TABLE I

RATE OF REACTION OF ALLYL BENZENESULFONATE WITH NaOEt IN ETHANOL AT 19.7°

Allyl benzenesulfonate, 0.0317 *M*; sodium ethoxide, 0.0398 *M*

Time, min.	Reacted, %	$k_2 \times 10^3$ (l. mole^{-1} sec.$^{-1}$)
39.2	19.6	2.67
52.7	27.9	3.07
69.3	32.2	2.80
83.5	35.0	2.62
101.7	41.0	2.73
151.2	52.1	2.75
220.3	61.6	2.67
307.1	71.2	2.73
	Weighted average	2.68
	Average	2.76 ± 0.09

The first-order rate constants were calculated from the equation

$$k_1 = \frac{2.303}{t} \times \log \frac{a}{(a - x)}$$

and the recorded value is an average of the individual values for k_1. The initial concentration of ester is represented by a, the other symbols are as given above. The variation in the rate constants for the runs at 20° was greater than those measured at higher temperatures. However, the estimated deviation in the constants is approximately 2 to 4%.

TABLE II

FIRST ORDER REACTION OF ALLYL BENZENESULFONATE WITH ABSOLUTE ETHANOL AT 25.10°

Allyl benzenesulfonate, 0.0345 *M*

Time, min.	Reacted, %	$k_1 \times 10^6$ (sec.$^{-1}$)
165	7.4	7.71
495	21.5	8.15
1213	44.5	8.10
1707	56.1	8.03
2702	72.4	7.93
4109	86.1	8.00
	Average	8.00 ± 0.11

TABLE III

REACTION RATES FOR THE ETHANOLYSIS OF ALLYL BENZENESULFONATE

Temp., °C.	Ester, mole/l.	NaOEt, mole/l.	$k_1 \times 10^6$, sec.$^{-1}$	$k_2 \times 10^3$, l. mole^{-1} sec.$^{-1}$
25.36	0.0469	0.0432	..	4.90
25.36	.0287	.0440	..	5.18
25.36	.0346	.0430	..	5.23[a]
19.70	.0317	.0398	..	2.68
19.70	.0304	.0445	..	2.63
19.70	.0317	.0422	..	2.73
14.70	.0250	.0448	..	1.57
14.70	.0287	.0418	..	1.52
34.79	.0344	....	23.3	..
34.79	.0492	....	23.8	..
25.10	.0345	....	8.0	..
25.10	.0419	....	7.9	..
20.15	.0408	....	4.5	..
20.15	.0332	....	4.2	..

[a] Solvent: 99% ethanol and 1% water.

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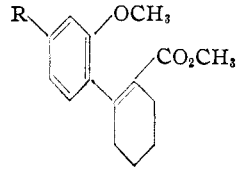
Coumarins as Possible Synthetic Intermediates[1]

BY V. BOEKELHEIDE AND A. P. MICHELS

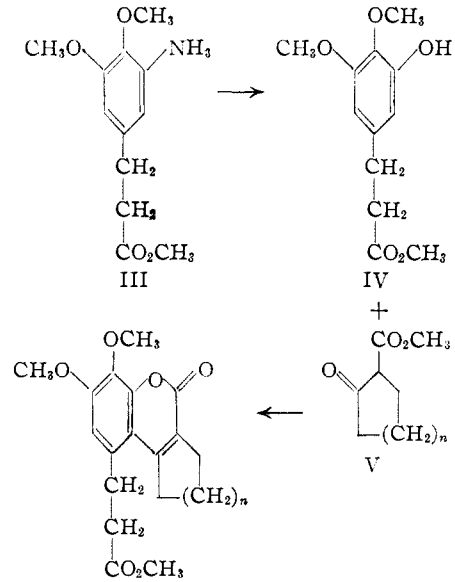
The von Pechmann coumarin condensation[2] is a convenient method for linking substituted aromatic compounds with alicyclic derivatives. Since the lactone ring of the resulting coumarins is susceptible to cleavage, intermediates can readily be obtained which would appear to have some value for the synthesis of certain natural products. It is the purpose of this note to describe some preliminary experiments directed toward this end.

As a model study directed toward the synthesis of morphine analogs, the intermediates I and II were prepared and treated with ethyl cyanoacetate in an attempt to obtain a Michael condensation. In each case the Michael condensation failed completely. Our work which was completed prior to recent publications on the limited reactivity of phenylcyclohexenone derivatives in the Michael condensation,[3,4,5] is further evidence of the limitations of the Michael reaction when applied to highly substituted molecules.



I, R = $-CH_3$
II, R = $-OCH_3$

Another possible application of coumarins as synthetic intermediates would be the synthesis of colchicine analogs. Thus, the condensation of a suitable phenol (IV) with β-keto esters, such as V, would yield intermediates of some promise for the synthesis of colchicine analogs in which the nature of ring C might readily be varied.[6] When



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the synthesis of III was attempted for this purpose, it was found that vanillin could be converted by the successive steps of nitration, condensation with malonic acid, and reduction to III, but that III could not be successfully diazotized to yield IV. However, other approaches utilizing coumarins for the synthesis of colchicine analogs are under investigation.

Experimental[7]

Methyl 2-(2′-Methoxy-4′-methylphenyl)-1-cyclohexenecarboxylate (I).—In accordance with the method of Canter and Robinson,[8] 14.3 g. of 3-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone[9] was dissolved in a boiling solution of 100 ml. of methanol and 100 ml. of 20% aqueous sodium hydroxide. The solution was cooled to 50° and 60 g. of dimethyl sulfate was added slowly with stirring followed by 200 ml. of a 20% sodium hydroxide solution. An additional 30 g. of dimethyl sulfate was then added dropwise, the solution was made basic and the mixture was extracted with ether. After the ethereal extract had been washed with water and dried, the ether was removed and the residue was distilled yielding 11.0 g. (62%) of a light yellow oil; b.p. 165–175° at 5 mm., $n^{27}D$ 1.5465.

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.84; H, 7.69. Found: C, 73.70; H, 7.71.

2-(2′-Methoxy-4′-methylphenyl)-cyclohexenecarboxylic Acid.—A solution of 4.0 g. of I in 30 ml. of methanol containing 5.0 g. of potassium hydroxide was boiled under reflux for two hours. When the cold reaction mixture was acidified with dilute hydrochloric acid, a white solid separated. This, on recrystallization from an ethanol–water mixture, gave 3.0 g. (85%) of white crystals, m.p. 175–176°.

Anal.[10] Calcd. for $C_{15}H_{18}O_3$: C, 73.17; H, 7.32. Found: C, 73.12; H, 7.35.

Methyl 2-(2′,4′-Dimethoxyphenyl)-cyclohexenecarboxylate (II).—This was prepared in the same manner as described for I. From 6.0 g. of 3-hydroxy-7,8,9,10-tetrahydro-6-dibenzopyrone)[9] there was obtained 2.5 g. (39%) of a light yellow oil, b.p. 175–180° at 5 mm.

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.53; H, 7.21. Found: C, 69.01; H, 7.06.

Attempts to obtain a condensation of either I or II with ethyl cyanoacetate under the usual conditions of the Michael condensation[11] were entirely unsuccessful and resulted in recovery of starting material. Also, hydrogen cyanide would not add to I.

3-Methoxy-4-hydroxy-5-nitrocinnamic Acid.—A solution of 32.5 g. of 5-nitrovanillin,[12] 88.0 g. of malonic acid and 2 ml. of piperidine in 100 ml. of dry pyridine was heated on the steam-bath for three hours, and then poured into a mixture of 100 g. of cracked ice and 80 ml. of concd. hydrochloric acid. The dark yellow solid, which separated, was washed with water and recrystallized from ethanol. There was obtained 36.0 g. (91%) of light yellow crystals, m.p. 230–231°.

Anal. Calcd. for $C_{10}H_9NO_6$: C, 50.25; H, 3.76; neut. equiv., 119. Found: C, 50.36; H, 3.80; neut. equiv., 124.

3-Methoxy-4-hydroxy-5-aminocinnamic Acid.—A solution of 10.0 g. of 3-methoxy-4-hydroxy-5-nitrocinnamic acid in 150 ml. of absolute ethanol was subjected to hydrogenation in the presence of Raney nickel catalyst at room temperature and 3 atm. pressure of hydrogen. Three moles of hydrogen was readily absorbed (90 min.). After removal of the catalyst and concentration of the solvent, there separated 8.3 g. (95%) of white crystals, m.p. 185–186°.

Attempts to convert this product to the corresponding phenol, 3-methoxy-4,5-dihydroxycinnamic acid, by means of the diazonium salt gave only intractable tars. Also attempted hydrogenation to the corresponding hydrocinnamic acid, using Raney nickel catalyst in the presence of base, failed.

Anal. Calcd. for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30. Found: C, 57.39; H, 5.20.

Methyl 3,4-Dimethoxy-5-nitrocinnamate.—A solution of 7.0 g. of 3,4-dimethoxy-5-nitrocinnamic acid[13] in 120 ml. of a saturated solution of methanolic hydrogen chloride was allowed to stand until separation of a yellow solid occurred. This was removed, washed with water and recrystallized from methanol. There was obtained 3.5 g. (48%) of creamy white crystals, m.p. 105–106°.

Anal. Calcd. for $C_{12}H_{13}NO_6$: C, 53.92; H, 4.87. Found: C, 54.22; H, 4.70.

Methyl 3,4-Dimethoxy-5-aminohydrocinnamate Hydrochloride (III).—A solution of 10.0 g. of methyl 3,4-dimethoxy-5-nitrocinnamate in 100 ml. of methyl acetate was subjected to low pressure hydrogenation using Adams catalyst. Four molar equivalents of hydrogen were rapidly absorbed. After removal of the catalyst and solvent, the residue was taken up in ether and treated with dry hydrogen chloride. This caused the separation of 8.9 g. (92%) of hygroscopic white crystals, m.p. 208–209° dec.

Attempts to convert III to IV by the usual procedures through the diazonium salt yielded only black intractable tars.

Anal. Calcd. for $C_{12}H_{18}NO_4Cl$: C. 52.27; H, 6.57. Found: C, 52.87, 51.60; H, 6.30, 6.21.

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Certain Derivatives of 2,5-Dihydroxyphenylacetic Acid

BY R. W. BOST* AND C. A. HOWE

Since 2,5-dihydroxybenzoic acid, gentisic acid, has been reported to exhibit anti-rheumatic activity,[1] it seemed desirable to establish whether 2,5-dihydroxyphenylacetic acid, homogentisic acid, and certain of its derivatives showed similar action.

2,5-Dimethoxyphenylacetic acid was synthesized through the Willgerodt reaction from 2,5-dimethoxyacetophenone by the procedure of Abbott and Smith.[2] Similar procedures were utilized to synthesize the 2,5-diethoxy-, 2,5-di-*n*-propoxy- and 2,5-di-*n*-butoxyphenylacetic acids. The amides and methyl esters of these four 2,5-dialkoxyphenylacetic acids were prepared by standard procedures. 2,5-Dihydroxyphenylacetic acid was synthesized by the demethylation of 2,5-dimethoxyphenylacetic acid[2] and also by the method of McElvain and Cohen.[3] The intermediate 2,5-dialkoxyacetophenones were prepared from the appropriate 1,4-dialkoxybenzene by Friedel–Crafts acylation.[2]

The molar refractions of the 2,5-dialkoxyacetophenones and methyl 2,5-dialkoxyphenylacetates show a considerable and fairly constant exaltation.

None of the compounds tested exhibited appreciable anti-rheumatic activity.

Experimental

2,5-Dialkoxyacetophenones.—The general method of Abbott and Smith[2] for the preparation of 2,5-dimethoxyacetophenone by the Friedel–Crafts acylation of 1,4-dimethoxybenzene was used. In the case of the di-*n*-propoxy- and di-*n*-butoxy-compounds, better yields were obtained if the aluminum chloride complex was hydrolyzed three hours after combination of the reactants was completed rather than allowing the mixture to stand overnight.

* Deceased.
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