydroxycoumarin, m.p. 277° (cor.) (dec.).

Benzaldehyde	Product,[a]	Aniline, ml.	Pyridine, ml.	Moles ald.	Time in hr.	Temp., °C.	Yield, %
o-OH	A	0.05	1	0.0164	2	27	83
m-OH	B	.1	2	.0164	5	55	90
p-OH	C	.025	1	.0041	7.5	65	84
4-OH,3-OMe	D	.05	2	.0165	14	55	86
2,4-Di-OH	E	.075	2	.0167	12	27	71
3,4-Di-OH	F	.05	3	.0167	13	55	77
2,6-Di-OH	G	.075	5	.0347	20	27	83

[a] Previously prepared: A, U. S. Patent 2,338,569, Dow Chemical Company; B, K. C. Pandya and T. A. Vahidy, *Proc. Indian Acad. Sci.*, **4A**, 144 (1936); C, P. N. Kurian, K. C. Pandya and V. R. Surange, *J. Indian Chem. Soc.*, 11, 823 (1934); D, K. C. Pandya, T. S. Sodhi and D. S. Mittal, *Proc. Indian Acad. Sci.*, **9A**, 511 (1939); E, S. Rangaswami, T. R. Seshadri and V. Venkateswarlu, *ibid.*, **13A**, 316 (1941); F, see D; G, reference 10.

In the condensation of molecules with *o*-hydroxy groups, 3-carboxycoumarins formed. The temperature was critical and had to be maintained at that of the room in order to avoid substantial amounts of polymeric styrenes which appeared at higher temperatures. The other by-products, Schiff bases, were less when a minimum quantity of aniline was used. In a series of reactions using salicylaldehyde, no yield of 3-carboxycoumarin resulted when the ratio of pyridine to aniline varied from 20 to 50:1 and the reaction mixture was allowed to stand for 5–25 hours, either at 27 or 55°. However, a mixture of 0.05 ml. of aniline, 1 ml. of pyridine, 1.5 g. (1 mole equivalent) of salicylaldehyde and 2.4 g. (2 mole equivalents) of malonic acid gave a yield of 77–83% after 1–2 hours. With double the quantities of 2-resorcylaldehyde, the pyridine was increased proportionately but not the aniline.

2-Resorcylaldehyde was prepared by a method similar to that used for 2,6-dihydroxy-4-methylbenzaldehyde; resorcinol dimethyl ether, after treatment with n-butyllithium, followed by N-methylformanilide, gave 2-resorcylaldehyde dimethyl ether. This was demethylated with alumi-

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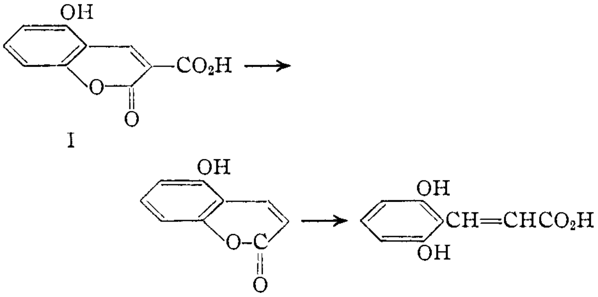
[1] An abstract of a thesis submitted by Mr. Theodore E. Bockstahler to the Graduate College of the University of Illinois, 1949, in partial fulfillment of the requirements for the Degree of Doctor of Philosophy.

[2] R. Adams, W. D. McPhee, R. B. Carlin and Z. W. Wicks, THIS JOURNAL, **65**, 356 (1943).

[3] R. Adams and J. Mathieu, *ibid.*, **70**, 2120 (1948); F. Vorsatz, *J. prakt. Chem.*, **145**, 265 (1936); U. S. Patent 2,338,569 [*C. A.*, **38**, 3671 (1944)].

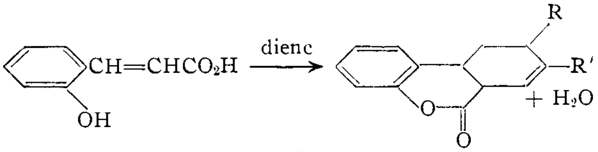
num bromide. 2-Resorcylaldehyde and malonic acid condensed to 3-carboxy-5-hydroxycoumarin (I). Upon heating this product with aqueous sodium bisulfite followed by strong aqueous sodium hydroxide, decarboxylation occurred with formation of 5-hydroxycoumarin (II). This procedure for decarboxylation was equally successful for producing coumarin from 3-carboxycoumarin, although refluxing with aqueous bisulfite followed by concentrated sulfuric acid instead of concentrated aqueous sodium hydroxide was preferable in this latter case in order to avoid contamination of the coumarin with *o*-coumaric acid. This method is probably applicable to any derivative of 3-carboxycoumarin.


I

II III

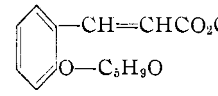
Treatment of 5-hydroxycoumarin (II) with aqueous sodium sulfite followed by aqueous potassium hydroxide,[4] a method previously described for converting coumarin to *o*-hydroxycinnamic acid, led to the desired 2,6-dihydroxycinnamic acid (III). By means of diazomethane the methyl ester of III was formed. Preparation of the methyl ester of III directly from the coumarin (II) by means of sodium methoxide failed, although this procedure was successful for obtaining methyl *o*-coumarate from coumarin.

When dienes and *o*-hydroxycinnamic acids or esters were heated in an autoclave, low yields of pyrones of type IV or V resulted. The same pyrone was produced whether the cinnamic acid or ester was used. Methyl *o*-coumarate and 2,3-dimethyl-1,3-butadiene reacted without solvent at 150° to give a 32% yield of pyrone.[5] In xylene the yields were lower.


IV, R = R′ = CH_3
V, R = CH_3; R′ = H

When isoprene was substituted for butadiene, no reaction occurred with *o*-coumaric acid or with 2,6-dihydroxycinnamic acid under various conditions. Methyl *o*-coumarate, however, gave a new pyrone whose structure is presumed to be V on the basis of the postulated mechanism of the diene reaction[6]; methyl 2,6-dihydroxycinnamate did not react similarly under the same conditions.

Since the dimethyl ether of 2,6-dihydroxy-4-methylcinnamic acid condensed[7] readily with isoprene but subsequent hydrolysis to the phenolic analog failed, the use of acetals as blocking groups,[8] which could be readily removed later, was attempted. Phenol and resorcinol are known to react with vinyl ethers to form stable acetals. The preparation of acetals from methyl *o*-hydroxycinnamate with dihydropyran and methyl 2,6-dihydroxycinnamate with both dihydropyran and ethyl vinyl ether was accomplished by using a trace of concentrated hydrochloric acid or, better, phosphoric acid as catalyst. Unlike the acetals of unsubstituted phenols, these ester acetals decomposed in part or completely on distillation. In spite of the sensitivity to heat, methyl *o*-(2-tetrahydropyranoxy)-cinnamate (VI) reacted with isoprene at 180–200° but yielded the same pyrone (V) which had been prepared from the ester with an unblocked hydroxy group. No addition products could be isolated from the bis-2-tetrahydropyranyl ether or the ethyl vinyl ether acetals of methyl 2,6-dihydroxycinnamate; in both cases 5-hydroxycoumarin (II) resulted from a decomposition of the acetals into their components followed by cyclization of the hydroxycinnamic acid.


VI

Experimental

2-Resorcylaldehyde.—A solution of 22 g. of freshly sublimed aluminum bromide in 400 ml. of carbon disulfide was placed in a 1-l. three-necked flask and stirred at maximum speed with a Hershberg stirrer. A boiling solution of 4.6 g. of 2,6-dimethoxybenzaldehyde[3] in 150 ml. of carbon disulfide was then added quickly and the mixture stirred without heating for 30 minutes. The dark red adduct formed a hard gum on the sides of the flask. The carbon disulfide was decanted into a separatory funnel, and 100 g. of crushed ice and 150 ml. of 3 *N* hydrochloric acid were added to the residual gum in the flask and stirred until the gum was decomposed. The carbon disulfide was washed with 50 ml. of 3 *N* hydrochloric acid, the carbon disulfide discarded, and the aqueous layer added to the mixture in the flask. The yellow precipitate was filtered and purified by recrystallization from 50 ml. of boiling water (Darco). Additional aldehyde could be recovered by ether extraction of the filtrate. This procedure was found superior to one involving extraction by base. The slightly yellow product weighed 2–3 g. (50–78%) and was of satisfactory purity for the next step. When sublimed, the aldehyde melted at 156.5–157° (cor.). Shah[9] reported 155–156°.

3-Carboxy-5-hydroxycoumarin.—A mixture of 7.2 g. of dry malonic acid, 5 ml. of pyridine and 3 drops of aniline was warmed carefully with stirring on a steam-bath until the acid was dissolved. To the warm solution was then added 4.8 g. of 2-resorcylaldehyde and stirring was continued until it became translucent. The mixture became a reddish-yellow color and was quite viscous. It was allowed to cool slowly to room temperature and left for 20 hours. After trituration with 50 ml. of 2 *N* hydrochloric acid, the yellowish solid was partially dried and then extracted with several small portions of ether. The insoluble residue weighed 6.0 g. (83%). It melted at 277° (cor.) (dec.) (lit. 272–274°).[10] The melting point did not change after recrystallization from nitrobenzene. Recovery of unreacted aldehyde was possible when the acidified filtrate was cooled in a salt–ice-bath.

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[4] B. B. Dey and K. K. Row, *J. Chem. Soc.*, **125**, 554 (1924); reference 3.

[5] W. D. McPhee and F. J. Ball, THIS JOURNAL, **66**, 1636 (1944).

[6] J. S. Meek and J. W. Ragsdale, *ibid.*, **70**, 2502 (1948).

[7] R. Adams and R. B. Carlin, *ibid.*, **65**, 360 (1943).

[8] W. E. Parham and E. L. Anderson, *ibid.*, **70**, 4187 (1948).

[9] R. C. Shah and M. C. Laiwalla, *J. Chem. Soc.*, 1828 (1938).

[10] H. A. Shah and R. C. Shah, *ibid.*, 1832 (1938).

5-Hydroxycoumarin.—A mixture of 4.2 g. of 3-carboxy-5-hydroxycoumarin and 56 ml. of a 20% aqueous sodium bisulfite solution was warmed slightly with a free flame while stirring rapidly. When decarboxylation was complete, a clear amber solution resulted. This was boiled 30 seconds, and then 45 ml. of a 50% aqueous potassium hydroxide solution was added in a steady stream. The red solution was then boiled 10 seconds and cooled in a freezing mixture. Dropwise addition of 60 ml. of concentrated hydrochloric acid produced a nearly colorless precipitate which was filtered after 2 hours of further cooling. The product was washed with two 25-ml. portions of water and then dried in a vacuum desiccator (P_2O_5). The product weighed 2.7 g. (82.5%) and was of satisfactory purity for the next step. A recrystallization with Darco from a large volume of water gave white woolly needles, m.p. 228.5–229° (cor.) (lit. m.p. 225°).[10]

Anal. Calcd. for $C_9H_6O_3$: C, 66.67; H, 3.73. Found: C, 66.57; H, 3.91.

2,6-Dihydroxycinnamic Acid.—A mixture of 2.6 g. of 5-hydroxycoumarin and 20.5 ml. of a 20% aqueous sodium sulfite solution was heated and stirred. When complete solution had occurred, the mixture was brought to boiling and the flask placed for 1.5 hours in an oil-bath at 100° without stirring. The stirrer was started again and 10.6 ml. of a 50% aqueous potassium hydroxide solution was added dropwise, after which the solution was boiled for 15 seconds. Upon cooling in a freezing mixture and dropwise addition of about 20 ml. of concentrated hydrochloric acid, an abundant tan precipitate formed. The product was filtered and recrystallized from 20 ml. of boiling water with Darco. After several similar recrystallizations, the acid formed colorless needles, m.p. 205° (cor.) (dec.). The yield of purified acid was 1.43 g. (52.5%).

Anal. Calcd. for $C_9H_8O_4$: C, 60.00; H, 4.48. Found: C, 60.08; H, 4.74.

Methyl 2,6-Dihydroxycinnamate.—A dried solution of diazomethane in ether was prepared from 2.5 g. of nitrosomethylurea. This solution was added dropwise with shaking to a solution of 1.00 g. of 2,6-dihydroxycinnamic acid in 50 ml. of dry ether. Esterification was complete when the solution remained yellow and blue litmus developed in water no longer tested acidic. Excess diazomethane was decomposed by the addition all at once of 25 ml. of a 10% aqueous sodium bicarbonate solution. The layers were separated, and the ether was washed successively with dilute hydrochloric acid, 10% aqueous sodium bicarbonate and water. The ether solution was then dried over sodium sulfate and evaporated to dryness. The white product weighed 0.94 g. (87%). The ester was decolorized in ethanol with Darco and reprecipitated by the addition of double the volume of water. The needle-like plates were best recrystallized from water, to which a few drops of ethanol were added while still hot, m.p. 185.5–186° (cor.).

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.83; H, 5.19. Found: C, 61.82; H, 5.39.

Decarboxylation of 3-Carboxycoumarin.—A mixture of 5 g. of 3-carboxycoumarin and 6 g. of sodium bisulfite in 20 ml. of water was warmed until no more was evolved. Then 20 ml. of concentrated sulfuric acid was added and refluxing was continued for one hour. The resulting solution was poured over crushed ice and filtered. After drying in a vacuum desiccator, the yield of coumarin was 3.6 g. (93.5%), m.p. 65–66.5° (cor.).

9,10-Dimethyl-7,8,11,12-tetrahydro-6-dibenzopyrone.—A mixture of 3 g. of methyl *o*-coumarate and 6 ml. of dimethylbutadiene was heated in a glass-lined bomb for 24 hours at 150°. The gummy crystals in the liner were washed out with cold ethanol and filtered. The crude pyrone was recrystallized from absolute ethanol and melted at 176.5–181° (cor.) and was obviously the same as that previously reported as melting at 181° after two sublimations.[2] The yield was 1.23 g. (32%). When the reaction was run in 2 ml. of xylene at 150°, the yield was 22%. When the reaction was run in 2 ml. of xylene at 180° for 44 hours, the yield dropped to 12.7%.

9-Methyl-7,8,11,12-tetrahydro-6-dibenzopyrone.—A mixture of 1 g. of methyl *o*-coumarate and 2.8 ml. of isoprene was placed in a glass-lined bomb together with a few crystals of picric acid and heated for 20 hours at 200°. The resulting solid was dissolved in boiling absolute ethanol and decolorized with Darco. When the filtrate was concentrated and cooled, transparent plates resulted. The crude pyrone was subjected to several recrystallizations from absolute ethanol or isopropyl alcohol, m.p. 140–140.5° (cor.). The yield was low. The same pyrone resulted when 2 ml. of xylene was used as a solvent.

Anal. Calcd. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.19; H, 6.77.

3,5-Bis-(β-ethoxyethoxy)-toluene.—To 7.2 g. of ethyl vinyl ether containing one drop of concentrated hydrochloric acid was added gradually 3.1 g. of orcinol with continuous mechanical stirring. The solution became warm within a few minutes and refluxing was prevented by external cooling when necessary. After the addition was complete, the solution was stirred at room temperature for 15 minutes and then 25 ml. of ether was added. The ether was extracted with three 15-ml. portions of 5% aqueous sodium hydroxide and three 15-ml. portions of water. After drying over sodium sulfate and removal of the ether, the oil was distilled, b.p. 110–115° (1 mm.), $n^{19}\text{D}$ 1.4835. The yield was 3.6 g. (54%).

Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.13; H, 9.01. Found: C, 67.11; H, 9.15.

Methyl *o*-(2-Tetrahydropyranoxy)-cinnamate.—To 1 g. of methyl *o*-hydroxycinnamate was added 3 ml. of dihydropyran. Solution did not take place until one drop of 85% phosphoric acid was added. Then a clear, slightly yellow solution formed. After 12 hours at room temperature, the solution was diluted with 10 ml. of ether and then extracted with five 10-ml. portions of 5% aqueous sodium hydroxide. The ethereal layer was dried over sodium sulfate and then freed of solvents and dihydropyran by evaporation at room temperature (aspirator). The resulting oil became a viscous liquid after 24 hours in a vacuum desiccator, and the index of refraction became constant, $n^{20}\text{D}$ 1.5329. All attempts to vacuum distil this tetrahydropyranyl ether without decomposition failed.

Phosphoric acid was found to be superior to concentrated hydrochloric acid for this reaction, since polymerization of the dihydropyran was prevented. Under these conditions, only traces of unreacted hydroxy ester were recovered from the basic washes. The use of ether or benzene as solvents for the reaction was not found desirable.

Methyl 2,6-bis-(2-tetrahydropyranoxy)-cinnamate and methyl 2,6-bis-(α-ethoxyethoxy)-cinnamate were made by a similar method. Neither could be distilled without decomposition.

Reaction of Isoprene with Methyl *o*-(2-Tetrahydropyranoxy)-cinnamate.—A mixture of 48 ml. of freshly distilled isoprene, 2.5 g. of unpurified methyl *o*-(2-tetrahydropyranoxy)-cinnamate and 5 crystals of picric acid was heated in a glass-lined bomb for 24 hours at 180°. The liner contents were extracted with two 50-ml. portions of absolute ethanol and crystals precipitated by the addition of water to the cloudy point. The precipitate was boiled with 5% aqueous sodium hydroxide until all dissolved, and after filtration the solution was acidified with concentrated hydrochloric acid. The solution was refluxed for 10 minutes when the oil became a solid. This was recrystallized from absolute ethanol, m.p. 140.3–140.5° (cor.). The product proved to be 9-methyl-7,8,11,12-tetrahydro-6-dibenzopyrone.

Reaction of Isoprene with Methyl 2,6-Bis-(β-ethoxyethoxy)-cinnamate.—Approximately 0.35 g. of the above cinnamate as prepared without distillation was placed in an autoclave together with 0.31 ml. of isoprene, 4 ml. of dry toluene and six crystals of hydroquinone. After being heated at 170° for 48 hours, the bomb was opened and a proportionately large quantity of crystals were found in the liner. Upon cooling additional crystals formed and were filtered off. These, after purification from xylene, melted at 228.5° and proved to be 5-hydroxycoumarin. The same product resulted when the addition of isoprene to methyl 2,6-bis-(2-tetrahydropyranoxy)-cinnamate was attempted.

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