TABLE II

APPROXIMATE RATE CONSTANTS FOR SOLVOLYSIS AND
IODINATION OF THE TOSYLATES

Tolsylate $C_2H_5(OCH_2CH_2)_xOTs$	Solvolysis $k_1{}^a$	Iodination $k_2{}^b$	$k_2{}^c$
x = 0	0.124	0.56	0.66
1	.017	.12	.06
2	.023	.15	
3	.019	.36	

[a] In aqueous methanol (1:9) at 65 ± 1°; first order; unit, hours^{-1}. [b] With 0.1 mole of tosylate and 0.3 mole of iodide per liter at 22 ± 0.5°; second order; units, liters, moles^{-1}, hours^{-1}. [c] With 0.15 mole per liter both of tosylate and of iodide.

toluenesulfonate ($x = 0$) obviously was most reactive, as might have been expected from the known depressing effect of a β-ether group on the reactivity of organic halides, and from the similarity between halides and sulfonates.[57] Tosylated ethylene glycol, for example, hydrolyzed twelve times more slowly than tosylated ethanol.[65] The differences between the solvolysis rate constants for the higher tosylates ($x = 1$, 2 and 3, Table II) probably fell within the experimental error, and the same remark was true of the iodination rate constants for the tosylates with $x = 1$ and 2. The results in general suggest that the tosylation–iodination reaction as applied to cellulose acetates and ethers is valid for research on hydroxyethylcelluloses.

Acknowledgment.—The authors greatly appreciate the interest that Dr. R. T. K. Cornwell, of the Sylvania Division, American Viscose

Corporation (formerly Sylvania Industrial Corporation), showed in the research. One of us (C. W. T.) also wishes to thank the same organization for the Fellowship, and the Canadian Pulp and Paper Association for the summer stipend, awarded to him for the period of the work (1945–1946).

Summary

1. The following compounds were obtained pure: triethylene glycol monoethyl ether, its p-toluenesulfonate, the p-toluenesulfonate of diethylene glycol monoethyl ether, β-ethoxyethoxy-β'-iododiethyl ether and β-ethoxy-β'-iododiethyl ether. A new preparation of β-iodoethyl ether was described.

2. Diethylene glycol monoethyl ether was particularly liable to peroxide formation, was partly decomposed by sodium methylate, and yielded a tosylate decomposing at 125° (0.13 mm.) to equimolar amounts of 1,4-dioxane and ethyl p-toluenesulfonate. The latter product was replaced by tosylated ethylene glycol monoethyl ether when tosylated triethylene glycol monoethyl ether was thermally decomposed at 134° (0.03 mm.). Ethyl p-toluenesulfonate was more reactive toward solvolysis in 90% methanol, and toward iodination with sodium iodide in acetonylacetone, than the higher tosylates.

3. Data for the molar refractivities of the above series of compounds were completed, and the molar refraction of the O–SO$_2$ group in p-toluenesulfonates was found to be 10.5 ± 0.35.

(65) Foster and Hammett, THIS JOURNAL, **68**, 1736 (1946).

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p-Toluenesulfonyl Chloro and Iodo Derivatives of an Alkali-Soluble Hydroxyethylcellulose[1]

BY CLINTON W. TASKER AND C. B. PURVES[2]

Hydroxyethyl ethers of cellulose were first described by Hubert[3] in 1920, but excited no general interest until 1933, when the publications of Shorygin and Rymaschewskaja[4] commenced. These articles, together with those of Sönnerskog,[5] and Schorger and Shoemaker,[6] and also the relevant patents[7–19] showed that hydroxyethyl-

(1) Presented at the Chicago meeting of the American Chemical Society, April, 1948. Abstracted from a Thesis presented to the Faculty of McGill University in June 1947, by C. W. Tasker in partial fulfilment of the requirements for the Ph.D. degree.

(2) At above address.

(3) Hubert, J. Soc. Chem. Ind., **42**, 348A (1923); German Patent 363,192 (1920).

(4) Shorygin and Rymaschewskaja, (a) Ber., **66**, 1014 (1933); (b) J. Gen. Chem. (U. S. S. R.), **7**, 2428 (1937); (c) ibid., **8**, 1903 (1938).

(5) Sönnerskog, Svensk. Papperstidn., (a) **48**, 413 (1945); (b) **49**, 409 (1946).

(6) Schorger and Shoemaker, Ind. Eng. Chem., **29**, 114 (1937).

(7) Schorger, U. S. Patent (a) 1,863,208 (June 14, 1932); (b) 1,914,172 (June 13, 1933); (c) 1,941,277; (d) 1,941,278 (Dec. 26, 1933).

(8) Powers, Bock and Houk, U. S. Patent 2,087,549 (July 20, 1937).

(9) Berger and Bidaud, U. S. Patent 2,047,189 (July 14, 1936).

(10) Ellis, British Patent 408,730 (April 19, 1934).

(11) Seymour and Salvin, U. S. Patent 2,134,895 (Nov. 1, 1938).

(12) I. G. Farbenindustrie Aktiengesellschaft, British Patent (a) 383,612 (Feb. 12); (b) 383,617 (Feb. 13, 1931).

(13) Lilienfeld, U. S. Patent (a) 1,589,606 (June 22, 1926); (b) 1,722,927 (July 30, 1929); (c) 2,265,919 (Dec. 9, 1941).

(14) Richter, U. S. Patent 2,054,299 (Sept. 15, 1936).

(15) Broderick, U. S. Patent (a) 2,173,470; (b) 2,173,471 (Sept. 19, 1939).

(16) Thomas and Oxley, British Patent 463,317 (March 23, 1937).

(17) Levesley and Craik, U. S. Patent 2,046,174 (June 30, 1936).

(18) Oxley, Thomas and Downing, U. S. Patent 2,184,564 (Dec. 26, 1939).

(19) Dreyfus, (a) U. S. Patent 1,502,379 (July 22, 1924); (b) British Patent 478,259 (Jan. 17, 1938).

celluloses were obtained by condensing cellulose, either aged or pretreated or not, with ethylene chlorohydrin in the presence of alkali,[6,7,13b,18,19a] or with ethylene oxide, usually in the presence of caustic soda or a wide variety of other inorganic bases and salts.[7,10,15,19b] Control over the experimental conditions and the relative amounts of the reactants made it possible to prepare substantially similar products either by the chlorohydrin or the ethylene oxide route.[7] Hydroxyethylcelluloses thought to average substantially less than one hydroxyethyl group per glucose unit[7] were usually soluble in cold 10% caustic soda, while solubility in weaker alkali and in water increased as the substitution increased from more than unity to three. Acetates,[4a] benzoates,[6,7,20] stearates, xanthates[6] and mixed methyl and ethyl ethers[5,6] were prepared, but Sönnerskog[5] could not correlate their properties accurately with the degree or the uniformity of substitution.

The existence of hydroxyethylcelluloses averaging four,[21] or even six[22] substituent groups per glucose residue made it clear that some of the substitution occurred at previously formed hydroxyethyl groups rather than at the free hydroxyl groups of the cellulose itself. It followed that such products contained structures of type I in which n was an integer greater than unity, although simpler structures with n equal to unity
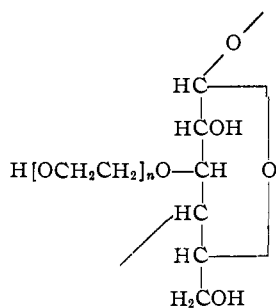
I, n an integer

were not excluded. With the possible exception of preparations made from cellulose dissolved in a quaternary ammonium base,[23] hydroxyethylcelluloses resulted from condensations between cellulose and ethylene oxide carried out in heterogeneous, or at best in quasihomogeneous, systems. Even samples of low average hydroxyethyl content might therefore contain local substitutions so high that units of type I, $n > 1$ might be present. Type I, $n > 1$ would also result, even in a homogeneous system, if ethylene oxide condensed preferentially with hydroxyethyl units. Consideration of structure I also shows that substitution in the sixth position of a glucose residue in cellulose failed to alter the number of primary alcohol

groups from the original value of unity. Substitution in the second or third positions, however, replaced a secondary alcohol by the primary hydroxyethyl unit. If the total number of primary hydroxyl groups was $1 + x$ per glucose residue, it followed that the number of hydroxyethyl groups attached to secondary positions was x, or an integral multiple thereof. One of the objects of the present research was to determine the value of x.

The preceding article[24] showed that the primary hydroxyl groups in the series $C_2H_5[OCH_2CH_2]_nOH$ were esterified at the normal rapid rate by excess p-toluenesulfonyl chloride (tosyl chloride) in pyridine. Although the resulting tosylates hydrolyzed with some rapidity and the higher members (n, 2 and 3) underwent quantitative decomposition during distillation in vacuo, all reacted normally with sodium iodide in acetonylacetone and yielded the corresponding β-halogen ethers. These experiments have now been extended to a commercial, alkali-soluble hydroxyethyl ether of cellulose of average substitution 0.44 and the molar amount of halogen in the final products has been assumed to be a measure of the moles of primary alcohol in the starting material. Although this method sharply differentiated unsubstituted primary from secondary hydroxyl groups in certain partly substituted glucose[25] and cellulose[26,27] derivatives, Malm and his collaborators[28] lately showed that with drastic conditions of halogenation, or with highly tosylated celluloses, the replacement extended to some secondary alcohol positions. The method has therefore to be used with discretion.

The hydroxyethyl content of hydroxyethylcelluloses has in the past been estimated from the gain in weight caused by the addition of ethylene oxide, and from the increase in carbon content,[20,22] but both methods are insensitive to appreciable changes in the substitution. Use was also made of the standard alkoxy estimation[20] because the hydroxyethyl group evolved ethyl iodide when heated with hydriodic acid. The recognition in 1946 by Morgan,[21] that ethylene was also evolved in this reaction and had to be included in the estimation, made it possible for him to devise the first reliable determination for the hydroxyethyl group. This valuable advance rendered the present work feasible.

Experimental

Materials and Analytical Methods.—The commercial hydroxyethylcellulose (Ceglin E. S. type H,[29] moisture 5.9%; ash 0.12%; substitution 0.443) consisted of white flocks that were freely soluble in cold caustic soda, that swelled in water, but were only incompletely gelatinized by prolonged steeping in pyridine.

After being ground in a Wiley mill to pass a 60-mesh

(20) Nikitin and Rudneva, J. Applied Chem. (U. S. S. R.), **8**, 1023 (1935).

(21) Morgan, Ind. Eng. Chem., Anal. Ed., **18**, 500 (1946).

(22) Davis, Ph.D. Thesis, New York State College of Forestry, Syracuse, N. Y. (1941).

(23) Bock, Ind. Eng. Chem., **29**, 985 (1937).

(24) Tasker and Purves, THIS JOURNAL, **71**, 1017 (1949).

(25) Oldham and Rutherford, ibid., **54**, 366 (1932).

(26) Mahoney and Purves, ibid., **64**, 9, 15 (1942).

(27) Gardner and Purves, ibid., **64**, 1539 (1942).

(28) Malm, Tanghe and Laird, ibid., **70**, 2740 (1948).

(29) The authors thank Dr. R. T. K. Cornwell and the Sylvania Division, American Viscose Corporation, for donating this material.

sieve, the material was carefully tested for peroxide oxygen by the ferrous–cyanate,[30] the benzidine–copper sulfate[31] and the acetic acid–potassium iodide[32] procedures, with uniformly negative results. Indeed, in the latter method the samples often failed to liberate the minute amount of iodine found in the blanks. Oxidations with 0.03 M iodine in a borate buffer at pH 9.2 and 25°, as recommended for the estimation of aldehyde groups in celluloses[33] revealed consumptions equivalent to 0.66, 1.31, 1.97 and 2.46 cc. of 0.1 N iodine per gram sample (iodine no.) after six, twelve, eighteen and twenty-four hours. The hydroxyethyl ether group was intrinsically unstable to hypoiodite because an iodine number greater than 4 was recorded for highly purified ethylene glycol monoethyl ether after twenty-four hours.

The sulfur and halogen analyses were by the semi-micro Carius method, with 20 to 30 mg. samples and 0.5 cc. of nitric acid. Over ninety consecutive analyses were made in this way without incident, but when the stated amount of nitric acid was exceeded, explosion of the glass Carius tube almost always resulted. Morgan's modified alkoxyl method[21] was used for all estimations of the ethylene oxide (hydroxyethyl) group, using 20 cc. of freshly distilled hydriodic acid for each 0.2 to 0.4 g. sample. If the sample contained a, b, c, and d moles of hydroxyethyl, tosyl, chlorine and iodine, respectively, per glucose unit, the base molecular weight, Z, was $162.14 + 44.04a + 154b + 18.5c + 110d$. The individual substitutions were found by solving the simultaneous equations, $\% \ OCH_2CH_2 = 4404 \ a/Z; \ \% \ S = 3206 \ b/Z; \ \% \ Cl = 3550 \ c/Z;$ and $\% \ I = 1274 \ d/Z.$ Either b, c, or d, of course, was often known to be zero. All percentages used in these calculations were the average of closely concordant duplicate or triplicate analyses.

All reagents and solvents were carefully purified as previously described,[24] and all equipment was connected through ground glass joints.

Tosylation of the Hydroxyethylcellulose.—The sample, 14.88 g. air dry or 14.0 g. oven dry, corresponded to 0.077 mole containing 0.231 mole of free hydroxyl groups. After being dissolved in 350 g. of 5% sodium hydroxide by stirring under nitrogen at −10°, the hydroxyethylcellulose was reprecipitated in ribbons and pellets of highly swollen gel by pouring the solution into 1.5 liters of gently stirred 50% aqueous acetic acid. After complete coagulation had taken place it was possible to stir the mixture vigorously for twenty minutes without producing a system so dispersed that easy separation was impossible. The gel was recovered and washed in a well-laundered muslin bag until the effluent had the same pH (5.7) as the water used. The weight of the dry bag before and after use showed no significant change. The gel was then transferred to a tared 2-liter flask and the water it contained was eliminated by the continous addition and evaporation of dry pyridine into a vacuum so regulated that the bath temperature never exceeded 60°. Distillation was stopped when the distillate had regained the refractive index, n^{20}D, 1.5090, of pure dry pyridine and was miscible without turbidity with petroleum ether. The resulting transparent hydroxyethylcellulose–pyridine gel was cooled to 5°, and 274.1 g. (1.44 moles) of tosyl chloride, dissolved in enough cold pyridine to give a total weight of 1540 g. (19.46 moles) of pyridine, was added. Thereafter the tightly stoppered flask was kept at 25 ± 0.1° and was periodically shaken vigorously by hand. All gel particles disappeared after about twelve hours and for a few hours subsequently the system appeared homogeneous, but after fifteen to twenty-one hours separated into a highly swollen gel and a slightly yellow supernatant liquid phase.

In contrast to the earlier state, it was possible, from twenty-one hours onward, to disperse the gel uniformly by

shaking and to withdraw representative aliquots of 100 to 150 cc. at various times. Each of these aliquots was slowly poured into 1.5 liters of chilled, rapidly stirred water, and the fibrous tosylate that precipitated was washed by decantation with 500 cc. of water, recovered quantitatively on a sintered glass funnel, and washed thoroughly until free from chlorine ions and pyridine. The fibers from the earlier aliquots were white, but those isolated from the later red-brown aliquots were tan in color. They were dried through methanol and ether and finally *in vacuo* over phosphorus pentoxide for at least two days at room temperature prior to analysis. Since reliable aliquots could not be obtained from the tosylation mixture prior to about twenty-one hours, separate 2-g. samples (dry weight) of the original hydroxyethylcellulose were precipitated from caustic soda, exchanged into pyridine and tosylated for varying brief times exactly as described, but using one-seventh quantities of reagents. Precipitation of each entire tosylation mixture into 2.5 liters of cold water yielded hard white pellets gradually giving place to white fibers as the time of tosylation increased. The percentage analyses of these products, isolated exactly as described, are included in Table I, the corresponding substitutions being in Figs. 1 and 2.

TABLE I

ANALYSES OF HYDROXYETHYLCELLULOSE TOSYLATED FOR INCREASING TIMES

Tosylation,[a] hours[b]	S, %	Cl, %	CH₂CH₂O, %	Yield,[d] %
0	0	0	10.76	
1	9.21	Trace		95.3
3	10.68	0.14		93.8
5	10.90	0.11	4.18	91.7
7	10.92	0.26		94.4
9	11.02	0.33		92.3
12	10.95	0.43		95.1
21.5	11.68	0.70	2.93	
Days[c]				
2	11.94	1.14	2.00	
3	11.95	1.38		
5	12.02	1.83		
8	12.17	2.38		
12	11.88	2.87		
20	11.84	3.65	1.57	
40	11.64	4.52	1.49	

[a] With excess tosyl chloride in pyridine at 25°. [b] Individual runs. [c] Aliquots from one large run. [d] Corrected for substitutions.

Partial Replacement of Tosyloxy Group by Chlorine.— A 1.2 g. (0.003 mole) sample of the product from twenty days of tosylation, dissolved in 20 cc. of dry pyridine, was mixed with 1.5 g. (0.041 mole) of dry hydrogen chloride gas dissolved in 30 cc. of the same solvent. After being heated under reflux at 85° for four hours, the mixture was cooled and poured into 200 cc. of dry, redistilled petroleum ether (b. p. 30 to 50°). The granular, light-tan precipitate together with pyridine salts was recovered as a filter cake which was macerated and thoroughly washed with water until free from chloride ion and pyridine. This product, 0.985 g. after drying as described above, did not swell or dissolve in water or in common organic liquids, even when the latter contained some water. *Anal.* Found: S, 9.30, 9.40; Cl, 8.51, 8.65; OCH₂CH₂, 1.99, 1.74, 1.68. The composition corresponded to cellulose substituted with 0.819 chlorine atom, 0.982 tosyl and 0.132 ethylene oxide groups per glucose unit, and the yield to 100%.

The tosylates obtained after seven hours and two days were submitted to the above reaction, but the chlorinated products were soluble, or so highly dispersed in water, aqueous pyridine and common organic liquids that they

(30) Trust, *Petroleum Engr.*, **13**, 53 (1942).

(31) Allen, "Commercial Organic Analyses," Churchill, London, 1924, Vol. I, p. 302.

(32) Liebhafsky and Sharkey, THIS JOURNAL, **62**, 190 (1940).

(33) Rutherford, Minor, Martin and Harris, *J. Research Natl. Bureau Standards*, **29**, 131 (1942).
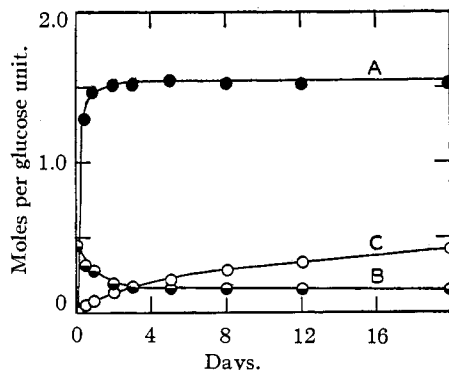
Fig. 1.—Changes in substitution of a hydroxyethyl cellulose during tosylation at 25°: plot A, tosyl; plot B, hydroxyethyl; plot C, chlorine substitution.
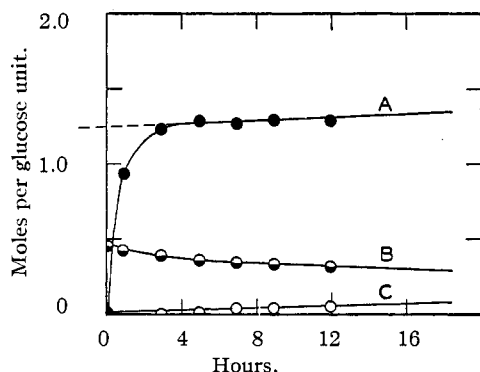

Fig. 2.—Initial changes in substitution of a hydroxyethyl cellulose during tosylation at 25°: plot A, tosyl; plot B, hydroxyethyl; plot C, chlorine substitution.

could not be isolated in good yield or adequately purified. A sample of the original hydroxyethylcelluose, when heated with a similar pyridine hydrochloride solution at 85° for four hours, was recovered chlorine-free and with the original hydroxyethyl content. Found: CH_2CH_2O, 10.69, 10.77; substitution, 0.44.

Partial Replacement of Tosyloxy Group by Iodine.—A 250-cc. flask containing 200 cc. of pure, dry acetonylacetone, 4 g. (0.027 mole) of sodium iodide and 2.42 g.(0.007 mole) of the three-hour tosylated hydroxyethylcellulose was heated under reflux for twelve hours at 115 to 120°. The ester was not completely soluble in the mixture, which developed a deep red color. Precipitation of the entire mixture into 1.8 liters of rapidly stirred ice-water yielded a granular, slightly yellow product that was repeatedly washed with water, then with 0.1 N sodium thiosulfate and again with water until all traces of iodide ion, free iodine and acetonylacetone had been removed. The iodinated product, 1.84 g., was dried *in vacuo* over phosphorus pentoxide for two days at room temperature. *Anal.* Found: S, 1.19, 1.15; I, 41.3, 41.4; CH_2CH_2O, 5.43, 5.44, 5.29. When the original trace of chlorine (0.14%) was neglected, these data corresponded to iodine, tosyl and ethylene oxide substitutions of 0.996, 0.114 and 0.373, respectively, and to a yield of 92%.

Results and Discussion

Although the pure monoethyl ethers of diethylene and triethylene glycol readily formed peroxides,[24] three different tests for peroxides were negative with the commercial hydroxyethylcellulose, of unknown age, that was used. The observation

that the latter, like the simpler analogs, slowly reduced alkaline hypoiodite discredited the use of the iodine number as a measure of average molecular weight[7,19b,22] in the hydroxyethylcellulose series.

Experiment showed that precipitation from alkali followed by careful solvent-exchange from water to dry pyridine converted the hydroxyethylcellulose to a uniform, highly swollen, completely translucent gel that seemed physically suitable for the tosylation with excess tosyl chloride and pyridine at 25°. This reaction was followed by the analyses of intermediate products (Table I) and from these data it was easy to calculate the corresponding changes in the tosyl, chlorine and ethylene oxide substitutions recorded in Figs. 1 and 2. The smooth nature of the plots, the high yields of the intermediate products, and the proved reliability of the analytical methods with simple analogs,[24] made it likely that these calculations were accurate to within ±0.02 mole per glucose unit. Figure 1, plot B shows that about half of the original 0.44 hydroxyethyl groups were eliminated during the first two days of tosylation but that the subsequent decrease was very slow, about one third remaining after twenty and also after forty days. Although pyridine hydrochloride was formed as a by-product of the tosylation and was used by Prey,[34] as an ether-cleaving agent, the original material was stable when heated at 85° with this substance in pyridine solution. It followed that the loss of hydroxyethyl groups occurred after, and not before, their tosylation and that these groups consisted of two distinct kinds, about one-third yielding stable, and the other two-thirds unstable, tosylates. When it was recalled that ethyl and β-ethoxyethyl p-toluenesulfonates were stable to vacuum distillation[35] but that the tosylates of higher homologs were nearly quantitatively cleaved to 1,4-dioxane and a stable lower tosylate,[24] it seemed likely that in the hydroxyethylcellulose one-third of the substituent was united as individual groups to the cellulose (structure I, $n = 1$) whereas the remaining two-thirds was present as polyethylene oxide chains (structure I, $n > 1$). The decomposition of an even-membered chain in the way suggested would transfer the tosyl group to the cellulose skeleton and would alter its nature from primary to secondary if the original chain was attached to a secondary alcohol position. An odd-membered chain, on the other hand, would yield a stable, tosylated, monomeric substituent and the ratio of primary to secondary tosyl groups would not be altered. Nothing in this mechanism would necessarily involve the permanent loss of tosyl units.

Plot C records a rather rapid chlorination, which probably resulted in the conventional way by the interaction of primary tosyl groups with by-product pyridine hydrochloride. The difference in reaction rates in plots B and C suggested

(34) Prey, *Ber.*, **75**, 350, 445 (1942).
(35) Tipson, *J. Org. Chem.*, **9**, 235 (1944).

that the loss of hydroxyethyl units and the gain in chlorine were independent side-reactions, and this inference was supported by the fact that the sum of the tosyl (plot A) and chlorine substituents increased steadily as hydroxyethyl groups decreased. Since both side reactions were insignificant during the early hours of the tosylation (Fig. 2, plots B and C), it seemed legitimate to determine the extent of the initial rapid tosylation by extrapolating the latter portion of plot A to zero time. The result, 1.22 moles, was taken as equal to the number of primary alcohol groups in the original hydroxyethylcellulose because their rate of reaction was comparable to that displayed by primary alcohol groups in cellulose ethers[27] and cellulose acetate[26] tosylated in closely similar circumstances. It then followed from the argument in the Introduction that 0.22 mole represented hydroxyethyl units substituted in the secondary alcohol positions of the cellulose, the actual number of such units being greater if they included polymers.

The fact that hydroxyethylcellulose tosylated for only three hours contained a negligible substitution (0.01 mole) of chlorine (Table II, line 2) made it possible to check the content of primary tosyl groups by the iodination method. Although the sample was heated with excess sodium iodide in acetonylacetone for twelve, instead of the usual two or four,[26] hours at 115 to 120°, and the replacement proceeded in over 90% yield, the product contained only 1.00 instead of the expected 1.22 moles of iodine (line 3), and the over-all substitution (tosyl plus halogen) decreased from 1.24 to 1.11 moles. According to Malm and his collaborators[28] the iodination method sometimes overestimated, but never underestimated, the content of primary tosyl groups. The replacement of primary tosyl by chlorine in the sample tosylated for twenty days (line 4) was completed by heating with pyridine hydrochloride in pyridine, the yield of the granular light tan product being nearly quantitative. A decrease in tosyl plus chlorine substitution from 1.93 to 1.80 moles, or of 0.13 mole, corresponded exactly to the similar decrease occasioned by iodination but the final chlorine content was only 0.82 mole. Halogenation, therefore, revealed only 1.00 and 0.82 mole of primary hydroxyl groups, whereas the minimum number possible was 1.0 for cellulose, or any hydroxyethylcellulose, and the number probable in the present case was 1.22. This large discrepancy, which could not be attributed to inadequate conditions of halogenation, suggested that another side-reaction occurred. No significant loss of the hydroxyethyl group was involved (Table II, lines 2 and 3, 4 and 5) but the reaction occasioned a decrease of 0.13 mole in the tosyl plus halogen substitution and another of at least 0.18 mole in primary tosyl. Although no direct evidence was obtained, this side-reaction was perhaps connected with the well-known ability of alkyl *p*-toluenesul-

TABLE II

CHANGES IN SUBSTITUTIONS CAUSED BY HALOGENATION OF TOSYLATED HYDROXYETHYLCELLULOSES

Sample	-OCH₂-CH₂	Tosyl	Halogen	Moles per glucose residue Primary hydroxyl	Secondary tosyl
Original	0.44	1.22[a]	0.0	1.22[a]	0.0
Three-hour ester	.39	1.23	0.01 Cl		
Iodinated	.37	0.11	1.00 I	1.00	.11
Twenty-day ester	.15	1.51	0.42 Cl		
Chlorinated	.13	0.98	0.82 Cl	0.82	.98

[a] Later tosylation rate plot extrapolated to zero time.

fonates to act as alkylating agents in basic media.[36] Let it be assumed that the 0.15 mole of hydroxyethyl group stable throughout the tosylation quickly became esterified and then slowly alkylated unsubstituted hydroxyl groups of the cellulose at some stage in the reactions. As structures II and III show, such an alkylation might involve either the tosyl or halogen group and would result in the formation of a cyclic ether of ethylene glycol, the ethylene oxide unit being retained while 0.15 mole of primary alcohol group was eliminated. Although structures II and III are quite arbitrary as to detail, the iodinated and halogenated derivatives were soluble in some organic liquids and therefore were not likely to contain glycol ether cross-links between different glucose residues.
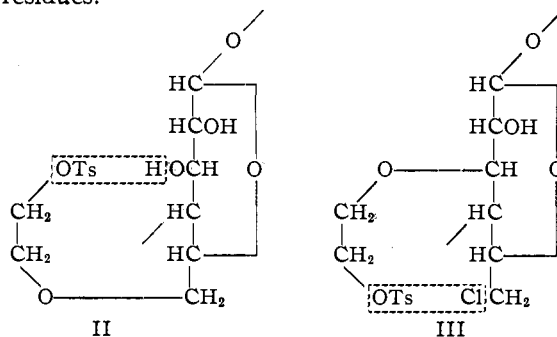

II   III

Table III contains an arbitrary distribution of monomeric and dimeric substituents in the primary and secondary positions of the hydroxyethylcellulose. The distribution was found by trial and error and its only merit is to summarize the experimental data and the series of unproved *ad hoc* assumptions outlined above.

The original material was assumed to have 0.05 primary plus 0.10 secondary position substituted by the dimeric unit, $-O-CH_2CH_2-O-CH_2-CH_2OH$, which during tosylation was gradually eliminated. This elimination reduced the ethylene oxide substitution from 0.44 to 0.38 and finally to 0.14 mole, and involved the transfer first of 0.02 and then of 0.10 mole of primary tosyl group to secondary positions on the cellulose. The monomeric hydroxyethyl substituents (0.02 plus 0.12 mole) were retained by the cellulose but the alkylating action of their tosylates converted them to cyclic

(36) Morgan and Cretcher, THIS JOURNAL, **70**, 375 (1948).

ether units. The same action caused the loss of at least 0.16 mole of primary tosyl or hydroxyl positions (structures II and III).

TABLE III

ARBITRARY DISTRIBUTION OF SUBSTITUENT IN AN ALKALI-SOLUBLE HYDROXYETHYLCELLULOSE

	Moles CH₂CH₂O per glucose unit					
	Primary position		Secondary position			
Sample	Monomer	Dimer	Monomer	Dimer	Total	Primary OH
Original	0.02	0.05	0.12	0.10	0.44	1.22
				Found	.44	1.22ᵃ
Three-hour	.02	.04	.12	.08	.38	1.06ᵇ
tosylate				Found	.39	1.00
Twenty-day	.02	.0	.12	.0	.14	0.86ᵇ
tosylate				Found	.15	0.82

ᵃ By extrapolation of tosylation rate plot. ᵇ All tosylated monomers (0.02 + 0.12 mole) assumed to have become alkylated at primary hydroxyl positions, with elimination of the tosyl group.

Summary

1. A commercial alkali-soluble hydroxyethylcellulose of substitution 0.44 was esterified at 25° with excess p-toluenesulfonyl chloride in pyridine. The rapid initial reaction was attributed to a primary hydroxyl content of 1.22 moles per glucose residue and in consequence at least 0.22 mole of the hydroxyethyl substituent was tentatively assigned to secondary positions in the cellulose.

2. When the tosylation was prolonged for twenty to forty days, only 0.14 mole of hydroxyethyl group remained in the product. The elimination of 0.30 mole might be a measure of the polyethylene oxide units originally present as even-membered chains. The residual 0.14 mole might be attached to the cellulose directly, either as a monomer or as the initial unit of an odd-membered polyethylene oxide chain.

3. Partial replacement of tosyloxy groups by halogen, using sodium iodide or pyridine hydrochloride, had little effect on the hydroxyethyl substitution, but decreased the combined tosyl plus halogen substitution by 0.13 mole. Iodine, 1.0 mole per glucose unit, was introduced into one sample and 0.82 mole of chlorine into another, the substitution in both cases presumably occurring in the primary alcohol positions remaining in the two samples. Possible causes for the apparent decrease from the original 1.22 moles of primary alcohol units were suggested.

Histamine Antagonists. IV. Indole and Carbazole Derivatives

BY JOHN B. WRIGHT

In conjunction with a broad study of histamine antagonists under way in this Laboratory a number of 1-(dialkylaminoethyl)-indole and 9-(dialkylaminoethyl)-carbazole derivatives have been prepared and tested for antihistaminic activity.

A degree of similarity of structure exists between certain of these derivatives, such as 1-dimethylaminoethyl-2-phenylindoline (I), and N,-N - dimethyl - N' - benzyl - N' - phenylethylenediamine ("Antergan") (II). Because of this resemblance and the comparative ease with

I   II
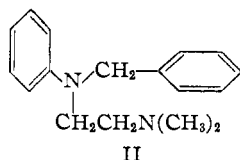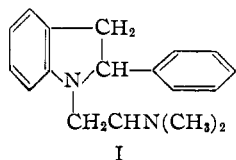
which indole and carbazole derivatives may be prepared by means of the Fischer synthesis it seemed of interest to investigate compounds of this type. In this work β-(1-pyrrolidyl)-ethyl and β-dimethylaminoethyl were chosen as substituting groups in the indole or carbazole nucleus. The former grouping was chosen because of the promise that it has shown with other nuclei.[1,2]

The preparation of these compounds was carried out by forming the sodium salt of the indole or carbazole derivative by heating with either sodium or sodium amide in toluene or xylene solution, followed by heating of the resulting mixture under reflux with the dialkylaminoethyl chloride, either as the free base or as the hydrochloride salt. The yields ranged from 34–96%. The method of preparation outlined is essentially that of Eisleb[3] who prepared 9-(β-diethylaminoethyl)-carbazole and 1-(β-diethylaminoethyl)-2-methylindole by this method.

The indole and carbazole nuclei that were used in this work were indole, indoline, 2-phenylindole,

(1) Wright, Kolloff and Hunter, THIS JOURNAL, 70, 3098 (1948).

(2) Reid, Wright, Kolloff and Hunter, ibid., 70, 3100 (1948).

(3) Eisleb, Ber., 74B, 1433 (1941).