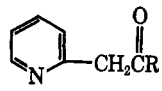
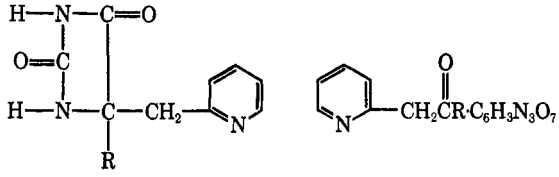
Table I. Alkyl 2-Picolyl Ketones



R	% Yield	Bp, °C/mm	$n^{20}D$	d_4^{20}
CH_3	20	79/1.9[a]	1.5282	1.072
C_2H_5	33	80/0.6[b]	1.5210	1.051
n-C_3H_7	49	94/1.7[c]	1.5195	1.027
iso-C_3H_7	48	84/0.7[d]	1.5203	1.026
n-C_4H_9	47	108/1.3[e]	1.5148	1.009
iso-C_4H_9	56	96/1.1[f]	1.5173	1.005
sec-C_4H_9[g]	58	88/0.7	1.5216	1.009
tert-C_4H_9[g]	49	98/1.8	1.5235	1.010
n-C_5H_{11}	52	112/1.0[h]	1.5146	0.998

[a] Reported bp 74–5°/1.5 mm (*3*). [b] Reported bp 99–103°/5 mm (*3*). [c] Reported bp 123°/10 mm (*2*). [d] Reported bp 79–85°/2 mm (*3*). [e] Reported bp 136°/10 mm (*2*). [f] Reported bp 114–17°/6 mm (*3*). [g] Elemental analyses (C, H, and N) in agreement with theoretical values have been obtained and submitted for review. [h] Reported bp 151°/10 mm (*2*).

Table II. Hydantoin[a] and Picrate[a] Derivatives of Alkyl 2-Picolyl Ketones



R	Mp, °C	Mp, °C
CH_3	202–3	140–1[b]
C_2H_5	163.5–4.5	146–7[c]
n-C_3H_7	184.5–5.5	130–1
iso-C_3H_7	212–13	146–7[d]
n-C_4H_9	171.5–2.5	116–17
iso-C_4H_9	165.5–7.5	103–4[e]
sec-C_4H_9[f]	205–6	84.5–6.5[f]
tert-C_4H_9	246–7	129–30
n-C_5H_{11}	122–3	85.5–6.5

[a] Elemental analyses (N) in agreement with theoretical values have been obtained and submitted for review. [b] Reported mp 140–0.5° (*1*). [c] Reported mp 144.2–5.5° (*3*). [d] Reported mp 144.5–5.2 (*3*). [e] Reported mp 103–3.8 (*3*). [f] Elemental analyses (C, H, and N) in agreement with theoretical values have been obtained and submitted for review.

fluxed rapidly. The reaction mixture was refluxed an additional 30 min, cooled, and 190 ml of water were slowly added, after which the entire mixture was poured into 250 ml of 6*N* hydrochloric acid and 1250 grams of ice.

The ether phase was separated and extracted several times with 6*N* hydrochloric acid, the aqueous extracts were combined and treated with 20% sodium hydroxide solution until a pH of 6.2 was reached. Solid sodium bicarbonate was added until a pH of 7.5 was reached. The basic mixture was extracted with ether until the extracts no longer gave a blue-green color with alcoholic iron III chloride. The ether extracts were combined and dried over anhydrous sodium sulfate. The ether was removed by flash distillation, and the ketone was distilled through a Nester-Faust annular Teflon spinning-band column under reduced pressure. Obtained were 52 grams (58%) of 1-(2-pyridyl)-3-methyl-2-pentanone, bp 88°C (0.7 mm), $n^{20}D$ 1.5216, d_4^{20} 1.009. A picrate was prepared by the method of Shriner et al. (*5*), mp 84.5–6.5°C.

5-*sec*-Butyl-5-(2-pyridinyl)hydantoin. A mixture of 4.5 grams of ammonium carbonate, 1.3 grams of potassium cyanide, and 1.0 gram of 1-(2-pyridyl)-3-methyl-2-pentanone in 50 ml of water was placed in a flask fitted with an air condenser. The flask was placed in a 70°C water bath for 4 hr, carefully acidified with concentrated hydrochloric acid, and cooled. The hydantoin precipitate was removed by filtration and recrystallized from water, mp 205–6°C.

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Preparation of Sulfate Esters with Various Carbodiimides and Solvents

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Dicyclohexylcarbodiimide (DCC), sulfuric acid, and various nucleophiles reacted in the solvent dimethylformamide (DMF) to produce sulfated products (*3*, *5–7*). Under these reaction conditions monoalkyl sulfates and/or dialkyl pyrosulfates were prepared from alcohols, phenols, mercaptans, and hydroxamates. When the reaction was conducted under dilute conditions (*3*), only unhindered alcohols were sulfated. The DCC-mediated reaction in DMF was selective, gave good yields, permitted short reaction times, and facilitated the use of an ^{35}S-label. Although the DCC-mediated sulfation gives excellent yields of monoalkyl sulfates, the formation of the relatively insoluble voluminous dicyclohexylurea impeded the direct isolation of the monoalkyl sulfate. Rather large volumes of methanol were required to elute the dicyclohexylurea in the DEAE-cellulose column isolation technique (*5*, *7*).

Since only DCC and DMF were used in the previous studies,

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Eight aromatic and four aliphatic carbodiimides were examined for mediation of the sulfation of 1-hexadecanol, α-naphthol, 1-octanethiol, and corticosterone in the solvent dimethylformamide. The aliphatic carbodiimides, in general, gave monoalkyl sulfates in good yields, of which the best were dicyclohexylcarbodiimide and 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-p-toluene sulfonate. The latter had considerable synthetic potential since the urea formed in the reaction was soluble. The aromatic carbodiimides gave monoalkyl sulfates in poor yields, of which the electron-donating para-substituted aromatic carbodiimides gave the best yields. None examined formed sulfated products (<2%) with α-naphthol, 1-octanethiol, or the hindered C-11 hydroxyl in corticosterone. Reaction conditions were investigated using tetrahydrofuran, dioxane, and alcohols as solvents for the carbodiimide-mediated sulfation. Monoalkyl sulfates were formed when tetrahydrofuran and dioxane were used as the solvent. However, many undesirable side products were obtained, and the reactions were uncontrollable. When alcohols were used both as the solvent and nucleophile, monoalkyl sulfates and dialkyl sulfates were produced.

investigating the versatility of using other carbodiimides and solvents was important. This article reports the comparative investigations of 12 carbodiimides for their capacity to mediate the sulfation of 1-hexadecanol, α-naphthol, 1-octanethiol, and corticosterone in the solvent DMF. The nucleophiles selected represent the classes of compounds previously sulfated by the DCC-mediated reaction (*3*). All the ureas of the carbodiimides used (except di-*p*-nitrophenylcarbodiimide and DCC) are soluble in DMF. Reaction conditions were investigated using tetrahydrofuran, dioxane, and alcohols as solvents.

EXPERIMENTAL

To 0.25 mmole of nucleophile (1-hexadecanol, α-naphthol, 1-octanethiol, and corticosterone) dissolved in 4 ml of anhydrous DMF (*8*) was added 1.00 mmole of carbodiimide dissolved in 4 ml of DMF. To this solution was added 0.25 mmole of ^{35}S-labeled sulfuric acid dissolved in 2 ml of DMF. The sulfated products were analyzed by tlc as previously reported (*3*).

All solvents and reactants were either redistilled or recrystallized, and their purity was determined by gas and thin-layer chromatography. Six carbodiimides were purchased: dicyclohexylcarbodiimide (Eastman Organic Chemicals), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide·HCl (EDC) (Cyclo Chemical Corp.), 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide (CMC), 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate, di-*p*-tolylcarbodiimide, and di-*o*-tolylcarbodiimide.

Six carbodiimides were synthesized by the catalytic decarboxylation of isocyanates (*1*): diphenylcarbodiimide, di-*p*-methoxyphenylcarbodiimide, di-*o*-methoxyphenylcarbodiimide, di-*p*-nitrophenylcarbodiimide, di-*o*-nitrophenylcarbodiimide, and di-*p*-chlorophenylcarbodiimide. The 3-methyl-1-phenyl-1-phospha-3-cyclopentene 1-oxide catalyst used in the decarboxylation of isocyanates was synthesized (*4*) by the addition of one mole of dichlorophenylphosphine to 3 moles of 2-methyl-1,3-butadiene in the presence of 2 grams of an antioxidant, 2,6-di-*tert*-butyl-*p*-cresol. All compounds were purchased from Aldrich Chemical Co., Inc., except those specifically mentioned.

RESULTS AND DISCUSSION

In all the reactions examined using DMF, only monoalkyl sulfates were produced. α-Naphthol, 1-octanethiol, and the hindered C-11 hydroxyl in corticosterone were not sulfated (<2%); therefore, the various carbodiimides examined showed the same nucleophilic and steric selectivity as DCC (*3*). The average yield of monoalkyl sulfate produced by the various carbodiimides is summarized in Table I. The three alkyl carbodiimides examined in addition to DCC were EDC, CMC, and CMC-metho-*p*-toluenesulfonate. With EDC and CMC 1-hexadecyl sulfate was formed in 15% and 0% yield, respectively, when the molar ratios were 1:4:1 (ROH:carbodiimide:H_2SO_4). The lack of sulfation with CMC was caused by the presence of the basic tertiary amine group.

The four mmoles of CMC present in the reaction mixture had the capacity to neutralize the one mmole of H_2SO_4 before the necessary CMC–H_2SO_4 adduct could be formed. How-

Table I. Yield Data for Carbodiimide-Mediated Sulfations of Various Nucleophiles

	Nucleophiles,[a] %			
Carbodiimide	1-Hexadecanol	α-Naphthol	1-Octanethiol	Corticosterone
Dicyclohexylcarbodiimide	92	0	2	19
1-Ethyl-3-(3-dimethylamino-propyl)-carbodiimide·HCl	15	<1	<1	3
1-Cyclohexyl-3-(2-morpho-linoethyl)-carbodiimide	0 56[b]			
CMC-metho-*p*-toluene-sulfonate	70	0	1	15
Diphenylcarbodiimide	10	0	0	2
Di-*p*-tolylcarbodiimide	15	<1	0	2
Di-*o*-tolylcarbodiimide	4	0	0	1
Di-*p*-methoxyphenylcarbodiimide	18	0	0	4
Di-*o*-methoxyphenylcarbodiimide	2	0	0	0
Di-*p*-nitrophenylcarbodiimide	0	0	0	0
Di-*o*-nitrophenylcarbodiimide	2	0		
Di-*p*-chlorophenylcarbodiimide	8	0	0	1

[a] Molar ratio of nucleophile:carbodiimide:H_2SO_4; 1:4:1. [b] Molar ratio of nucleophile:carbodiimide:H_2SO_4; 1:4:5.

ever, on increasing the ratio of H_2SO_4 to 1:4:5 (ROH:CMC:H_2SO_4), 1-hexadecyl sulfate was obtained in 56% yield. To obviate the requirement of excess H_2SO_4, the *N*-methylated CMC (CMC-metho-*p*-toluenesulfonate) was next examined under normal reaction conditions; 1-hexadecyl sulfate was obtained in 70% yield.

The various aromatic carbodiimides examined were diphenylcarbodiimide, di-*p*-tolylcarbodiimide, di-*o*-tolylcarbodiimide, di-*p*-methoxyphenylcarbodiimide, di-*o*-methoxyphenylcarbodiimide, di-*p*-nitrophenylcarbodiimide, di-*o*-nitrophenylcarbodiimide, and di-*p*-chlorophenylcarbodiimide. In general, these aromatic carbodiimides gave monoalkyl sulfates in poor yields (Table I). Of these aromatic carbodiimides, di-*p*-methoxyphenylcarbodiimide formed 1-hexadecyl sulfate in the largest yield (18%) while di-*p*-tolylcarbodiimide and diphenylcarbodiimide gave slightly lower yields of 15% and 10%, respectively. Corticosterone-21-sulfate was produced in small yields.

A factor of mechanistic importance is that the electron-donating group (methoxy, chloro, and methyl) substituted in the para-positions on diphenylcarbodiimide contributes to increased yields as compared to the electron-withdrawing group (nitro). However, both electron-donating and electron-withdrawing groups in the ortho-position prevent the formation of sulfate esters. Apparently, steric hindrance caused by the ortho-positioned groups prevents the formation of the necessary reaction intermediates. The aromatic carbodiimides produce monoalkyl sulfates in significantly lower yields than alkyl carbodiimides. This factor and the effects observed with para-substitution suggest that factors which decrease the electron density surrounding the nitrogen atoms of the carbodiimide (—N=C=N—) result in lower yields of monosulfates. These results are consistent with the proposed mechanism (*3*).

In comparison to the other 11 carbodiimides investigated, the DCC-mediated sulfation produced 1-hexadecyl sulfate in the largest yield. However, the other aliphatic carbodiimides, particularly CMC-metho-*p*-toluenesulfonate, resulted in the formation of 1-hexadecyl sulfate in good yields and with the added advantage that the resulting ureas of these carbodiimides are soluble in DMF. These aliphatic carbodiimides are commercially available and relatively stable and, therefore, warrant additional consideration for the preparation of sulfate esters.

The DCC-mediated sulfation with various nucleophiles was investigated using tetrahydrofuran (THF), dioxane, and alcohols as solvents. In all these cases ^{35}S-labeled products were found. However, with dioxane and THF, the sulfation was not selective for the nucleophile, as is the case with DMF, and the reaction mixture was nonhomogeneous. The sulfuric acid formed a separate phase resulting in undesirable dehydrating conditions. Discoloring was observed, and additional products other than the monoalkyl sulfates were formed.

As previously reported, sulfuric acid and an alcohol will react to form monoalkyl sulfates in very poor yields (*2*). However, when an alcohol served both as a solvent and a nucleophile (DCC, H_2SO_4, and an alcohol; 1:1:5), two ^{35}S-labeled products were observed in 100% yield based on the $^{35}SO_4^{2-}$. One product was the monosulfate and the other ^{35}S-product was nonionic, moving to nearly the front on tlc and not possessing the dialkyl pyrosulfate structure. These experiments were conducted with ethanol, 1-butanol, 2-methyl-2-propanol, and 1-decanol. The second product could also be formed in the presence of DMF as a solvent (H_2SO_4:1-decanol:DCC:DMF; 1:4:1:10). Since this front-running product was formed only in the presence of DCC and excess alcohol, it was theorized that this product was probably a symmetrical dialkyl sulfate. This assumption was also supported by data obtained from an experiment utilizing two-dimensional thin-layer chromatographic analysis of the products produced with 1-butanol.

The reaction mixture (H_2SO_4:1-butanol:DCC:DMF; 1:5:1:10) was applied to the bottom left-hand corner of a tlc plate and developed with chloroform–methanol–water (65:25:4, v/v/v). Two products were observed: monoalkyl sulfate (M) and presumably the dialkyl sulfate (D) (Figure 1*A*). To compound D were added several drops of 6*N* H_2SO_4. To compound M were added several drops of a DCC-1-butanol solution, followed by one drop of HCl as a proton source. The plate was then developed in the second direction in the same solvent system. The results are shown in Figure 1*B*. As a control the original reaction mixture was applied to a tlc plate and developed two-dimensionally (Figure 1*C*).

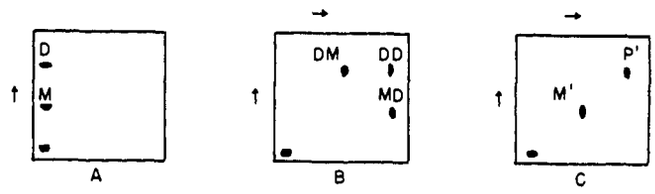
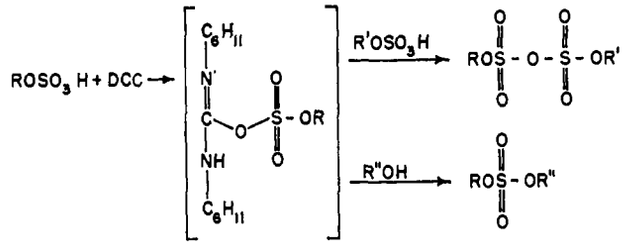


Figure 1. Radioautogram drawings of tlc plates of 1-butanol mixture experiment suggesting diester formation

Thin-layer plates were developed in chloroform–methanol–water (65:25:4, v/v) in both vertical and horizontal directions

The radioautogram results indicate that some of the compound D is hydrolyzed to 1-butyl sulfate (DM) with no residual H_2SO_4 evident. The portion of compound D not hydrolyzed moves to spot DD in the second dimension and is undistinguished from that of compound D. The monoalkyl sulfate, M, reacted completely with the DCC and excess alcohol to form compound MD, which had the same R_F as compounds DD and D. Therefore, it appears that the front-running compound is dibutyl sulfate for it is hydrolyzed to, and synthesized from, the monoalkyl sulfate. Similar results were obtained with ethanol and 1-decanol.

The use of THF or dioxane as solvents for the DCC-mediated sulfation of nucleophiles does not appear desirable because of the lack of control of the formation of side products. However, if the sulfation is conducted in the presence of excess alcohol, dialkyl sulfates are produced. The formation of dialkyl sulfate is important mechanistically because the monoalkyl sulfate and the H_2SO_4 react with DCC. Depending on the molar ratio of reactants or concentration of the reactants. either the dialkyl pyrosulfate or dialkyl sulfate is produced,



This DCC-mediated reaction thus potentially should be useful for the synthesis of dialkyl sulfates and, particularly, the unsymmetrical dialkyl sulfates.

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