[CONTRIBUTION FROM THE CELLULOSE ACETATE DEVELOPMENT DIVISION, EASTMAN KODAK COMPANY]

Relative Rates of Acetylation of the Hydroxyl Groups in Cellulose Acetate

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Several samples of hydrolyzed cellulose acetate, 30–40% acetyl, were reacetylated under a variety of reaction conditions. Most of the reactions were carried out without any catalyst, using acetic anhydride as the acetylating agent. Variations were made in the temperature and in the amount of anhydride. Catalysts were also investigated, including sulfuric acid, perchloric acid, zinc chloride and pyridine. Finally, acetylations were made with acetyl chloride and pyridine. The relative reactivities of the primary and secondary hydroxyls were calculated from the total amounts of hydroxyl and the amounts of primary hydroxyl in the products taken during the course of these acetylations. The primary hydroxyls were always more reactive than the secondary. In general, factors which accelerated the reaction diminished the difference in reactivity between primary and secondary hydroxyls. Thus in the uncatalyzed reaction with acetic anhydride at room temperature the primary hydroxyls reacted ten times as fast as the secondary, whereas, in the reaction catalyzed with sulfuric acid they reacted only two and one-half times as fast. Optical rotations throughout these acetylations correlated with the amounts of primary hydroxyl and the acetyl contents.

Instances of the superior reactivity of primary hydroxyl groups in esterification are numerous in the chemical literature. From simple organic compounds containing both primary and secondary hydroxyl groups, the ester of the primary hydroxyl sometimes can be isolated as a pure compound.

A knowledge of the reactivities of the various hydroxyl groups during the acetylation of cellulose is of fundamental importance. The acetylation of cellulose itself, however, presents the difficulty that the reaction is usually started with the cellulose in suspension, so that the reagents must penetrate the fiber.[1] The ease of penetration may vary in amorphous and crystalline portions of the fiber, and with the accumulation of a surface-acetylated layer.

The present work was undertaken with hydrolyzed cellulose acetate to avoid these difficulties. The starting materials contained 30–40% acetyl, and they were soluble in acetic acid. They were prepared from commercial acetone-soluble cellulose acetate by further hydrolysis in various acetic acid–water mixtures to obtain products with different amounts of acetyl and primary hydroxyl.[2]

The acetylations were carried out with acetic anhydride and with acetyl chloride, and samples were taken during the course of each acetylation. The reaction products were soluble in a variety of organic solvents, permitting measurements of water-tolerance value and optical rotation. All of the reaction products were tritylated under standardized conditions to determine the amount of primary hydroxyl present.[2] The secondary hydroxyl was obtained by difference between the total hydroxyl (from per cent. acetyl by saponification) and the primary hydroxyl.

It was observed in every instance that the primary hydroxyls acetylated more rapidly than the secondary. In an effort to obtain a quantitative expression for this difference, the results were plotted in various ways, and it was found, when the amount of primary hydroxyl was plotted against the amount of secondary on log–log paper, that fairly straight lines resulted (Figs. 1 and 2). The slope of the line is an approximate measure of the relative reactivities of the primary and secondary hydroxyls.

The acetylation is a second-order reaction, depending on the concentrations of hydroxyl and anhydride. For the present purpose, the concentration of anhydride can be eliminated as a variable by assuming that it does not affect the *relative* rates of acetylation of the primary and secondary hydroxyls. The esterifications can then be treated as concurrent first-order reactions.

Let x and y = number of primary and secondary hydroxyls, respectively, per glucose unit, at time t. These will react with an excess of acetic anhydride at rates proportional to the amounts present

$$dx = k_1 x dt \text{ and } dy = k_2 y dt, \text{ whence}$$

$$dx/x = k_1 dy/k_2 y$$

By integration

$$\log x = k_1/k_2 \log y + c$$

where k_1/k_2 is the relative reactivity of primary to secondary hydroxyls, and is the slope of the line on log–log paper.

Actually, the amount of anhydride in excess had only a minor effect on the relative reactivities of the primary and secondary hydroxyls (Table I, samples G and J).

In the above derivation, no distinction is made between the reactivities of the secondary hydroxyls in positions 2 and 3. The straight lines obtained on the log–log plots would indicate comparable reactivities of both of the secondary hydroxyls in the acetylation reaction. In the tosylation of cellulose acetate, Gardner and Purves[3] found the hydroxyls in position 2 twenty times more reactive than those in position 3, and that the primary hydroxyls in position 6 were ten times as reactive as the secondary hydroxyls in position 2. Apparently, differences in relative reactivity of the various hydroxyls are more pronounced on tosylation than on acetylation.

Some concern was felt for the reliability of the tritylation reaction for determining a small amount of primary hydroxyl in the presence of a large amount of secondary. Tritylation time series were carried out on such a sample of cellulose acetate containing 38.1% acetyl (0.71 hydroxyl per glucose unit). The normal amount of trityl chloride for a sample of this hydroxyl content is 1.25 parts, based

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(1) E. Heuser, W. Shockley, A. Adams and E. A. Grunwald, *Ind. Eng. Chem.*, **40**, 1500 (1948). In this work the cellulose was first dissolved in phosphoric acid.

(2) C. J. Malm, L. J. Tanghe and B. C. Laird, THIS JOURNAL, **72**, 2674 (1950).

(3) T. Gardner and C. B. Purves, *ibid.*, **64**, 1539 (1942).

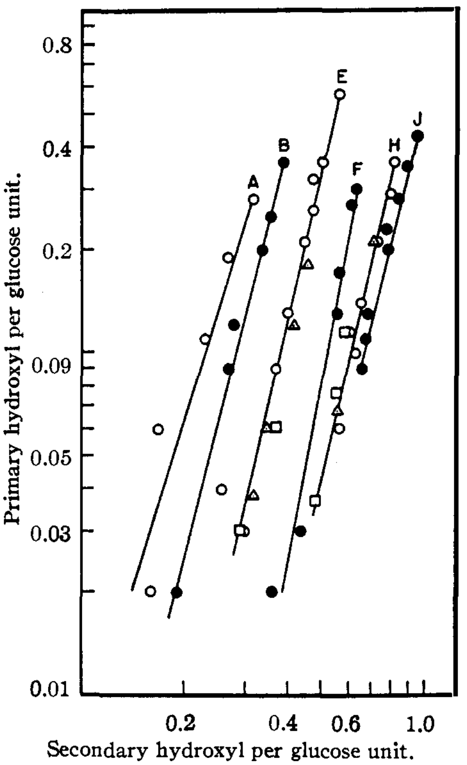

Fig. 1.—Acetylation of various cellulose acetates: ○ or ●, Ac_2O without catalyst; △, Ac_2O and $ZnCl_2$; □, CH_3COCl and C_5H_5N.

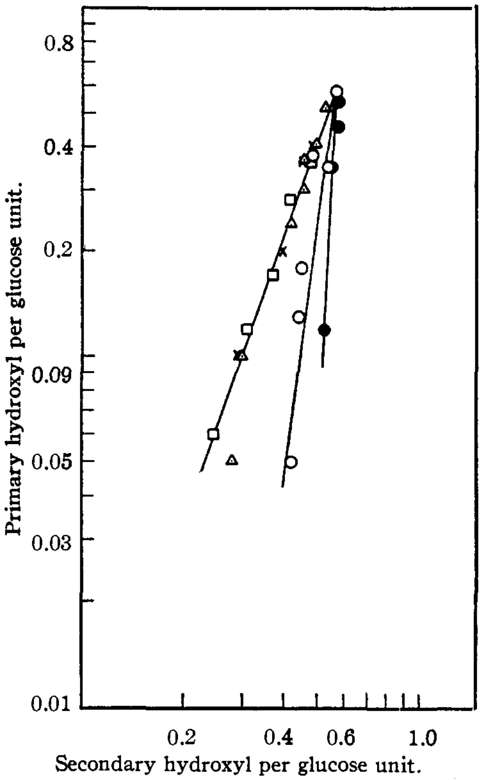

Fig. 2.—Acetylation of cellulose acetate, sample D: ○, Ac_2O without catalyst, steam-bath; ●, Ac_2O without catalyst, room temp.; △, Ac_2O and $HClO_4$ catalyst, room temp.; □, Ac_2O and H_2SO_4 catalyst, room temp.; ×, Ac_2O and C_6H_5 catalyst, room temp.

on cellulose acetate.[2] This is an excess of 40% over that required to react with *all* of the hydroxyl groups. With this amount of trityl chloride, under conditions previously described, 0.038 hydroxyl reacted after 24 hours, and 0.045, after 72 hours at 70°. Using half as much trityl chloride 0.030 hydroxyl reacted, and using twice as much trityl chloride 0.054 hydroxyl reacted, in each case the reaction time being 24 hours. These data indicate a very low rate of tritylation of the secondary hydroxyls under the conditions used.

TABLE I

RELATIVE RATES OF ACETYLATION OF THE PRIMARY AND SECONDARY HYDROXYLS IN HYDROLYZED CELLULOSE ACETATE

Sample	Ac, %	Hydroxyl per g.u. Primary	Hydroxyl per g.u. Secondary	Catalyst	Temp., °C.	Parts Ac_2O[a]	Relative reactivity
A	39.3	0.28	0.32	None	100	1	4
B	37.7	.36	.39	None	100	1	4
C	35.6	.46	.48	None	100	1	5
D	33.2	.58	.57	None	100	1	6
E	33.4	.57	.57	None	100	1	5
F	35.8	.30	.62	None	100	1	5
G	33.4	.46	.67	None	100	1	7
H	32.9	.36	.81	None	100	1	5
I	32.2	.40	.83	None	100	1	5
J	30.3	.43	.95	None	100	1	4
G	33.4	.46	.67	None	100	2	5
J	30.3	.43	.95	None	100	2	3
D	33.2	.58	.57	None	R.T.	1	16
G	33.4	.46	.67	None	R.T.	1	10
D	33.2	.58	.57	$HClO_4$	R.T.	1	2.5
D	33.2	.58	.57	H_2SO_4	R.T.	1	2.5
D	33.2	.58	.57	C_6H_5N	65	1	2.5
D	33.2	.58	.57	C_5H_5N[b]	65	1	4
E	33.4	.57	.57	$ZnCl_2$	R.T.	1	5
H	32.9	.36	.81	$ZnCl_2$	R.T.	1	4.5
E	33.4	.57	.57	AcCl	R.T.		5
H	32.9	.36	.81	and	R.T.		5
I	32.2	.40	.83	C_6H_5N	R.T.		4.5

[a] Based on cellulose acetate. [b] Suspended in benzene.

To the extent that straight lines are obtained in plots of this kind, the assumptions in the above derivation appear to be justified. The slopes of the lines are recorded in the last column of Table I, and while they give only approximate values for the relative reactivities of the primary and secondary hydroxyls, they are nevertheless useful for comparing different starting materials and different reaction conditions.

A summary of all the acetylations is given in Table I. This gives the relative rates of reactivity of the primary and secondary hydroxyls in the various starting materials under different reaction conditions. In the uncatalyzed reactions in which one part of anhydride was used for one part of cellulose acetate at steam-bath temperature, the relative reactivities range from 4 to 7, with 5 being a representative average value. Detailed data on one of these reactions are given in Table II. When the amount of anhydride was doubled the relative reactivities decreased from 7 to 5 for sample G and from 4 to 3 for sample J.

When the acetylation was carried out at room temperature with one part of acetic anhydride, the reaction became very selective for the primary hydroxyls, giving relative reactivities of 16 and 10 for samples D and G, respectively. This was a very slow reaction, requiring two to three months to acetylate half of the hydroxyls in the starting material.

The reactions were all very fast when catalyzed with perchloric acid, sulfuric acid and pyridine. The entire sampling time extended over a period of only one hour. The primary hydroxyls reacted only two and one-half times as fast as the secondary in these acetylations (Fig. 2). When the acetylation with pyridine catalyst was carried out in benzene suspension, the reaction was considerably slower, and was somewhat more selective toward the primary hydroxyl than when carried out in solution.

With acetic anhydride and zinc chloride catalyst, the reaction was not quite as fast as with the abovementioned catalysts. The relative reactivity of the primary and secondary hydroxyls was about 5.

The acetylation with acetyl chloride and pyridine was fast, and the relative reactivity of the primary and secondary hydroxyls was also about 5. In order to avoid considerable heat of mixing of reagents, the addition compound of acetyl chloride and pyridine was prepared separately with good cooling and then added to the solution of the cellulose acetate. The details on one of each of these reactions are given in Table II.

TABLE II

ACETYLATION OF HYDROLYZED CELLULOSE ACETATE UNDER VARIOUS REACTION CONDITIONS

Sample	Time	% Ac.	Hydroxyls per g.u. Primary	Hydroxyls per g.u. Secondary	$[\alpha]^{25}\text{D}$	Water tolerance value
One part of Ac_2O at 100°, uncatalyzed						
E	Start	33.4	0.57	0.57	−10.6°	154
E-1	0.5 hr.	36.4	.36	.51	− 4.6	107
E-2	1	37.2	.32	.48	− 4.4	98.8
E-3	2	38.7	.21	.45	− 3.0	84.0
E-4	4	40.0	.13	.40	− 3.0	81.0
E-5	7	40.7	.09	.37	− 2.7	70.9
E-6	24	41.9	.03	.30	− 5.8	64.5
E-7	48	42.7	.02	.21	− 9.9	60.0
Two parts of Ac_2O at 100°, uncatalyzed						
G	Start	33.4	0.46	0.67	− 2.1	142
G-5	1 hr.	36.2	.28	.66	+ 1.5	120
G-6	2	37.5	.20	.57	+ 3.3	87.3
G-7	4	38.8	.11	.55	+ 2.9	76.8
G-8	7	39.6	.07	.50	+ 1.5	69.2
G-9	24	41.4	.02	.36	− 5.3	57.8
One part of Ac_2O at R.T., uncatalyzed						
G	Start	33.4	0.46	0.67	− 2.1	142
G-10	2 days	34.4	.38	.67	− 0.4	124
G-11	8	35.3	.31	.67	+ 2.0	111
G-12	15	36.4	.23	.64	+ 3.1	98.0
G-13	26	37.2	.17	.63	+ 3.8	88.2
G-14	40	37.9	.11	.62	+ 4.6	82.1
G-15	69	38.4	.10	.58	+ 4.2	74.8
G-16	99	39.1	.07	.55	+ 3.9	71.8
Perchloric acid catalyst at R.T.						
D	Start	33.2	0.58	0.57	− 9.6	156
D-6	5 min.	34.4	.52	.53	− 7.8	138
D-7	10	36.4	.38	.49	− 5.5	111
D-8	20	41.2	.10	.30	− 6.0	67.6
D-9	30	41.9	.05	.28	− 7.8	63.4
D-10	60	42.9	.02	.20	−11.5	59.2
Sulfuric acid catalyst at R.T.						
D	Start	33.2	0.58	0.57	− 9.6	156
D-11	5 min.	36.7	.36	.48	− 6.2	118
D-12	10	38.0	.28	.42	− 6.2	101
D-13	20	39.9	.17	.37	− 6.6	84.6
D-14	30	40.9	.12	.31	− 7.9	77.3
D-15	60	42.1	.06	.25	−11.2	64.0
Pyridine catalyst at 65°, in solution						
D	Start	33.2	0.58	0.57	− 9.6	156
D-16	7 min.	36.1	.41	.48	− 5.6	116
D-17	15	37.2	.34	.46	− 5.2	101
D-18	30	39.3	.20	.40	− 5.9	86.8
D-19	60	41.3	.10	.29	− 7.9	65.6
Pyridine catalyst at 65°, in suspension						
D	Start	33.2	0.58	0.57	− 9.6	156
D-20	1 hr.	36.0	.39	.52	− 5.6	109
D-21	3	37.1	.32	.49	− 5.3	95.5
D-22	8	38.8	.23	.42	− 5.7	80.1
D-23	24	40.3	.13	.37	− 7.0	65.4
D-24	48	41.5	.05	.32	− 9.4	58.7
D-25	168	42.3	.03	.28	−13.3	55.1
Zinc chloride catalyst at R.T.						
E	Start	33.4	0.57	0.57	−10.6	154
E-8	0.5 hr.	37.8	.26	.48	− 5.0	91.0
E-9	1	38.9	.18	.46	− 4.6	81.0
E-10	2	39.9	.12	.42	− 5.3	72.6
E-11	4	41.1	.06	.35	− 7.1	65.1
E-12	7	41.6	.04	.32	− 8.9	62.3
E-13	2[a]	44.7			−22.6	
Acetyl chloride and pyridine at R.T.						
E	Start	33.4	0.57	0.57	−10.6	154
E-14	10 min.	40.3	.12	.38	− 5.5	70.1
E-15	30	40.9	.06	.37	− 6.6	63.7
E-16	60	41.9	.03	.30	− 9.0	59.5
E-17	90	42.6	.03	.22	−13.0	55.1

[a] Separate esterification, using one part of zinc chloride and two parts of acetic anhydride, two hours at 50°.

The speed of the reaction, which is in turn determined largely by the temperature, the amount of acetylating agent, and the nature and amount of the catalyst, appears to be the major factor affecting the relative rate of reaction of the primary and secondary hydroxyls.

Optical Rotation.—The optical rotation was measured on all starting materials and products except a few which were insoluble or poorly soluble. Chloroform:3A alcohol (85:15, by weight) was chosen as a solvent because it dissolves cellulose acetate over a wide range of acetyl content. The optical reactions during the course of the uncatalyzed reactions are given in Fig. 3. In every case the optical rotation went through a maximum during the course of the reaction. This appears to be due to opposing trends. The higher the primary hydroxyl the lower is the optical rotation.[4]

Since the percentage of primary hydroxyl is reduced as the acetylation progresses, the rotation

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(4) C. J. Malm, L. J. Tanghe, B. C. Laird and G. D. Smith, THIS JOURNAL, **74**, 4105 (1952).

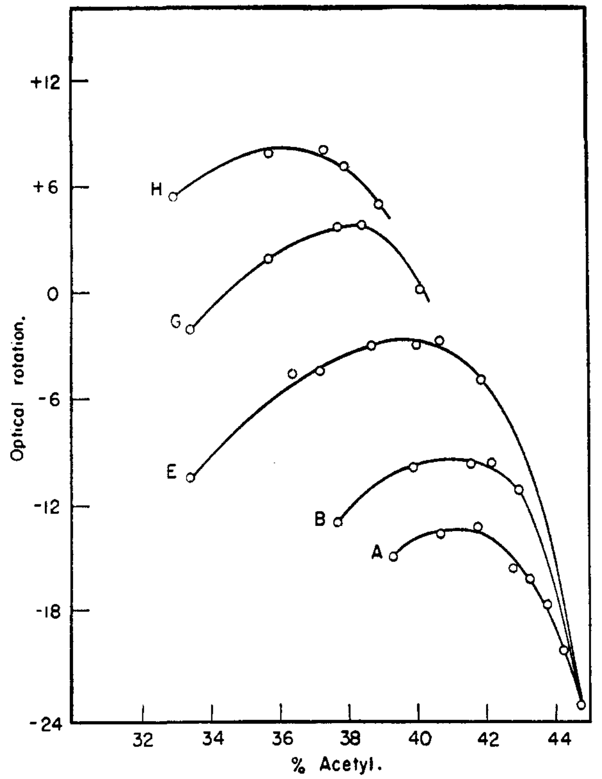

Fig. 3.—Optical rotation during acetylations without catalyst.

increases. On the other hand, cellulose triacetate has a rotation of −23°, more negative than that of any partially esterified cellulose acetate, and the optical rotation of the product must approach that of triacetate as the acetylation progresses. Thus, under certain conditions the optical rotation passes through a maximum. A starting material with sufficiently low primary hydroxyl obviously would not pass through a maximum during acetylation.

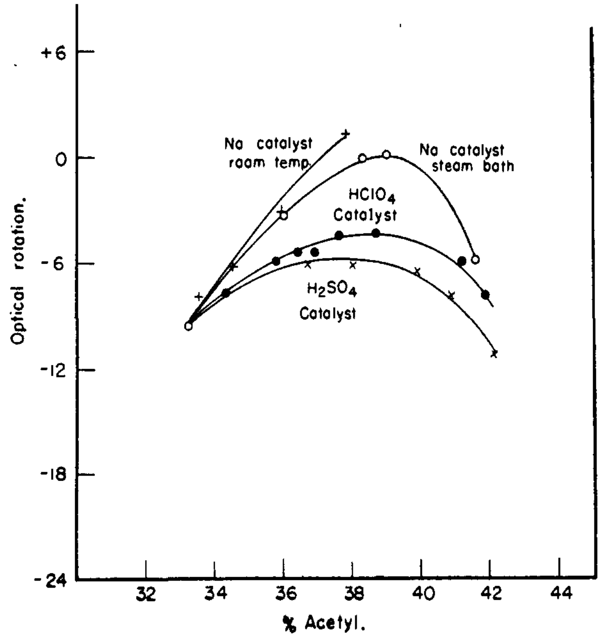

Fig. 4.—Optical rotation during acetylation of sample D under various conditions.

In general, the more selective the acetylation for the primary hydroxyl, the higher the maximum in optical rotation during the course of the reaction. This is shown in Fig. 4, where the steepest rise in rotation is obtained in the acetylation at room temperature without catalyst, and the smallest rise with sulfuric acid catalyst. The correlation between primary hydroxyl and optical rotation does not hold in detail in all cases, since the optical rotation may also be affected by differences in substitution at positions 2 and 3, both of which are secondary.

Water Tolerance.—The water tolerance of cellulose acetate is known to increase during the course of hydrolysis. In the present work it was found to decrease, as expected, during the course of acetylation. Figure 5 shows the water tolerance values of the products when dissolved in acetone. The water tolerance decreased both with increasing degree of acetylation and, upon comparing different samples acetylated to the same point, with decrease in the percentage of primary hydroxyl.

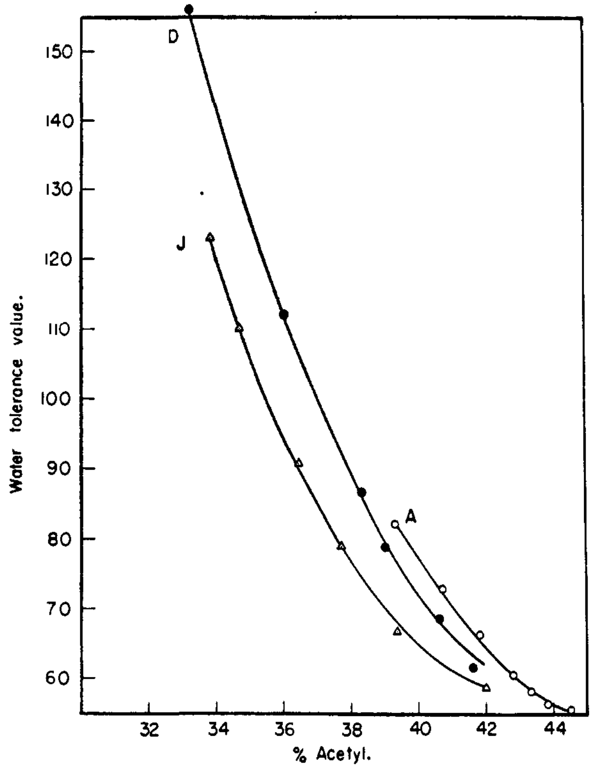

Fig. 5.—Water tolerance values during acetylation.

Experimental

Starting Materials.—The starting materials were a commercial cellulose acetate, containing 39.3% acetyl, and various products derived from it by further hydrolysis.[2] Hydrolysis in 50% acetic acid at steam-bath temperature gave products high in primary hydroxyl, whereas hydrolysis at room temperature with hydrochloric acid catalyst and lesser amounts of water gave products lower in primary hydroxyl. The intrinsic viscosity of the starting material was 1.4 in acetic acid solution. Numerous intrinsic viscosity measurements on the hydrolyzed and reacetylated products showed minor changes from this value. All products were dried at least two hours at 105° before acetylating.

Uncatalyzed Acetylation with Acetic Anhydride.—Two hundred grams of cellulose acetate was dissolved in two liters of acetic acid. The solution was heated by total immersion in a steam-bath and vigorously stirred during the addition of 200 g. of acetic anhydride and for one hour afterward. Samples were taken as indicated in Table II. Portions of the solution were poured into distilled water with vigorous stirring to precipitate the product, which was then washed to neutrality and dried in a current of air at 70°. The portions used for analyses were further dried at 105°.

Acetylation with Perchloric Acid Catalyst.—Two hundred grams of cellulose acetate was dissolved in two liters of acetic acid at room temperature, and 200 g. of acetic anhydride at 0° was added with good stirring. Then 80 ml. of acetic acid containing 0.10 ml. of perchloric acid was added. Samples were taken during the course of one hour at room temperature, constant stirring being maintained.

Acetylation with Sulfuric Acid Catalyst.—This acetylation was similar to the above, except that 0.70 ml. of sulfuric acid was added. The sulfuric acid combined quantitatively with the cellulose acetate during this acetylation,[5] giving products containing 0.17–0.18% sulfur. They were rendered stable to drying by adding sufficient sodium carbonate to the last wash to impart a pink color to phenolphthalein indicator.

Acetylation in Solution with Pyridine Catalyst.—Eighty grams of cellulose acetate was dissolved in 1000 ml. of acetic acid and 200 g. of pyridine. The mixture was heated to 65° and 80 g. of acetic anhydride was added with stirring. Samples were taken during the course of one hour.

Acetylation in Suspension with Pyridine Catalyst.—These acetylations were carried out in individual screw-cap bottles on a tumbler heated to 65°. Each bottle was charged with 20 g. of cellulose acetate, 280 ml. of benzene, 20 g. of pyridine and 20 g. of acetic anhydride. The products were filtered off and washed with benzene.

Acetylation with Zinc Chloride Catalyst.—Fifty grams of cellulose acetate was dissolved in 500 ml. of acetic acid, and 50 g. of acetic anhydride was added with good stirring at room temperature. This was followed by a solution of 10 g. of zinc chloride dissolved in 20 ml. of acetic acid. Samples were taken during the course of seven hours. Triacetates were prepared by acetylating several of the starting materials with two parts of acetic anhydride and one part of zinc chloride for two hours at 50°. These products contained the theoretical amount of acetyl, no free hydroxyl, and had an optical rotation of −23 ± 1°.

Acetylation with Acetyl Chloride and Pyridine.—Fifty grams of cellulose acetate was dissolved in a mixture of 60 ml. of anhydrous pyridine and 540 ml. of anhydrous dioxane. To this solution, at room temperature or slightly below, was added a slurry of the acetyl chloride–pyridine addition compound, prepared as follows: In a one-liter, three-necked flask were placed 75 ml. of pyridine and 425 ml. of dioxane, and the mixture was cooled to +3°, at which point the dioxane began to crystallize. Fifty grams of acetyl chloride was added through a dropping funnel during an interval of ten minutes, with cooling and stirring. The addition compound separated from solution immediately on adding the acetyl chloride. The temperature was maintained under 15° during this step. The solution of cellulose acetate was cooled to 15°, and the slurry of the addition compound was added as rapidly as possible with good stirring. Samples were taken during the course of 1.5 hours. Toward the end of the reaction the mixture was heated to 40° in order to obtain a greater range of acetyl content in the products.

Analyses.—Acetyl determinations were made by saponification in suspension[6] or in solution.[7] Tritylations were carried out as previously described,[2] and most of the trityl determinations were made by ultraviolet absorption. Optical rotations were determined at a concentration of 5 g. of cellulose acetate in 100 ml. of solution, using 2-dm. tubes. The solvent was chloroform:3A alcohol (85:15 by weight). Water tolerance values were determined by adding water to 125 ml. of acetone containing 125 mg. of cellulose acetate in solution[8,9] and determining photometrically the point at which turbidity appeared. The values reported in Tables II are the ml. of water required to produce turbidity. Samples too low in acetyl content to be soluble in acetone alone became soluble upon addition of water but, finally, precipitated out as water was added in excess. Samples too high in acetyl content to be soluble in acetone were first dissolved in a small amount of tetrachloroethane. In these cases a correction was applied to make the results comparable with those run in acetone alone.

Acknowledgment.—We wish to thank Mr. J. R. Olson of the Physical Chemistry Department, Kodak Research Laboratories, for measuring the optical rotations reported herein.

ROCHESTER, N. Y.

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[5] C. J. Malm, L. J. Tanghe and B. C. Laird, *Ind. Eng. Chem.*, **38**, 77 (1946).

[6] L. B. Genung and R. C. Mallatt, *Ind. Eng. Chem., Anal. Ed.*, **13**, 369 (1941).

[7] C. J. Malm, L. B. Genung, R. F. Williams and M. A. Pile, *ibid.*, **16**, 501 (1944).

[8] D. R. Morey and J. W. Tamblyn, *J. Applied Phys.*, **16**, 419 (1945).

[9] C. J. Malm, J. W. Mench, D. L. Kendall and G. D. Hiatt, *Ind. Eng. Chem.*, **43**, 684 (1951).

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Derivatives of 2,2-Diphenylcyclohexanone. II. Some Anomalous Absorption Spectra

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Additional derivatives of 2,2-diphenylcyclohexanone are described and the relative inertness of the parent ketone toward carbonyl reagents is discussed. 2,2-Diphenyl-5-cyclohexenone and some of its derivatives possess strikingly unexpected absorption spectra.

In continuation of previous work on cyclic analogs of methadon,[1] we have prepared further derivatives of 2,2-diphenylcyclohexanone for pharmacological testing and have noted some unexpected chemical and physical properties of certain compounds in this system.

2,2-Diphenyl-6-morpholinocyclohexanol (V) was prepared by two methods, either by reducing 2,2-diphenyl-6-morpholinocyclohexanone (III)[1] with lithium aluminum hydride or by reduction of 2,2-diphenyl-6-bromocyclohexanone (II)[1] with the same reagent followed by reaction of the resulting bromohydrin (IV) with morpholine.

Two types of addition reactions to 2,2-diphenyl-5-cyclohexenone were studied. When this unsaturated ketone VI[1] was dissolved in an excess of a secondary amine, 2,2-diphenyl-5-dialkylaminocyclohexanone derivatives (VIII) were obtained. One of these amino ketones, 2,2-diphenyl-5-piperidinocyclohexanone, was reduced to 2,2-diphenyl-5-piperidinocyclohexanol (IX) by lithium aluminum hydride. 2,2-Diphenyl-5-(*p*-acetamidobenzenesulfonyl)-cyclohexanone (VII) was pre-

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[1] A. Burger and W. B. Bennet, THIS JOURNAL, **72**, 5414 (1950).