type of curve for the three reaction times measured. The amount of coloration increases rapidly from about zero in the anhydrous state to a maximum at about 4.3 g. of water per 10 g. of solids (30% water). A more gradual decrease occurs to the right of this peak with the degree of coloration approaching zero at a water concentration of about 90%. The homogeneous reactions follow the expected pattern of a roughly first-order increase in the rate of coloration with an increase in reactant concentration. Those portions of the curve in the heterogeneous reaction region are difficult to interpret and are undoubtedly affected by rates of solution and by diffusion. Nevertheless, our model system demonstrates that browning is at a minimum at high and low water concentrations and passes through a maximum value at an intermediate point of rather low (*ca.* 30%) water concentration. The retardation with an increase in the water content has been recorded in related model systems.[4]

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Acylation[1] of 5-(*p*-Acetoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3

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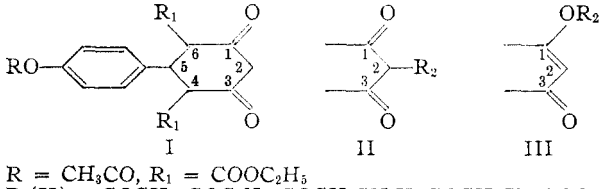
A previous publication[2] described the synthesis of 5-(*p*-acetoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3 (I) and some of its derivatives. The present paper reports a study of the acylation of this substance, presumably leading to both C-acylation (II) and O-acylation (III).



I II III

R = CH_3CO, R_1 = $COOC_2H_5$
R_2(II) = $COCH_3$, COC_2H_5, $COCH_2CH_2X$, $COCH_2CH_2COOCH_3$, or $SO_2C_6H_4NHCOCH_3$
R_2(III) = $COCH_3$ or COC_2H_5

C-Acylation at the 2-position gives compounds which are structurally similar to usnic acid and chalcones, both of which show antibiotic activity[3,4] against gram-positive organisms and against human and bovine tubercle bacilli.

The procedures outlined by Claisen[5] and Dieckmann and Stein[6] for the acylation of 1,3-dicarbonyl compounds were used. These authors report C-acylation with acid halides and sodium alkoxide, or by acid anhydrides and the sodium salt of the acid; and O-acylation with the anhydride. The conversion of O-acyl into C-acyl derivatives by potassium carbonate, pyridine, or sodium acetate in acetic anhydride was also reported; the two latter methods were used in this work.

The acyl derivatives obtained can be divided into two classes: those which give a yellow color (presumably the C-acyl derivatives) and those which give a reddish purple color when treated with alcoholic ferric chloride. The O-acyl derivatives were found to be more soluble in ether and in benzene than the C-acyl. This difference in solubility proved helpful in the separation of these compounds.

Dieckmann and Stein[6] showed that O-acyl derivatives can be hydrolyzed by alkali, while the C-acyl group under similar conditions is not affected. These investigators claimed also that when C-acetyldimethylhydroresorcinol was boiled with dilute sulfuric acid, it was cleaved to dimethylhydroresorcinol, m.p. 144°, and acetic acid. In the present work, cleavage of the C-acetyl group of 5 - (*p* - acetoxyphenyl) - 2 - (C - acetyl) - cyclohexanedione-1,3 did not occur when the compound was refluxed with sodium carbonate solution, and the mixture then acidified and refluxed again. This is in contrast to Dieckmann and Stein's finding.

p-Acetaminobenzene sulfones have been used in the therapy of tuberculosis and leprosy. The sodio derivatives of I and of the *m*-methoxy derivative of I were heated with *p*-acetaminobenzenesulfonyl chloride to give the corresponding sulfones, presumably at position 2 of the cyclohexanedione.

Experimental

The general experimental procedures parallel those of Dieckmann and Stein[6] in expts. 1 to 10, and those of Claisen[5] in expts. 11 to 18.

In expts. 1 to 10, 3 g. of the cyclohexanedione (I) and 7 ml. of the acid anhydride were used (acetic anhydride in 1 to 5; propionic anhydride in 6 to 10). The other specific reagents were 0.15 g. of sodium acetate in 1; 0.15 g. of sodium propionate in 6; excess pyridine (2 ml.) in 3 and 8; and the calculated quantity of pyridine (0.65 ml.) in 4, 5, 9 and 10. In all of these cases ice-water was added to the mixture after reaction, and the solid product was isolated and recrystallized from absolute ethanol.

In expts. 11 to 15 about 5 to 10 g. of the cyclohexanedione (I) was converted into the sodium salt with an equivalent of sodium methylate. The dry sodium salt was isolated and then heated with potassium iodide and an equivalent amount of the appropriate acid halide in dry ether; no potassium iodide was used in expt. 14. In expt. 16 the sodio derivative of 5-(*p*-methoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3 and cinnamoyl chloride were used. After the ether was removed, the residue was washed free of halide ion; then the dried residue was extracted with small portions of ether. As the O-acyl derivatives are more soluble in ether than the C-acyl, the residue consisted mostly of the C-acyl which was finally recrystallized from ethanol. A little petroleum ether was added to the ether solution to precipitate any C-acyl which was filtered off. The filtrate, upon evaporation, gave the O-acyl derivative.

In expt. 17 the sodium salt of I and in expt. 18 the sodium salt of the *m*-methoxy derivative of I were heated with *p*-aminobenzenesulfonyl chloride in dry dioxane. The dioxane was then removed and the residue treated as in expts. 11 to 15.

Conversions.—The compound melting at 145° (obtained in expts. 2 and 11 and assumed to be an O-acetyl derivative) was converted into that melting at 116° (obtained in expts. 1, 3 and 4 and assumed to be a C-acetyl derivative) by the action of acetic anhydride and sodium acetate for eight hours at the temperature of the water-bath.

(1) Part of this paper was presented at the 116th meeting of the American Chemical Society at Atlantic City, N. J., Sept. 1949. The paper is based on a manuscript submitted to THIS JOURNAL, May 9, 1950.

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TABLE I

ACYL DERIVATIVES OF CYCLOHEXANEDIONE (I)

Expt.	Time[b]	Color[c]	M.p., °C.[d]	Analyses, % Carbon Found	Hydrogen Found
$R_2 = COCH_3$[a]					
	10	Y	116	60.76	5.70
1		Y	148		
	10	RP	145	61.48	5.76
2	10	RP	115		
3	48	Y	116		
	16	Y	116		
4	12	RP	115	61.19	5.52
5	10	Y	148	60.95	5.72
$R_2 = CH_3CH_2CO$[a]				$C_{23}H_{26}O_9$[e]	
6	10	Y	129	62.30	6.31
	10	RP	102	62.31	6.06
7		RP	115	62.35	5.93
8	48	Y	163		
9	16	RP	102		
10	10	Y	129		

Expt.	R_2[a]	Time[b]	Color[c]	M.p., °C.[d]	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
			RP	145					
11	$COCH_2$	10	Y	162	$C_{22}H_{24}O_9$	61.10	61.38	5.59	5.72
			Y	163	$C_{23}H_{26}O_9$	61.87	61.56	5.87	5.99
12	$COCH_2CH_3$	22	RP	115					
13	$COCH_2CH_2I$	26	Y	145	$C_{23}H_{25}O_9I$	48.44	48.95	4.45	4.89
14	$COCH_2CH_2Cl$	21	Y	150	$C_{23}H_{25}O_9Cl$	57.44	57.62	5.24	5.47
15	$COCH_2CH_2COOCH_3$	5	Y	133	$C_{25}H_{28}O_{11}$	59.52	59.74	5.59	5.96
16[f]	$COCH{=}CHC_6H_5$	24	Y	140	$C_{28}H_{26}O_8$	68.26	68.57	5.75	5.90
17	$SO_2C_6H_4NHCOCH_3$	6	Y	203	$C_{28}H_{29}O_{11}SN$	57.23	56.74	4.97	4.92
18[g]	$SO_2C_6H_4NHCOCH_3$	6	Y	175	$C_{27}H_{29}O_{11}SN$	56.33	56.66	5.07	5.46

[a] Acyl substituent. [b] Reaction time in hours. Expts. 3, 4, 8 and 9 were run at room temperature, the others at approximately 100°. [c] Color in ferric chloride test: Y = yellow, RP = reddish purple. [d] Mixed melting points indicated that, in general, the compounds with the same melting point and empirical formula are identical: 116 in expts. 1, 3 and 4; 148 in 1 and 5; 129 in 6 and 10; 145 in 2 and 11; 115 in 2 and 4; 102 in 7 and 9; 115 in 7 and 12; and 163 in 8 and 12. [e] Calcd. for $C_{22}H_{24}O_9$: C, 61.10; H, 5.59. Calcd. for $C_{23}H_{26}O_9$: C, 61.87; H, 5.87. [f] 5-(*p*-Methoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3 was used instead of I. [g] The *m*-methoxy derivative of I was used.

A portion of the substance melting at 145° (obtained in expt. 2) was dissolved in sodium carbonate solution. It was allowed to stand at room temperature 24 hours, refluxed for 12 hours, acidified and further refluxed for seven hours. Upon cooling, a precipitate formed which was filtered and recrystallized from boiling distilled water. The product, dried over phosphorus pentoxide in a vacuum desiccator, was found to be identical with 5-(*p*-hydroxyphenyl)-cyclohexanedione-1,3.[2] The O-acyl at position 1 (or 3) was hydrolyzed.

5-(*p*-Acetoxyphenyl)-2-acetylcyclohexanedione-1,3, m.p. 117°, prepared from 5-(*p*-hydroxyphenyl)-cyclohexanedione-1,3[2] by the method[6] of expt. 5, was refluxed for five hours with sodium carbonate solution. The mixture was acidified and refluxed again for one hour. After cooling, the mixture was extracted with 20 ml. of each of the following solvents: benzene, ethyl acetate and ether. The combined solvents were evaporated; water followed by a little ethanol was added to the viscous residue. The crystals formed were recrystallized from ethanol, m.p. 179°. The analysis indicates that the product retained one acetyl group.

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.77. Found: C, 68.08; H, 6.04.

The compound melting at 115° (obtained in expts. 2 and 4 and assumed to be an O-acetyl derivative) was converted into the isomer melting at 148° (obtained in 1 and 5 and assumed to be a C-acetyl derivative) by the action of acetic anhydride and pyridine for ten hours on the water-bath. Similarly, the compound melting at 102° (obtained in expts. 7 and 9 and assumed to be O-propionyl) was converted into the isomer melting at 129° (obtained in expt. 10 and assumed to be a C-propionyl derivative) by the use of propionic anhydride and pyridine.

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5-(*p*-Hydroxyphenyl)-4,6-dicarboxy-2-(β-diethylaminopropanol)-cyclohexanedione-1,3 and Derivative[1]

BY PHILIPPOS E. PAPADAKIS AND JOSEPH SCIGLIANO

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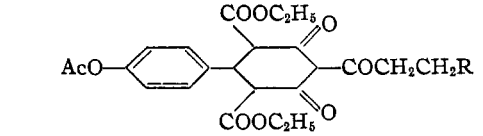
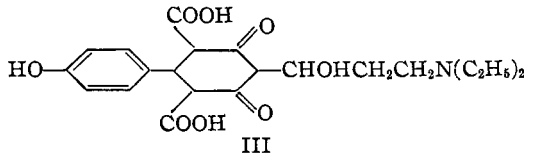
In the search for antimalarials, a great many substituted diethylaminoalkanols have been prepared.[2-6] The object of the present work was the preparation of dialkylaminoalkanol derivatives of cyclic 1,3-diones, and we describe below the synthesis of 5-(*p*-hydroxyphenyl)-4,6-dicarboxy-2-(β-diethylaminopropanol)-cyclohexanedione-1,3 and a derivative.

Compound I, prepared by acylation of 5-(*p*-acetoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3 with β-chloropropionyl chloride followed by treatment with potassium iodide, was transformed into II by the action of diethylamine. On reduction by the Meerwein–Ponndorf–Verley method, II yielded the expected secondary alcohol III and a further substance $C_{21}H_{25}O_7N$, assumed to be a lactone.

Physiological properties of these compounds will be examined and reported later.



I, R = I
II, R = $N(C_2H_5)_2$



III

Experimental

5-(*p*-Acetoxyphenyl)-4,6-dicarbethoxy-2-(β-chloropropionyl)-cyclohexanedione-1,3.—To a solution of 230 mg. of sodium in methanol, 3.90 g. (0.01 mole) of 5-(*p*-acetoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3[7] was added and the mixture refluxed for one hour. The methanol was distilled and the residue dried under vacuum. To the dry material absolute ether and one ml. of freshly distilled β-chloropropionyl chloride was added and the mixture was

(1) Based on a paper submitted to THIS JOURNAL, Dec. 17, 1951.

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