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STEAROYL PARATOLUENESULFONATE. A POWERFUL ACYLATING AGENT FOR LIPID SYNTHESIS

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The utility of the mixed carboxylic–sulfonic acid anhydride stearoyl *p*-toluenesulfonate as a powerful, mild acylating agent for lipid synthesis is shown by the synthesis of *rac* 1,2-distearoyl-3-iodopropane, lecithin and a spin-labeled choline derivative from the corresponding alcohols. The method constitutes a significant improvement of earlier acylating methods.

I. Introduction

Mild, efficient procedures for affecting acylations are essential to progress in lipid synthesis [1]. In certain key instances mild acylating conditions have not been available, an example being the rather difficult (see below) acylation of lysolecithin [2–4]. Despite the fact that mixed carboxylic–sulfonic acid anhydrides have been known to be powerful acylating agents for some time [5,6] and the fact that the preparation of stearoyl methanesulfonate has been reported [7], application of mixed carboxylic–sulfonic acid anhydrides in lipid synthesis has not been hitherto described.

Stearoyl *p*-toluene sulfonate (I) was chosen as a representative long chain fatty acid derived mixed anhydride for our studies. Anhydride (I) was conveniently prepared by a modification of the general mixed anhydride synthesis of Overberger and Sarlo [5]. Thus, owing to the rather low solubility of stearoyl chloride in acetonitrile, anhydride (I) was generated by reaction of a suspension of silver tosylate in dichloromethane with stearoyl chloride. The rapid formation of silver chloride together with the presence of a strong peak at 1800 cm^{-1} [5,7] in the infrared spectrum of the supernatant dichloromethane solution confirmed the formation of

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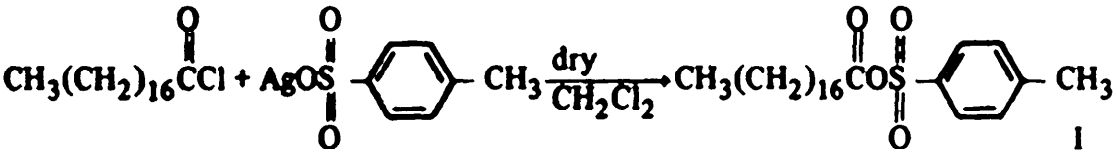
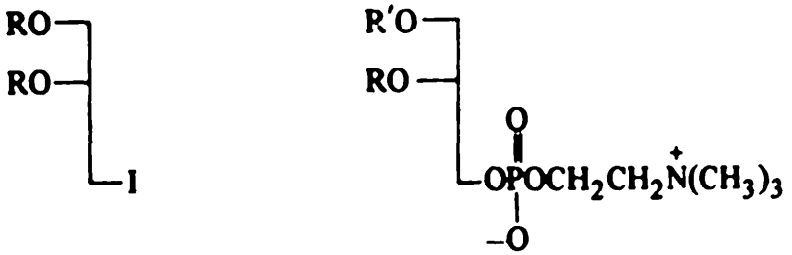
mixed anhydride (I).



+ AgCl

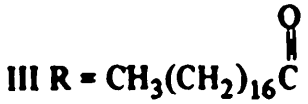
Stearoylations with a dichloromethane solution of anhydride (I) were readily achieved in dichloromethane at 0–25°C for 1–2 hr. Thus, *rac* 1, 2-dihydroxy-3-iodopropane (II) was converted into the distearoyl derivative (III) in 86% yield. By way of comparison Hessel et al. [8] synthesized compound III by a 6-day reaction of (II) with excess stearoyl chloride in chloroform containing quinoline.

An even better calibration of the reactivity of anhydride (I) was revealed in its reaction with lysolecithin (IV) derived from egg yolk. Thus, lecithin (V) was obtained in 48% yield (>95% when adjusted for recovered lysolecithin) after purification over Sephadex LH-20. Earlier acylations of lysolecithin have typically involved fusion of a mixture of the lysolecithin, stearic anhydride and sodium oxide at 75°C for 48 hr [2,3]. A recent improvement [4] involving the heating at 50°C for 3 days of a melt containing lysolecithin and a spin-labeled acylimidazole has led to a spin-labeled lecithin in 14% yield.

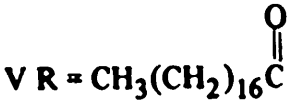


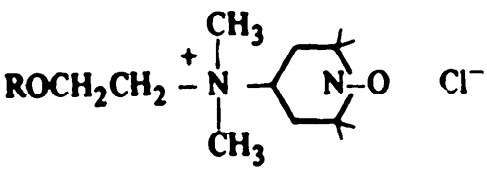
II R = H

R′ = Predominantly a mixture of C_{16} and C_{18} esters

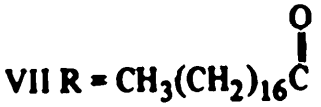


IV R = H





VI R = H



water and brine and then was filtered through 10 g of anhydrous K_2CO_3 followed by an ether rinse. Evaporation of the organic layer afforded 218 mg of a white solid, recrystallization of which from petroleum ether–methanol gave 178 mg (86%) of compound (III) as white flakes, m.p. 52–53°C (lit. [8] m.p. 54–55°C). The NMR spectrum was identical to that of a sample of (III) prepared by a modification of the method of Hessel et al. [8].

C. N-Desmethyl-N-(2, 2, 6, 6-tetramethylpiperidine-1-oxyl-4-yl)-O-stearoylcholine chloride (VII)

To a stirred suspension of 93.7 mg (0.335 mM) of choline derivative (VI) [9] in 1.0 ml of dichloromethane at 0°C was added 5.9 ml (~0.67 mM) of the stock solution of (I) (see above). The resulting stirred suspension was allowed to warm to 25°C over a 2 hr period, during which time all the orange crystals of (VI) had dissolved. The solution was diluted with dichloromethane and washed with water followed by brine. Evaporation afforded 282 mg of a pale orange solid. A 103 mg portion was purified by preparative TLC (silica GF, 6:8:2:2:1 chloroform–acetone–methanol–acetic acid–water, R_f = 0.5). The resulting orange solid was taken up in dichloromethane and washed with saturated $Ca(OH)_2$ followed by brine. Evaporation of the organic layer afforded 34 mg (corresponding to 51% yield) of crude salt (VII) as a cream colored solid. Two precipitations from ether–hexane afforded the analytical specimen as an orange powder: m.p. 46.5–47.5°C; mass spectrum: *m/e* 510 (cation of salt (VII) determined by field desorption mass spectrometry), 496 ($M-CH_3Cl$).

Anal. Calcd. for $C_{31}H_{62}N_2O_3Cl \cdot 2C_2H_5OC_2H_5$: C, 67.44; H, 11.90; N, 4.03. Found: C, 67.18; H, 11.59; N, 4.01.

D. Lecithin (V)

Lysolecithin was treated 3 times with anhydrous dichloromethane and reisolated by evaporation of the solvent. To a stirred mixture of 50.4 mg (0.096 mM) of the dried lysolecithin and 1.0 ml of dichloromethane at 0°C was added 2.7 ml (~0.31 mM) of the chilled stock solution of compound (I) (see above). The stirred reaction mixture was allowed to warm to 25°C over a 2 hr period. The resulting solution was diluted with chloroform and washed with water. Evaporation of the organic layer afforded 149 mg of a white solid. The ratio of lecithin to lysolecithin was found to be 1.0:1.0 by a combination of TLC [11]–inorganic phosphate [12] analysis. A 64 mg portion was redissolved in 95% ethanol and chromatographed over a 1.5 cm X 200 cm Sephadex LH-20 column (37°C). 16 mg of lecithin (corresponds to 48% yield; >95% when adjusted for recovered lysolecithin) and 10 mg of recovered lysolecithin was obtained. Purity was verified by analytical TLC. The stearic acid from the excess mixed anhydride was also nearly quantitatively recovered from the chromatography.

Acknowledgements

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