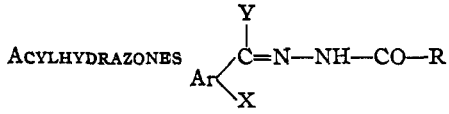
TABLE I

ACYLHYDRAZONES



Y = H, CH_3; X = OH, NH_2; R = $(CH_2)_{12}$–CH_3, C_6H_5, CH_2–C_6H_5, $C_6H_4NO_2$; Ar = C_6H_4, $C_{10}H_6$.

Hydrazone	Formula	M.p., °C.	Crystals	Nitrogen, % Calcd.	Found
Salicylaldehyde myristyl	$C_{21}H_{34}O_2N_2$	104–105	White	8.10	8.23
Salicylaldehyde *o*-nitrobenzoyl	$C_{14}H_{11}O_4N_3$	175–177	Yellow	14.73	15.17
o-Oxynaphthaldehyde myristyl	$C_{25}H_{36}O_2N_2$	129–130	Yellow	7.07	7.00
o-Oxynaphthaldehyde benzoyl	$C_{18}H_{14}O_2N_2$	211–212	White	9.74	9.75
o-Oxynaphthaldehyde fenylacetyl	$C_{19}H_{16}O_2N_2$	204–206	Yellow	9.20	9.12
o-Oxyacetophenone benzoyl	$C_{15}H_{14}O_2N_2$	180–181	White	11.06	10.92
o-Aminobenzaldehyde myristyl	$C_{21}H_{35}ON_3$	103–104	White	12.16	12.00
o-Aminobenzaldehyde benzoyl	$C_{14}H_{13}ON_3$	180–181	Yellow	17.57	17.67
o-Aminobenzaldehyde fenylacetyl	$C_{15}H_{15}ON_3$	164–165	Yellow	16.59	16.50
Salicylaldehyde picolinyl	$C_{13}H_{11}O_2N_3$	171–173	White	17.42	17.37
o-Oxynaphthaldehyde picolinyl	$C_{17}H_{13}O_2N_3$	189–190	Yellow	14.43	14.35
o-Oxyacetophenone picolinyl	$C_{14}H_{13}O_2N_3$	184–186	White	16.47	16.35
o-Aminobenzaldehyde picolinyl	$C_{13}H_{12}ON_4$	216–218	Yellow	23.33	23.42
Salicylaldehyde nicotinyl	$C_{13}H_{11}O_2N_3$	175–177	White	17.42	17.57
o-Oxynaphthaldehyde nicotinyl	$C_{17}H_{13}O_2N_3$	252–253	Yellow	14.43	14.53
o-Oxyacetophenone nicotinyl	$C_{14}H_{13}O_2N_3$	183–185	White	16.47	16.43
o-Aminobenzaldehyde nicotinyl	$C_{13}H_{12}ON_4$	208	Yellow	23.33	23.28
5-Bromosalicylaldehyde nicotinyl	$C_{13}H_{10}O_2N_3Br$	216–217	Yellow	13.12	13.09
Salicylaldehyde isonicotinyl	$C_{13}H_{11}O_2N_3$	244–245	White	17.42	17.48
o-Oxynaphthaldehyde isonicotinyl	$C_{17}H_{13}O_2N_3$	155–157	Yellow	14.43	14.15
o-Oxyacetophenone isonicotinyl	$C_{14}H_{13}O_2N_3$	235–237	White	16.47	16.43
o-Aminobenzaldehyde isonicotinyl	$C_{13}H_{12}ON_4$	232–233	Yellow	23.33	23.20
5-Bromosalicylaldehyde isonicotinyl	$C_{13}H_{10}O_2N_3Br$	251–252	Yellow	13.12	13.10

All hydrazones, except those of *o*-aminobenzaldehyde, are soluble in dilute sodium hydroxide and in aqueous ammonia with yellow color.

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Chemical Interactions of Amino Compounds and Sugars. VIII.[1] Influence of Water[2]

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This Laboratory has been concerned with a rather extended study of the color-producing (browning) reaction between a reducing sugar (such as D-xylose) and an amino acid (such as glycine, in excess) in dilute aqueous solution. From an applied food product standpoint, most of these browning reactions occur in relatively low water concentrations and such environments have been recently studied extensively by Lea and associates.[3] While our immediate program is not concerned with these applied aspects, it was nevertheless considered of interest to investigate the parameter of water concentration in our model system. To this end solid mixtures, each containing D-xylose and glycine in 1:5 molar ratio, were heated at 65°, under nitrogen and with mechanical stirring, with various proportions of water. The degree of color formation was determined by measuring the optical density at 490 mμ at a suitable standard dilution after heating periods of four, six and eight hours. The results are plotted in the accompanying figure. Below the abscissa value of about 18.6 (65% water) the reactions were heterogeneous. The degree of coloration increases with time but follows the same

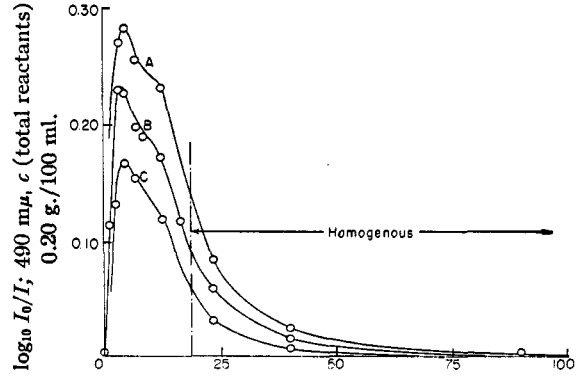

Fig. 1.—Browning of D-xylose–glycine (6.00 g.: 15.00 g. or 1:5 molar ratio) mixtures mechanically stirred (except at 0–1.8 on abscissa) at 65° under nitrogen at various water ratios: curve A, 8 hr. reaction time; curve B, 6 hr.; curve C, 4 hr.; Lumetron (Model 402E) photoelectric colorimeter; 1-cm. cell.

(1) Previous communication in this series: M. L. Wolfrom, Doris K. Kolb and A. W. Langer, Jr., THIS JOURNAL, **75**, 3471 (1953).

(2) This paper represents research undertaken in coöperation with the Quartermaster Institute for the Armed Forces under Contract No. DA11-009-qm-13294 with The Ohio State University Research Foundation (Project 477), and has been assigned number 420 in the series of papers approved for publication. The views or conclusions contained in this report are those of the authors. They are not to be construed as necessarily reflecting the views or indorsement of the Department of Defense.

(3) C. H. Lea and R. S. Hannan, *Biochem. et Biophys. Acta*, **3**, 313 (1949); **4**, 518 (1950); V. M. Lewis and C. H. Lea, *ibid.*, **4**, 532 (1950); C. H. Lea, R. S. Hannan and D. N. Rhodes, *ibid.*, **7**, 366 (1951); R. S. Hannan and C. H. Lea, *ibid.*, **9**, 293 (1952).

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]

(4) G. P. Volgunov and M. T. Pokhno, *Biokhimiya*, **15**, 67 (1950); M. F. Mashkovtsev, *ibid.*, **16**, 615 (1951).

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

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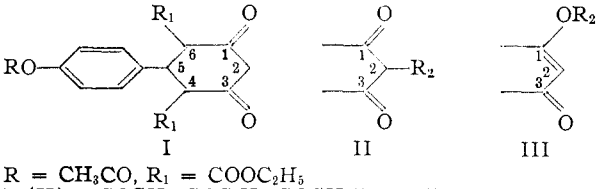
A previous publication[2] described the synthesis of 5-(*p*-acetoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3 (I) and some of its derivatives. The present paper reports a study of the acylation of this substance, presumably leading to both C-acylation (II) and O-acylation (III).



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.

(2) P. E. Papadakis, THIS JOURNAL, **67**, 1799 (1945).

(3) Tynosin Ukita, Tomie Tamura, Reiko Matsuda and Etsuko Kashiwabara, *Japan J. Exptl. Med.*, **20**, 109 (1949).

(4) A. Marshak, G. T. Barry and L. C. Craig, *Science*, **106**, 394 (1947).

(5) L. Claisen and E. Haase *Ber.*, **33**, 1242, 3778 (1900).

(6) W. Dieckmann and R. Stein, *ibid.*, **37**, 3370, 3384 (1904).