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[12] 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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TABLE I

General name	Alkoxy groups	Yield, %	B.p., °C.[a] or crystn. solv.	Mm.	M.p.,[b] °C.	Molecular formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
2,5-Dialkoxyacetophenone	CH_3O	68	116	2	21°,[d]	$C_{10}H_{12}O_3$				
	C_2H_5O	52	129	3	41°[e]	$C_{12}H_{16}O_3$				
	n-C_3H_7O[f]	63	138	2	19°[e]	$C_{14}H_{20}O_3$	71.1	70.8	8.53	8.67
	n-C_4H_9O[g]	72	152	2	26°[e]	$C_{16}H_{24}O_3$	72.7	72.6	9.15	9.08
2,5-Dialkoxyphenylacetic acid	CH_3O	64	Water		123°[h]	$C_{10}H_{12}O_4$				
	C_2H_5O	37	37% EtOH		89	$C_{12}H_{16}O_4$	64.3	64.3	7.22	7.25
	n-C_3H_7O	63	Pet.[i]		66	$C_{14}H_{20}O_4$	66.6	66.3	7.99	8.17
	n-C_4H_9O	29	30% EtOH		53	$C_{16}H_{24}O_4$	68.6	68.5	8.63	8.44
2,5-Dialkoxyphenylacetamide	CH_3O	82	Water		133	$C_{10}H_{13}O_3N$	31.8[j]	32.1[j]	7.18[k]	7.01[k]
	C_2H_5O	70	Water		111	$C_{12}H_{17}O_3N$			6.28[k]	6.19[k]
	n-C_3H_7O	88	C_6H_6–Pet.[i]		115	$C_{14}H_{21}O_3N$			5.57[k]	5.55[k]
	n-C_4H_9O	86	C_6H_6–Pet.[i]		88	$C_{16}H_{25}O_3N$			5.02[k]	4.99[k]
Methyl 2,5-dialkoxyphenylacetate	CH_3O	93	128	3	44°[l]	$C_{11}H_{14}O_4$				
	C_2H_5O	69	127	2	[m]	$C_{13}H_{18}O_4$	65.5	65.0	7.60	7.54
	n-C_3H_7O	84	134	2	[m]	$C_{15}H_{22}O_4$	67.6	67.3	8.32	8.49
	n-C_4H_9O[n]	50	178	3	18°[e]	$C_{17}H_{26}O_4$	69.4	69.2	8.90	9.24

[a] Uncorrected; lower limit of 2 degree range listed. [b] Taken in apparatus calibrated with standard compounds. [c] Freezing point. [d] Lit.: 20–22° (ref. 4). [e] Lit.: 42° (ref. 4.) [f] 2,4-Dinitrophenylhydrazone, m.p. 107°. *Anal.* Calcd. for $C_{20}H_{24}O_6N_4$: N, 13.45. Found: N, 13.68. [g] 2,4-Dinitrophenylhydrazone, m.p. 116°. *Anal.* Calcd. for $C_{22}H_{28}O_6N_4$: N, 12.61. Found: N, 12.61. [h] Lit.: 123–124° (ref. 2). [i] Pet. ether, b.p. 60–90°. [j] Methoxyl. [k] Nitrogen %. [l] Lit.: 45° (ref. 5). [m] Did not solidify after 4 hr. in Dry Ice-bath. [n] $n^{25}D$ 1.4954.

TABLE II

Alkoxy groups	T, °C.	n^tD	d_4^t	Molar refraction Found[a]	Molar refraction Calcd.[b]
2,5-Dialkoxyacetophenones					
CH_3O	20	1.5430	1.1401[b]	49.82	48.77[c]
n-C_3H_7O	25	1.5150	1.0368	68.72	67.24[c]
n-C_4H_9O	30	1.5067	1.0076	78.07	76.47[c]
Methyl 2,5-dialkoxyphenylacetates					
C_2H_5O	25	1.5070	1.0997	64.38	63.57
n-C_3H_7O	25	1.4991	1.0564	74.05	72.81

[a] From Lorentz–Lorenz equation. [b] Lit.: 1.1385 (ref. 4). [c] Includes exaltation of 0.69 for conjugation of carbonyl and aromatic double bonds.

The yields, physical constants and analyses are listed in Tables I and II.

2,5-Dialkoxyphenylacetic Acids.—The general method of Abbott and Smith[2] for the preparation of 2,5-dimethoxyphenylacetic acid from 2,5-dimethoxyacetophenone by the Willgerodt reaction was used. In the case of the di-*n*-propoxy- and di-*n*-butoxy-compounds, acidification of the basic hydrolysis solution yielded a dark oil which was dissolved in ether and extracted repeatedly with potassium bicarbonate solution followed by acidification of the aqueous extracts. The yields, physical constants, analyses and crystallization solvents are listed in Table I.

2,5-Dialkoxyphenylacetamides.—One-tenth of a mole of the 2,5-dialkoxyphenylacetic acid and 22 ml. of thionyl chloride were refluxed for 30 minutes. The resulting solution was poured slowly into 100 ml. of ice-cold concentrated ammonium hydroxide. The crude product was filtered off and recrystallized. The yields, physical constants, analyses and crystallization solvents are listed in Table I.

Methyl 2,5-Dialkoxyphenylacetates.—One-tenth of a mole of the 2,5-dialkoxyphenylacetic acid and 22 ml. of thionyl chloride were refluxed for 30 minutes. Then 150 ml. of absolute methanol were added dropwise with cooling. After addition was complete, the reaction mixture was allowed to stand at room temperature for 30 minutes and then refluxed for 30 minutes. Excess volatile reagents and by-products were removed by evaporation, and the residual oil was fractionated twice through a 15-cm. Vigreux column. The yields, physical constants and analyses are listed in Tables I and II.

2,5-Dihydroxyphenylacetic Acid.—This compound was prepared in a yield of 76% by the demethylation of 2,5-dimethoxyphenylacetic acid[2] and in yields of 38–47% by the condensation of *p*-quinone with ketene diethylacetal followed by hydrolysis.[3]

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The Preparation of Di- and Triphenylacetonitrile and Their Cuprous Halide Complexes

BY WALTER M. BUDDE AND SYLVESTER J. POTEMPA

Although a good preparation for diphenylacetonitrile (II) has been described[1] it was decided to attempt a method which would involve fewer time-consuming steps and no lachrymatory intermediates. The process developed was the reaction of benzhydryl bromide (I) with anhydrous cuprous cyanide.

$$\underset{\text{I}}{(C_6H_5)_2CHBr} + CuCN \longrightarrow \underset{\text{II}}{(C_6H_5)_2CHCN} + CuBr$$

I was prepared in 70–75% yield by the action of phosphorus tribromide on benzhydrol. Heating I with a slight molar excess of oven-dried cuprous cyanide at 125° produced pure II in 75–80% yield after distillation. It was noticed that if impure I was used there was a pronounced tendency to form a stable complex molecule, III, dec. pt. 155°.

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