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Cellulose Trityl Ether[1a]

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The trityl (triphenylmethyl) ether of cellulose has been mentioned several times in the literature. Its original preparation, by Helferich and Koester[1b] in 1924, gave a product which by carbon and hydrogen analysis and by weight of trityl chloride recovered on hydrolysis contained about one trityl group for each glucose unit. They stated that the substituted groups would appear to be on the 6 position but that this had not been proved and served only as a working explanation.

Sakurada and Kitabatake[2] followed Helferich's procedure and stated without further proof that the product was 6-monotritylcellulose. In 1937 Schorygin and co-workers[3] prepared trityl cellulose and attempted to xanthate, methylate and acetylate it without much success. They then tritylated a dimethyl cellulose and a cellulose diacetate and in the latter case stated arbitrarily that only the primary groups were tritylated.

That the trityl group shows a preference for primary hydroxyls is well-known. However, it is not a reagent which attacks primary hydroxyls exclusively, as has been demonstrated by the preparation of a number of derivatives in which a secondary position must have been attacked.[4,5,6,7] Hence, there is room for questioning whether or not the trityl group in trityl cellulose is all in the primary or number 6 position.

The present work was undertaken with a threefold purpose: (1) to provide a more complete study of trityl cellulose preparation, including precautions necessary to avoid badly degraded and discolored products, (2) to develop specific conditions for detritylation with as little degradation of the cellulose as possible, and (3) to evaluate the extent to which the trityl group is specific for the 6 position.

Preparation of Trityl Cellulose

The cellulose used as starting material for preparation of the trityl ether was found to be of importance. That regenerated from viscose or from cuprammonium solutions reacted satisfactorily, although somewhat less readily than cellulose regenerated from cellulose acetate by treatment with 15% aqueous ammonia. Cotton linters did not give soluble products. Cellulose regenerated from the acetate was therefore adopted as starting material for this study.

Repetition of Helferich and Koester's trityl cellulose preparation gave a dark, powdery product. A series of experiments resulted in modification of this procedure to include a presoaking treatment in aqueous pyridine, which greatly reduced the reaction time. Products so made were nicely fibrous and nearly white, resembling the usual commercially available cellulose derivatives.

Preparation: a. Direct Reaction.—Twenty-five grams of cellulose (deacetylated cellulose acetate) was dried by distilling benzene from it. After adding 250 g. of dry pyridine and 100 g. of trityl chloride, the mixture was stirred on a steam-bath in a closed flask. After three days a dark colored solution resulted. After dilution with 250 cc. of pyridine and filtering through felt, the product was precipitated by methanol. The dark reddish-tan precipitate was washed with methanol until free of tritanol; yield, 61.5 g., 95%; trityl, 63.0%, equivalent to 1.13 trityl groups per glucose unit.

b. Effect of Presoaking.—Thirty grams of cellulose was heated with 600 cc. of 1:1 pyridine–water on a steam-bath for one hour, after which the cellulose was recovered on a Buchner funnel. The product was then treated in the same way with three 600 cc. volumes of dry pyridine in order to displace the water.

Without letting the fibers become dry after the last filtration, 120 g. of trityl chloride (2.25 times theory for one hydroxyl) and 500 cc. of dry pyridine were added. The mixture was then stirred on a steam-bath for sixteen hours, after which the clear, dark solution was filtered through felt and precipitated into methanol. After reprecipitation from pyridine solution into methanol, the product was fibrous and nearly colorless; yield, 71 g., 93%; trityl, 61.0%, equivalent to 1.04 trityl groups for each glucose unit.

In Table I are recorded the results of reactions using quantities of trityl chloride up to six times the calculated amount for one trityl group for each glucose unit. It will be seen that the concentration of trityl chloride determines not only the time of reaction but also the amount of trityl which enters. Also, the more reagent used, the less color in the product, because of shorter time of reaction.

Seven samples of cellulose each weighing 2 g. were presoaked as usual. These were then heated on a steam-bath with 40-cc. portions of pyridine and increasing quantities of trityl chloride. After the cellulose was completely dissolved the products were isolated and purified.

Complete solution of the cellulose was used as a criterion of reaction time. Prolonged heating of the reaction mixture after the cellulose had dissolved gave an apparent reduction in trityl content (Table II). This reduction was

TABLE I

EFFECT OF TRITYL CHLORIDE CONCENTRATION ON REACTION WITH CELLULOSE AT 100°

Calcd. amount of TrCl	Reaction time, hrs.	Tr./g. u.[a]	Color
1.0	No soluble product	..	
1.5	136	1.05	Yellow
2.0	56	1.09	
2.5	31	1.11	
3.0	23	1.13	
4.0	23	1.19	
6.0	10	1.21	Colorless

[a] Tr./g. u. = moles of trityl for each glucose unit.

(1a) Presented before the Division of Cellulose Chemistry at the 105th meeting of the American Chemical Society at Detroit, Michigan.

(1b) B. Helferich and H. Koester, *Ber.*, **57**, 587–591 (1924).

(2) I. Sakurada and T. Kitabatake, *J. Soc. Chem. Ind.* (Japan), **37**, 604, B-5 (1934).

(3) P. P. Schorygin, A. J. Weitzman and N. N. Makarowa-Semljanskana, *J. Gen. Chem.* (U. S. S. R.), **7**, 430–439 (1937).

(4) R. C. Hockett and C. S. Hudson, THIS JOURNAL, **56**, 945–946 (1934).

(5) E. L. Jackson, R. C. Hockett and C. S. Hudson, *ibid.*, **56**, 947–949 (1934).

(6) P. E. Verkade, J. van der Lee and W. Meerburg, *Rec. trav. chim.*, **56**, 613–622 (1937).

(7) C. D. Hurd, C. O. Mack, E. M. Filachione and J. C. Sowden, THIS JOURNAL, **59**, 1952–1954 (1937).

TABLE II

EFFECT OF EXTENDED REACTION TIME AT 100°

(2.25 times theoretical trityl chloride)

Time, hrs.	% Tr.	Tr./g. u.	Appearance of product Color	Form
17	61.5	1.06	Cream	Fibers
41	60.7	1.02	Brown	Small fibers
138	55.0	.81	Dark brown	Powder

accounted for by the fact that these samples were found to contain nitrogen. No explanation is given for this other than that obviously the source of nitrogen must have been the pyridine. Such products precipitated out as dark powders and showed signs of considerable degradation.

Ten gram samples of cellulose, treated with 45 g. of trityl chloride (2.25 times theory for one hydroxyl) and 200 cc. of dry pyridine, were allowed to react for varying lengths of time. Sodium fusions on the 41 and 138 hour samples showed nitrogen to be present.

In Table III are shown the results of variation of reaction temperature. Soluble products were not obtained at 40°. However, at 68° etherification did take place, although slower than at higher temperatures. Products corresponding to low reaction temperatures were of better appearance and color than those made at higher temperatures.

TABLE III

VARIATION OF REACTION TEMPERATURE IN PREPARATION OF TRITYL CELLULOSE

(2.5 times theoretical trityl chloride)

Temp., °C.	Reaction time, hrs.	Tr./g. u.	Color
40	...	..	....
68	113	1.18	Colorless
80	50	1.07	Nearly colorless
100	15	1.06	Cream

Four samples of cellulose (2 g.) were treated at varying temperatures with 40 cc. of dry pyridine and 9 g. of trityl chloride (2.5 times theory of one hydroxyl). As soon as solution occurred, the samples were worked up as usual. Each product was nicely fibrous.

Stirring of the reaction mixture was found to speed up the rate of reaction, as is generally true in two-phase systems. This effect can be seen by comparison of the products of Table I, prepared without stirring, with those of Table III where stirring was used. In the former case reaction with 2.5 times the theoretical quantity of trityl chloride required thirty-one hours to produce a soluble product, while under similar conditions but with stirring (Table III) only fifteen hours were necessary.

A suitable analytical method was required for the trityl derivatives prepared. The trityl group was hydrolyzed by concentrated sulfuric acid, precipitated as triphenylcarbinol, and estimated gravimetrically. The cellulosic material was rendered water soluble by this treatment.

This procedure has worked satisfactorily on trityl cellulose, trityl cellulose acetates, and trityl cellulose carbanilates.

Determination of Trityl Group.—At least 2 g. of the material to be analyzed was dried for one hour at 100°. One-gram samples were then weighed and placed into 250-cc. Erlenmeyer flasks.

Each sample was treated with 10 cc. of concentrated sulfuric acid and stirred until complete solution occurred. Darkening generally took place during this digestion.

The technique used in precipitation of the triphenylcarbinol was important in determining how readily the precipitate could be filtered off. The flask containing the digested sample was swirled continually while a stream of distilled water from a wash bottle was directed into the flask. The solution darkened and as the carbinol precipitated the color changed to dark green, to yellow, and finally to a gray. At this point, the stream from the wash bottle was discontinued and the mixture was diluted with 90 cc. of distilled water. The granular precipitate of triphenylcarbinol was filtered through a weighed filtering crucible, and washed with water until free from sulfate ion. The crucible was dried in a 100° oven for exactly one hour, placed in a desiccator until cool, and weighed.

$$\frac{\text{Wt. of carbinol} \times 243 \times 100}{\text{Wt. of sample} \times 260} = \%\ \text{Trityl}$$

Detritylation of Cellulose Trityl Ether.—Quantitative removal of the trityl groups from trityl cellulose by treatment with acid has been shown in previously reported work. Although Helferich and Koester had detritylated their products using hydrogen chloride in a solvent, they were primarily interested in recovering the trityl chloride formed rather than the regenerated cellulose produced. A similar detritylation carried out by suspension in methanol containing concentrated hydrochloric acid resulted in better preservation of the cellulose. The product was found to be free of trityl but still retained its fibrous structure.

The removal of trityl made it possible to determine at least approximately how much degradation had occurred during the tritylation of deacetylated cellulose acetate. Viscosities of the original cellulose and that obtained after tritylation and subsequent detritylation were determined. The value was found to change from 12.7 to 5.95 centipoise. This change in viscosity could occur either during tritylation or detritylation. However, the acid conditions used in the latter process indicated the probability that most of the degradation occurred there rather than during tritylation, which is carried out in an anhydrous pyridine medium. To test this assumption, samples of deacetylated acetate were treated under the conditions of detritylation for varying lengths of time, and after sixteen hours were found to be reduced to a viscosity of 5.92 centipoises, which corresponds to that of the detritylated ether. From this it may be concluded that at least the greater part of viscosity loss occurred during the detritylation treatment.

A 10-g. portion of trityl cellulose (1.04 Tr./g. u.) in 500 cc. of methanol and 20 cc. of concentrated hydrochloric acid was stirred at room temperature for sixteen hours. The fibers, unchanged in appearance, were washed with methanol and dried; yield, 4.0 g., 100%; cuprammonium viscosity (2.5% cellulose concentration) 5.95 cps.

A sample dissolved in cold concentrated sulfuric acid gave no yellow color and on dilution with water gave no precipitate, hence detritylation was complete.

Three samples of deacetylated cellulose acetate (used as the starting material in the preparation of the trityl cellulose) each weighing 4 g. were suspended in 500 cc. of methanol and 20 cc. of concentrated hydrochloric acid. The mixtures were stirred at room temperature for seven, sixteen and twenty-four hours, respectively. The fibers were washed with methanol and dried. All were white and unchanged in external appearance. Cuprammonium viscosities (2.5% cellulose concentration) 7.2 cps.; 5.92 cps.; 5.05 cps.; compared with 12.7 cps. for starting material.

Position of the Trityl Group

From results thus far it could be seen that cellulose trityl ethers containing appreciably less than about one trityl group for each glucose unit were not soluble products. By variation of reaction conditions soluble products of 1–1.2 trityl groups for each glucose unit could be prepared. It thus became obvious that under severe reaction conditions the trityl group reacted with other than primary hydroxyl groups. There remained the possibility, however, that a product made by well chosen conditions adjusted to introduce approximately one substituted group for each glucose unit might be of very nearly specific configuration.

Oldham and Rutherford[8] in 1932 found that when *p*-toluenesulfonyl (tosyl) esters of glucose were heated with an excess of sodium iodide in acetone the residues in the sixth or primary position were exclusively and quantitatively replaced by iodine. This measure of primary hydroxyl has been proven to be valid for cellulose deriva-

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(8) Oldham and Rutherford, THIS JOURNAL, 54, 336 (1932).

tives by Cramer and Purves[9] and the latter[10,11,12] has used these reactions extensively in further investigations into the structure of cellulose derivatives. This procedure would lend itself to the present problem if the free hydroxyl groups in trityl cellulose could be quantitatively covered by a suitable reagent which would permit detritylation and subsequent tosylation treatment.

Work with phenyl isocyanate[13] has shown that reagent to react readily and, in general, completely with all free hydroxyls in cellulose or its derivatives. Furthermore,[14] the carbanilate group which is formed is extremely resistant toward hydrolysis in both alkaline and acid media. Hence it would appear that phenyl isocyanate would be an excellent "covering" reagent.

Trityl cellulose was first prepared, adjusting conditions to give a product containing about 1.03 trityl groups for each glucose unit. Carbanilation of the remaining free hydroxyl groups yielded a trityl cellulose carbanilate which was nicely fibrous, practically colorless, and showed good solubilities in many of the usual solvents.

To 18 g. of trityl cellulose (dried at 110° for twenty hours) in 100 cc. of dry pyridine was added 33 g. of phenyl isocyanate (3 times theory). After heating sixty-six hours at 100°, the product was precipitated and washed with methanol and purified by reprecipitation from pyridine solution into methanol. The product was fibrous and a light yellow color; yield, 27.3 g., 97%; trityl, 38.9%; N, 4.40%. Calculated for complete carbanilation: trityl, 38.8%; N, 4.28%.

Detritylation of this ester gave a white, fibrous product which was free of trityl and which still retained all its carbanilate groups.

A solution of 20 g. of trityl cellulose dicarbanilate in 240 cc. of dioxane, to which had been added with stirring 8 cc. of concentrated hydrochloric acid, was held at room temperature for twenty-three hours. After precipitation of the product into methanol and reprecipitation twice from pyridine solution the fibrous, nearly colorless product was dried. A sample dissolved in cold concentrated sulfuric acid gave no yellow color and when diluted with water gave no precipitate. Detritylation was therefore complete; yield, 11.9 g., 97%; N, 6.98%, 7.00%; calculated for complete detritylation, 6.97%.

The cellulose carbanilate thus produced was allowed to react with a large excess of tosyl chloride in pyridine solution and the rate of tosylation followed (Table IV). By sulfur analysis, the entering tosyl was found to increase rapidly and then to level off after about sixteen hours. Nitrogen analyses on the one- and seventy-hour samples showed no loss of carbanilate had occurred. All products were fibrous and nearly colorless, showing good solubility in many solvents.

TABLE IV

REACTION OF *p*-TOLUENESULFOCHLORIDE WITH CELLULOSE DICARBANILATE

Time, hrs.	Weight, g.	% S found	% N found	Ts./g. u.
1	3.2	3.96	5.53	0.60
3	2.7	4.95	..	.79
5	2.7	5.21	..	.85
20	2.5	5.52	..	.91
44	3.0	5.53	..	.92
70	6.2	5.55	5.06	.93

To a solution of 20 g. of cellulose dicarbanilate in 120 cc. of dry pyridine was added a cold solution of 160 g. of tosyl chloride (15 times theory) in 320 cc. of dry pyridine. After thorough mixing, the clear solution was maintained at 20°. Samples were removed at intervals, cooled to 0° and treated with sufficient 3:1 acetone–water (also cooled to 0°) to decompose all excess tosyl chloride present. The additions of dilute acetone were made slowly to maintain the temperature below 30° at all times. These were left at room temperature for ten minutes, then precipitated into large volumes of cold water. The fibers were reprecipitated from acetone into distilled water. All samples were nicely fibrous and light tan color. None gave a positive Beilstein test for halogen except the seventy-hour sample, which showed a trace present.

A sample of tosyl cellulose carbanilate (containing a high amount of tosyl) was then treated with sodium iodide in acetone. A slightly yellow, fibrous product was obtained which was found to contain 0.90 iodine atom for each glucose unit of the cellulose.

A 6-g. sample of the tosyl cellulose dicarbanilate containing 0.94 tosyl group per glucose unit, was dissolved in 100 cc. of acetone and treated with 30 g. of sodium iodide. After two and one-half hours reaction in a bomb at 100° the product was isolated by water precipitation of the solution after filtration. The fibrous yellow precipitate was washed with distilled water until the washings were free of halogen; yield, 4.6 gr. I, 22.6%; S, 0.35%; N, 5.43%; equivalent to 0.05 tosyl group and 0.90 iodine atoms for each glucose unit.

The entire series of reactions can best be seen in the chart of Fig. 1.

FIG. 1

Cellulose	3.00 OH/g. u.
↓ TrCl, pyridine	
Trityl cellulose	1.03 Tr./g. u.
↓ Phenyl isocyanate, pyridine	
Trityl cellulose carbanilate	1.03 Tr./g. u. 1.97 Carb./g. u.
↓ HCl, dioxane	
Cellulose carbanilate	1.97 Carb./g. u.
↓ TsCl, pyridine	
Tosyl cellulose carbanilate	1.97 Carb./g. u. .95 Ts./g. u.
↓ NaI, acetone	
Iodo (tosyl) cellulose carbanilate	1.97 Carb./g. u. .90 I/g. u. .05 Ts./g. u.

Interpretation of Results

Two facts stand out at once. First, of the original trityls, at least 0.03 were in a secondary position. This is necessarily true since 0.03 trityls entered in excess of the primary hydroxyl content. Second, of the original 1.03 trityl groups per glucose unit, at least 0.90 were in the primary position.

These facts leave 0.10 groups undetermined. The cellulose carbanilate contained 1.03 free hydroxyls which exactly represent those originally covered by trityl. These hydroxyls were then allowed to react with tosyl chloride which attacked both primary and secondary groups, but certainly the former at a much faster rate. By the time the sample was taken for iodination, the tosylation had almost stopped. Assuming a rate of primary tosylation twelve times as fast as that for the average of the secondary,[9,10] the amount of original primary may be shown by calculation to be 0.902 as compared with 0.90 found by iodination. Hence it is obvious that essentially all of

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[9] F. B. Cramer and C. B. Purves, THIS JOURNAL, **61**, 3458–3462 (1939).

[10] J. F. Mahoney and C. B. Purves, *ibid.*, **64**, 9 (1942).

[11] J. F. Mahoney and C. B. Purves, *ibid.*, **64**, 15 (1942).

[12] T. S. Gardner and C. B. Purves, *ibid.*, **64**, 1539 (1942).

[13] W. M. Hearon, G. D. Hiatt and C. R. Fordyce, *ibid.*, **65**, 829 (1943).

[14] W. M. Hearon, G. D. Hiatt and C. R. Fordyce, *ibid.*, **65**, 833 (1943).

the primary groups in the cellulose carbanilate were tosylated.

This shows 0.90 of the original 1.03 to be primary, and the remaining 0.13 to be secondary. Thus the rate of tritylation is 0.90 × 2/.13, or 13.8 times as fast in the primary as in the average of the secondary positions. These data point to the conclusion that under well-controlled reaction conditions tritylation of cellulose or cellulose derivatives may be effected to cover approximately 90% of the primary hydroxyl groups, with simultaneous reaction to a minor degree with secondary hydroxyl groups.

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Summary

1. Reaction conditions for preparation of cellulose trityl ethers have been studied in detail. Regenerated celluloses provide the most suitable starting materials. Products of from approximately 1.0 to 1.2 trityl groups for each glucose unit readily may be obtained. By proper choice of reaction conditions, very little degradation of cellulose occurs during tritylation.

2. Detritylation by treatment with acid may result in appreciable degradation of the cellulose. This may be largely avoided by use of a solution of hydrochloric acid in an organic solvent.

3. The tritylation reaction has been shown to be 13.8 times as fast with primary as with the average of secondary hydroxyl groups. Under moderate reaction conditions tritylation may be carried out to cover approximately 90% of the available primary hydroxyl groups, with simultaneous reaction to a small degree with secondary hydroxyl groups.

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Boron Fluoride as a Condensing Agent in the Fischer Indole Synthesis

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The preparation of indoles from the phenylhydrazones of aldehydes and ketones having an α-methylene group has been carried out with the aid of a number of acidic reagents, but a search of the literature revealed no instance of the use of boron fluoride as the condensing agent. In order to test the value of this reagent in the indole synthesis, a number of phenylhydrazones now have been treated with boron fluoride.

Those phenylhydrazones which have been converted to indoles by the aid of other reagents generally have undergone the reaction under the influence of the new condensing agent. The boron fluoride may be used in various ways. The gas may be bubbled into a solution of the phenylhydrazone in an organic solvent, with subsequent heating of the mixture to bring about decomposition of the phenylhydrazone–boron fluoride compound; if a non-polar solvent is used, this compound may separate as a heavy oil and the decomposition then may be effected by heating the oil either alone or under the solvent. Another technique consists in bubbling boron fluoride through a refluxing solution of the phenylhydrazone in a solvent such as benzene or xylene. Boron fluoride etherate may be employed to advantage, since the liquid etherate can be handled more conveniently than the gaseous boron fluoride. The phenylhydrazones, being stronger bases than ether, react with the etherate to form the phenylhydrazone–boron fluoride complexes and the liberated ether can be removed by distillation. The use of the liquid etherate permits convenient and accurate measurement of the amount of boron fluoride, an excess of which is to be avoided.

The formation of the phenylhydrazone–boron fluoride complexes is only slightly exothermic, and their decomposition in the presence of solvents proceeds smoothly; the decomposition in the absence of solvents may be so violent as to be mildly explosive. Acetic acid appears to be the best solvent for the reaction. For example, the decomposition of the complex of boron fluoride with the phenylhydrazone of methyl ethyl ketone, carried out in refluxing acetic acid, produced 2,3-dimethylindole in 85% yield; decomposition in refluxing ethanol gave a 69% yield and decomposition in the absence of a solvent gave only a 50% yield.

The yields of the various indoles prepared by the use of boron fluoride are shown in the accompanying table, along with the best yields reported in preparations carried out with other condensing agents. With few exceptions the yields obtained with boron fluoride are comparable to those of other procedures. A notable exception is the preparation of 2-methylindole from acetone phenylhydrazone; none of the product was obtained from the attempts with boron fluoride, although it has been prepared in 60% yield with zinc chloride. It is not surprising that the synthesis of indole from acetaldehyde phenylhydrazone failed, since this transformation apparently has not been carried out with any of the condensing agents. The synthesis of 2-carbethoxyindole-3-acetonitrile apparently is an unusually difficult preparation also. Alcoholic sulfuric acid is reported to be ef-