water. The yield dropped to 70.5% and the product still melted poorly (103–110°). However, after recrystallization from dilute alcohol the melting point was satisfactory. When this same experiment was carried out at 200° for 6 hr. an 83.5% yield of X was obtained. It melted at 110–113° before recrystallization.

Hydrolysis with sodium hydroxide. When the sodium salt of the barbituric acid in water (*p*H 9.0) was heated at 200° for 5–10 min. a 78% yield of X melting at 110–112° was obtained. However, when the free acid was hydrolyzed in the presence of an equivalent of sodium hydroxide under the same conditions, the yield dropped unless the *p*H of the solution had been adjusted with acetic acid to about *p*H 9.0 before reaction.

2-Allyloctanamide (XXIII). *Hydrolysis of 5-allyl-5-hexylthiobarbituric acid.* 5-Allyl-5-hexylthiobarbituric acid (8.05 g., 0.03 mole) in 25 cc. of water and 25 cc. of concd. aqueous ammonia were placed in a glass lined Hastelloy bomb and heated for 5–10 min. at 200°. After cooling, the vessel was vented. A strong odor of hydrogen sulfide was noted. The white crystalline solid was filtered and washed with cold water. It did not give satisfactory analysis after recrystallization from petroleum ether (b.p. 63–68°). It was then dissolved in anhydrous ether, filtered from insoluble material, and dried in a rotary drier with slight warming while under reduced pressure. After thorough drying, the product gave a satisfactory analysis (see Table I).

Several other thiobarbituric acids were subjected to the same conditions, but isolation difficulties caused us to abandon any further work with them.

2-Propargyl-3-methylhexanoylurea. A solution of 9.0 g. (0.038 mole) of 5-propargyl-5-(1-methylbutyl) barbituric acid in 40 cc. of water and 40 cc. of concd. aqueous ammonia was heated for 5–10 min. at 200°. After removal from the source of heat and cooling as in the other examples a crystalline solid plus some oily material was obtained. The mixture was treated with anhydrous ether and filtered. The solid was ether insoluble. The filtrate was further extracted for work up and distillation and isolation of compound XXX.

The ether insoluble product weighing 2.0 g. was recrystallized from dilute alcohol. It melted at 200°.

Anal. Calcd. for $C_{11}H_{18}N_2O_2$: C, 62.82; H, 8.62; N, 13.32. Found: C, 62.92; H, 8.85; N, 13.32.

α-Allyl-γ-methylbutyrolactone. Thirty-three grams (0.146 mole) of 5-allyl-5-(2-hydroxypropyl)barbituric acid was hydrolyzed in 75 cc. of water and 75 cc. of concd. aqueous ammonia for 5–10 min. at 200°. The resulting product was an oil which was extracted from the reaction mixture with ether. The ether extract was dried over anhydrous magnesium sulfate and then the ether was removed. The residue was distilled and the fraction boiling at 77–80°; 1 mm., n^{25}_D 1.4519 was collected. The yield amounted to 60%.

Anal. Calcd. for $C_6H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.87; H, 8.77.

Similar runs at 150° and even at 120° yielded the same product. All were shown to be identical by infrared analysis.

α-Ethyl-β-methylbutyramide (III). A mixture of 17.2 g. (0.1 mole) of α-ethyl-β-methylbutyrylurea and 75 cc. of water was heated in a 183 cc. stainless steel bomb for 5–10 min. at 200°. After cooling the bomb and contents, 12.0 g. (93.5% yield) of III melting at 137° was obtained.

In a similar experiment with 5-ethyl-5-isopropylbarbituric acid in diluted aqueous ammonia 91.8% yield of III melting at 137.5° was obtained. The melting point did not change after recrystallization from water.

Acknowledgment. The authors are indebted to Mr. E. F. Shelberg and Mr. O. F. Kolsto and staff for the microanalyses. They also wish to thank Mr. W. Washburn and his group for infrared analysis.

NORTH CHICAGO, ILL.

[CONTRIBUTION FROM THE ANIMAL RESEARCH INSTITUTE, RESEARCH BRANCH, CANADA DEPARTMENT OF AGRICULTURE]

Syntheses of N^{ϵ}-Tosyl-L-lysine Peptides[1a]

JOHN D. CIPERA

Received March 18, 1960

A novel approach to the incorporation of N^{ϵ}-tosyl-L-lysine into the peptide chains is outlined. The syntheses of several sequences appearing in the ACTH and MSH molecules are described in detail.

Lysine figures prominently in the active portions of the adrenocorticotropic hormones,[1b] melanotropic hormones,[2] and other biologically active peptides.[3] Thus, efficient methods for linking lysine into peptide chains are of considerable interest. Such methods must, however, take into account the difficulties inherent in the condensation reactions involving the carboxyl group of lysine.[4] These difficulties are compounded when two lysine moieties are to be coupled together.

Best results with this general type of reaction have been reported when both α- and ε-amino groups of lysine were protected by a carbobenzyloxy radical.[4,5] However, such products cannot be used effectively for selective reactions involving only one of the two amino groups, since both amino groups are protected by the same

(1) (a) Supported by a grant from the American Cancer Society, this investigation was carried on in the Biochemistry Department of the School of Medicine, University of Pittsburgh. It was presented in part at the 136th Meeting of the American Chemical Society in Atlantic City, N. J., September 1959.

(1) (b) P. H. Bell, *J. Am. Chem. Soc.*, **76**, 5565 (1954).

(2) I. I. Geschwind, C. H. Li, and L. Barnafi, *J. Am. Chem. Soc.*, **79**, 620 (1957).

(3) F. Sorm, B. Keil, V. Holeysovsky, V. Knesslova, V. Koska, P. Masiar, B. Meloun, O. Mikes, V. Tomasek, and J. Yanecek, *Collection Czech. Chem. Commun.*, **22**, 1310 (1957).

(4) J. S. Fruton, *Advances in Protein Chem.*, **5**, 58 (1949); M. Goodman, and G. W. Kenner, *Advances in Protein Chem.*, **12**, 507 (1957).

(5) B. F. Erlanger and E. Brand, *J. Am. Chem. Soc.*, **73**, 4025 (1951); S. G. Waley and J. Watson, *J. Chem. Soc.*, 475 (1953).

radical. Consequently the possibilities of selective introduction of these products into longer peptide chains are limited.

The choice of protecting groups was determined, beside the usual considerations of high yield and a lack of racemization, by their positioning on particular amino groups and by the requirement that they should be selectively removable. On the basis of these considerations it was decided to use *p*-toluenesulfonyl (tosyl) radical for protecting the ϵ-amino groups and the carbobenzyloxy radical for the α-amino groups.

While the carbobenzyloxy radical can be removed by catalytic hydrogenation,[6,7] the tosyl radical resists this cleavage. Thus, the α-amino group can be freed whenever it is required for linking with a carboxyl of another amino acid or peptide. The protecting action of the tosyl radical on the ϵ-amino group will be needed until the whole intended peptide is assembled. It can then be removed *e.g.* by the action of sodium in liquid ammonia.[8]

The selective tosylation of ϵ-amino group was made possible by immobilizing the α-amino group in a copper complex.[9] The N^{ϵ}-tosyl and N^{α}-carbobenzyloxy-N^{ϵ}-tosyl derivatives of L-lysine were prepared by procedures similar to those described by Roeske, *et al.*[10]

In the choice of coupling methods the primary consideration was the possible degree of racemization. Therefore the azide method was chosen for the first coupling experiments with the above-mentioned derivatives. The intermediate, N^{α}-carbobenzyloxy-N^{ϵ}-tosyl-L-lysine hydrazide, which is a novel compound,[11] was found to be useful for introducing the N^{ϵ}-tosyl-L-lysine moiety into a peptide chain. For example, it was used to introduce lysine into the position 11 of the α-MSH type peptide.[11] However, side-reactions apparently accompanied this type of coupling reaction as indicated by the need for extended purification of the products.

In a more difficult case, when it was attempted to couple this azide with another N^{ϵ}-tosyl-L-lysine moiety, the product failed to crystallize. No crystals were obtained even after subsequent saponification and catalytic hydrogenation.

Results similar to the above were obtained also when other methods of carboxyl activation, *e.g.*, the mixed carboxylic–carbonic acid anhydride[12] or the carbodiimide[13a] methods, were tested.

The chromatographic studies confirmed the presence of unwanted side-reactions during the attempted couplings of two N^{ϵ}-tosyl-L-lysine moieties by the carboxyl-activating methods. When aliquots of these products were saponified, decarbobenzoxylated by catalytic hydrogenation, and subjected to paper chromatography in either acidic or basic solvent systems,[13b] the chromatograms of products from all three methods (azide, mixed anhydride, or diimide) were very similar. In the acidic solvent system two spots appeared, a weaker one of R_f 0.75, which is the same as that of N^{ϵ}-tosyl-L-lysine, and a stronger one of R_f 0.90, which was later found to be the R_f value of N^{ϵ}-tosyl-L-lysyl-N^{ϵ}-tosyl-L-lysine. In the basic solvent system four spots appeared, a weaker one of R_f 0.53, which is the same as that of N^{ϵ}-tosyl-L-lysine, a stronger one of R_f 0.65, which was later found to be the R_f value of N^{ϵ}-tosyl-L-lysyl-N^{ϵ}-tosyl-L-lysine, and two weaker spots of R_f 0.74 and 0.89, the origin of which can only be conjectured. Since these two spots did not appear in the acidic solvent system, there is a possibility that they were formed by the effect of alkaline *p*H on the side-products. Another possible explanation is that these two compounds were not resolved by the acidic solvent system and stayed combined in either one of the two spots.

The possible character of these side-reactions is indicated by the relative ease with which the ϵ-amino group can be brought to close proximity with the carboxyl group. Although the lactam-formation is most facile when the amino and carboxyl groups are in a δ-position with respect to each other, thus producing a single-plane five-membered ring, the lactam forming tendency of the compounds with amino and carboxyl groups farther apart cannot be discounted as a significant factor, particularly when one or both of these groups are activated.[14] Even the tosyl-protected amino groups may undergo such reactions.[15]

In order to eliminate these side-reactions, it was decided to avoid the carboxyl-activating methods and to attempt the formation of the peptide bond by activating the α-amino group instead. Of the methods for activation of the amino group, the best known are those employing

(6) M. Bergmann, and L. Zervas, *Ber.*, **65**, 1192 (1932).

(7) G. W. Anderson, J. Blodinger, and A. D. Welcher, *J. Am. Chem. Soc.*, **74**, 5309 (1952).

(8) V. du Vigneaud and D. J. Behrens, *J. Biol. Chem.*, **117**, 27 (1937).

(9) A. Neuberger and F. Sanger, *Biochem. J.*, **37**, 515 (1943).

(10) R. Roeske, F. H. C. Stewart, R. J. Stedman, and V. du Vigneaud, *J. Am. Chem. Soc.*, **78**, 5883 (1956).

(11) K. Hofmann, T. A. Thompson, M. E. Woolner, G. Spühler, H. Yajima, J. D. Cipera, and E. T. Schwartz, *J. Am. Chem. Soc.*, in press.

(12) R. A. Boissonnas, *Helv. Chim. Acta*, **34**, 874 (1951); J. R. Vaughan, Jr., *J. Am. Chem. Soc.*, **73**, 1389 (1951); Th. Wieland and H. Bernhard, *Ann.*, **572**, 190 (1951).

(13) (a) J. C. Sheehan and G. B. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1958).

(13) (b) Acidic solvent system (Partridge): upper phase of 1-butanol–acetic acid–water (4:1:5); basic solvent system: 2-butanol–3% ammonia (3:1).

(14) F. Wrede, *Z. Physiol. Chem.*, **206**, 146 (1932); D. W. Adamson, *J. Chem. Soc.*, 39 (1943).

(15) C. R. Harington and R. C. G. Moggridge, *J. Chem. Soc.*, 706 (1940).

the isocyanates,[16] the phosphazo compounds,[17,18] and the amides of phosphoric,[19] phosphorous,[7,18,20] and arsenous[21] acid. The most promising appeared to be that based on the phosphorous acid derivative, the pyrophosphite method of Anderson.[7] Using freshly prepared phosphorous acid anhydride (pyrophosphite) and following the "amide", *i.e.*, the amino-group activating procedure of the Anderson method, crystalline derivatives were easily obtained even in the case when two N^{ϵ}-tosyl-L-lysine moieties were coupled together into a dilysine derivative.

A brief test of an analogous method employing phosphorus pentoxide[19] had shown it to be inferior to the Anderson method.

Two methods for the preparation of the tetraethylpyrophosphite, that of Arens[22] and Anderson,[7] appeared to be superior to the other ones. Application of the Arens method would involve a rather risky preparation of acetylene ether. Therefore it was decided to use the Anderson method. Since the present modification of the Anderson method of the preparation of tetraethylpyrophosphite resulted in its improved yield, this procedure is also described here. Each batch of tetraethylpyrophosphite was tested on a condensation of benzoic acid with aniline. The yields of these trial runs were used to compute the amounts of tetraethylpyrophosphite used for the peptide bond formations.

A speculative thought about a possible means of synthesizing such a symmetric dipeptide, like N^{ϵ}-tosyl-L-lysyl-N^{ϵ}-tosyl-L-lysine, from the corresponding diketopiperazine derivative[23] led toward the experiments testing the feasibility of preparing this type of cyclic intermediates. A marked difference was found in the behavior of the free esters of N^{ϵ}-tosyl-L-lysine and of N^{ϵ}-carbobenzyloxy-L-lysine. While the latter were easily converted into ninhydrine-negative crystals, the esters of N^{ϵ}-tosyl-L-lysine did not undergo any apparent change whatsoever, except for darkening at very high temperatures.

The product obtained from the N^{ϵ}-carbobenzyloxy-L-lysine was of little interest, since cleavage of the carbobenzyloxy group would be expected under the conditions necessary for the opening of the diketopiperazine ring. Further experiments in this direction were not pursued following the successful application of the pyrophosphite amide method to the preparation of the desired compounds.

Syntheses of those peptides, sequences of which appear in the ACTH and MSH molecules, are described in the experimental section. They were all tested for purity, subjected to elementary analyses by outside laboratories, and their sterical configurations were tested by the digestibility by leucine aminopeptidase and chromatography of the digestion products.

EXPERIMENTAL

Tetraethylpyrophosphite. Following the original procedure of Anderson, *et al.*,[7] it was observed that triethylammonium chloride continued to separate as a precipitate even during the removal of tetraethylpyrophosphite from the reaction mixture by distillation. Therefore the reaction time was prolonged from 30 min. to 3 hr., when no further precipitation occurred during the distillation. The yields were increased from 40% with the original procedure to 55% with the modified procedure. Further prolongation of the reaction time did not increase the yield but, on the contrary, tended to decrease it. Private communication from Dr. Anderson confirmed that his group also obtained higher yields when they allowed more time for the reaction to proceed.

The products were tested for refractive indices which varied between n_D 1.430 to 1.434°, and for %-yields of benzanilide obtained by the tetraethylpyrophosphite reaction.

N^{α}-Carbobenzyloxy-N^{ϵ}-tosyl-L-lysyl-N^{ϵ}-tosyl-L-lysine ethyl ester. N^{ϵ}-Tosyl-L-lysine ethyl ester hydrochloride[10] (1.25 g.) was dissolved in 5 ml. of diethyl hydrogen phosphite. Triethylamine (0.50 ml.) was added which resulted in a formation of a white precipitate. The mixture was heated on a steam bath and tetraethylpyrophosphite (1.26 g.) was quickly added to it. Heating on steam was continued for 2 min., after which time a solution of N^{α}-carbobenzyloxy-N^{ϵ}-tosyl-L-lysine (1.46 g.) in 2 ml. of diethyl hydrogen phosphite was added. After 30 min. of continuous stirring and heating on steam, the solution, which was clear and almost colorless, was diluted by 50 ml. water. This resulted in a separation of an oil, which was decanted. Since this oil did not yield crystals on trituration with 5% aqueous sodium bicarbonate (*cf.* the preparation of other dipeptides described below), it was dissolved in ethyl acetate and extracted first with 2*N* hydrochloric acid, then with 5% aqueous sodium bicarbonate. The ethyl acetate layer was then washed with water till the washings were neutral, dried over anhydrous magnesium sulfate, and evaporated on the flash evaporator with the bath temperature kept below 40°. The residue, which before the treatment in ethyl acetate weighed 2.24 g. (89.5% yield), now amounted to 2.08 g. (93% recovery). It was dissolved in methanol and water was slowly added till permanent turbidity was reached. The mixture was placed in a refrigerator, where well defined white crystals began to form. They were separated by filtration and dried *in vacuo* over phosphorus pentoxide to constant weight, 1.4 g. (56% yield), m.p. 114–116°. Recrystallization of an aliquot of this product from methanol and water increased the m.p. to 116.5–117°; $[\alpha]_D^{26}$ −10.5° (*c*, 1.12 in methanol).

Anal. Calcd. for $C_{38}H_{48}O_9N_4S_2$: C, 58.04; H, 6.49; S, 8.61. Found: C, 58.06; H, 6.40; S, 8.48.

N^{α}-Carbobenzyloxy-N^{ϵ}-tosyl-L-lysyl-N^{ϵ}-tosyl-L-lysine methyl ester. This methyl ester was prepared in the same way as the ethyl ester above. It was found that the crystallization of methyl ester took more time than that of the ethyl ester.

(16) O. Bayer, *Angew. Chem.*, 59, 257 (1957); S. Goldschmidt and M. Wick, *Z. Naturforsch.*, 5*b*, 170 (1950); *Ann.*, 575, 217 (1952); S. Peterson, *Ann.*, 562, 205 (1950).

(17) S. Goldschmidt, *Angew. Chem.*, 62, 538 (1950); *Ann.*, 580, 68 (1953); O. Süs and H. Hofmann, *Ann.*, 572, 96 (1951).

(18) G. W. Anderson, J. Blodinger, R. W. Young, and A. D. Welcher, *J. Am. Chem. Soc.*, 74, 5304 (1952).

(19) G. Schramm, *Ber.*, 91, 1073 (1958).

(20) G. W. Anderson and R. W. Young, *J. Am. Chem. Soc.*, 74, 5307 (1952).

(21) J. R. Vaughan, Jr., *J. Am. Chem. Soc.*, 73, 1389 (1951).

(22) J. F. Arens, *Rec. trav. chim.*, 74, 79 (1955).

(23) E. Katchalski, J. Grossfeld, and M. Frankel, *J. Am. Chem. Soc.*, 68, 879 (1946); M. Brenner and R. W. Pfister, *Helv. Chim. Acta*, 34, 2093 (1951).

The yield of the former was about two-thirds that of the latter.

The product melted at 110–111°; $[\alpha]_D^{28}$ −8.5° (*c*, 1.04 in methanol).

N^{ϵ}-Tosyl-L-lysyl-N^{ϵ}-tosyl-L-lysine. Saponification of N^{α}-carbobenzyloxy-N^{ϵ}-tosyl-L-lysyl-N^{ϵ}-tosyl-L-lysine ester (either methyl or ethyl) by shaking it with *N* sodium hydroxide, acidification of the aqueous solution and extraction with ethyl acetate yielded an oil from which no crystals could be obtained.

Hydrogenation of this oil in 15% solution of glacial acetic acid in anhydrous methanol, with palladium as a catalyst, yielded a glossy residue which was not readily soluble in water. Addition of absolute ethanol resulted in formation of crisp, white microcrystals, m.p. 167–168°.

The product was ninhydrin-positive and gave a single spot on a paper chromatogram developed either with the Partridge solvent system (R_f 0.90) or with the 2-butanol–ammonia (3:1) system (R_f 0.65). The sterical configuration of the product was confirmed by the leucine aminopeptidase digestion which completely hydrolyzed the dipeptide leaving only N^{ϵ}-tosyl-L-lysine in the digest. The elementary composition of the product was also confirmed.

Anal. Calcd. for $C_{26}H_{38}O_7N_4S_2$: C, 53.28; H, 6.57; N, 9.61. Found: C, 52.92; H, 6.63; N, 9.72.

Carbobenzyloxyglycyl-N^{ϵ}-tosyl-L-lysyl-N^{ϵ}-tosyl-L-lysine ethyl ester. N^{ϵ}-tosyl-L-lysyl-N^{ϵ}-tosyl-L-lysine ethyl ester hydrochloride was prepared from its N^{α}-carbobenzyloxy derivative by a catalytic hydrogenation in methanol in the presence of equimolecular amount of *N* hydrochloric acid, with palladium as a catalyst. An oil was obtained in a virtually quantitative yield, which gave a single ninhydrin spot in either of the above-described solvent systems. Leucine aminopeptidase hydrolysis of the oil gave a single ninhydrin spot of N^{ϵ}-tosyl-L-lysine.

This oil was coupled with an equimolecular amount of carbobenzyloxyglycine by the carbodiimide method; *i.e.*, N^{ϵ}-tosyl-L-lysyl-N^{ϵ}-tosyl-L-lysine ethyl ester hydrochloride (1.25 g.), carbobenzyloxyglycine (0.41 g.), triethylamin (0.30 ml.) and dicyclohexylcarbodiimide (0.41 g.) were dissolved in dioxane (20 ml.). The mixture was left to stand overnight at room temperature. A precipitate formed which was removed by filtration (0.40 g., corresponds to 2.05 mmoles of dicyclohexylurea). The filtrate was evaporated *in vacuo* to dryness (40° bath temp.) and the oily residue dissolved in ethyl acetate. This solution was purified in the usual way (washed consecutively with 2*N* hydrochloric acid, *N* sodium bicarbonate, followed with distilled water until the washings were neutral), then dried over magnesium sulfate, and evaporated *in vacuo* to dryness. An oily residue (1.15 g.) was obtained. This residue was dissolved in methanol and water was added until permanently turbid. On standing overnight crystals appeared. Slow addition of water yielded more crystals. Both crops (0.82 g., 53% yield) had a melting point of 121–124°. Recrystallization of an aliquot increased the m.p. to 125.5–126°; its optical rotation was $[\alpha]_D^{23}$ −12.6° (*c*, 1.06 in ethanol).

Anal. Calcd. for $C_{38}H_{51}O_{10}N_5S_2$: C, 56.90; H, 6.41; N, 8.73; S, 7.99. Found: C, 56.77; H, 6.29; N, 8.80; S, 8.00.

Catalytic hydrogenation of the aliquot produced in virtually a stoichiometric yield an oil, R_f 0.91 (Partridge), 0.85 (2-butanol–ammonia), completely digestible by leucine amino peptidase, amino acid ratios in digest $gly_{1.0}$-ϵ-tos-$lys_{1.9}$.

Dicarbobenzyloxy-L-lysyl-N^{ϵ}-tosyl-L-lysine ethyl ester was prepared from dicarbobenzyloxy-L-lysine and the ethyl ester of N^{ϵ}-tosyl-L-lysine hydrochloride following the procedure described above for the preparation of N^{α}-carbobenzyloxy-N^{ϵ}-tosyl-L-lysyl-N^{ϵ}-tosyl-L-lysine ethyl ester. On addition of water to the reaction mixture an oil was obtained. Trituration of this oil with 5% aqueous sodium bicarbonate resulted in a formation of crystals. These were washed twice with water, filtered, and dried *in vacuo* over phosphorus pentoxide; 72.4% yield, m.p. 115–118°. Recrystallization from methanol and water increased the m.p. to 121–122° $[\alpha]_D^{27.5}$ −11.3° (*c*, 2.47 in methanol).

Anal. Calcd. for $C_{37}H_{48}O_9N_4S$: C, 61.30; H, 6.67; S, 4.42. Found: C, 61.19; H, 6.85; S, 4.33.

N^{α}-Carbobenzyloxy-N^{ϵ}-tosyl-L-lysyl-L-valine methyl ester was prepared from N^{α}-carbobenzyloxy-N^{ϵ}-tosyl-L-lysine (2.27 g.) and the methyl ester of L-valine hydrochloride (1.05 g.) following the procedure described above for N^{α}-carbobenzyloxy-N^{ϵ}-tosyl-L-lysyl-N^{ϵ}-tosyl-L-lysine ethyl ester. The yield (1.81 g.) was 63.4%; m.p. 97.5–98.5°, on recrystallization from methanol-water raised to 99.5–100°; $[\alpha]_D^{28}$ −14.3° (*c*, 2.51 in ethanol).

Anal. Calcd. for $C_{27}H_{37}O_7N_3S$: C, 59.21; H, 6.81; S, 5.85. Found: C, 59.14; H, 6.64; S, 5.84.

Catalytic hydrogenation of a small aliquot resulted in an almost quantitative yield of decarbobenzoxylated dipeptide, R_f = 0.89 (Partridge), single spot in (2-butanol–ammonia), completely digestible by LAP, amino acid ratios in digest ϵ-tos-lys_1val_1.

Acknowledgment. Gratitude is expressed to Dr. K. Hofmann for numerous discussions and to Mrs. E. T. Schwartz for the chromatographic and leucine aminopeptidase-digestion assays.

OTTAWA, CANADA

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DEPARTMENT, COLGATE-PALMOLIVE CO.]

Distribution of *para* and *ortho* Isomers in Some Model Long Chain Alkylbenzenesulfonates

FREDERICK W. GRAY AND IRVING J. KREMS[1a]

Received March 11, 1960

A series of long chain 1-phenyl- and 2-phenylalkanes has been prepared and sulfonated. The sulfonate distribution was about 80% *para*, 15% *ortho* for the 1-phenylalkanes and about 90% *para*, 7% *ortho* for the secondary 2-phenylalkanes. The isomers were characterized by conversion to their *S*-benzylisothiuronium salts and by infrared spectra. Some physical properties of the alkylbenzenesulfonates are described.

The preparation and properties, including surface activity, of some isomeric sodium alkylbenzenesulfonates were described in a previous publication.[1b] The position of the sulfonate group in the

(1a) Present address: Medical Faculty, University of Vienna, Vienna, Austria.

(1b) F. W. Gray, J. F. Gerecht, and I. J. Krems, *J. Org. Chem.*, 20, 511 (1955).