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## Synthesis of fatty acid anhydrides by reaction with dicyclohexylcarbodiimide

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SUMMARY A simple method is described for the preparation of caprylic, palmitic, stearic, and oleic anhydrides. Reaction of the free fatty acid and dicyclohexylcarbodiimide in carbon tetrachloride at room temperature gives the corresponding anhydrides in high yield (87-94%).

KEY	WOR	DS	caprylic	•	palmitic		stearic
• •	oleic	•	fatty acid	•	anhydride	•	prep-
aratio	n	•	dicyclohexylca	rbodii	mide		

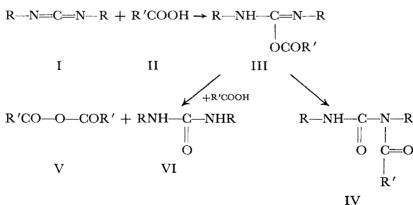
THE PREPARATION of aliphatic acid anhydrides has been based on the reaction of the free acids with acetic anhydride (1-3), acid chlorides (4, 5), alkylchloroformate (6), imidazolides (7), and phosgene (8). Diimides are known to react rapidly with a variety of acids (9)and in the absence of competitive reactants such as amino compounds or alcohols lead to the formation of anhydrides (V) and N,N'-substituted ureas (VI). Carboxylic acids can, however, also yield the corresponding N-acyl urea (IV). The substituents on the carbodiimide molecule, the acid, and the solvent are known to influence the course of the reactions (9).

TABLE 1	REACTION OF FATTY ACIDS W	VITH DCC IN DIF-									
FERENT SOLVENTS											

		Yield			
Solvent	Fatty Acid	Anhy- dride	DCU	DCAU	
· · · · · · · · · · · · · · · · · · ·		% of theoretical			
Diethyl ether	Oleic	74	63	20	
	Palmitic	44.3	44.5	41.6	
Petroleum ether (bp	Oleic	87	92	9. <b>1</b>	
40–60°)	Palmitic	86.3	85	7.1	
Benzene	Oleic	88	83	10.3	
	Palmitic	85	85	8.1	
Pyridine	Oleic Palmitic	41 39.3	36.7 42	49	
Chloroform	Oleic	86	81	8	
	Palmitic	86.5	76.4	8.9	
Carbon tetrachlorid <del>e</del>	Oleic	91	87	8	
	Palmitic	94.5	92	4	
	Stearic	88.5	91	7.2	
	Caprylic	87.5	89	5.2	

Reaction conditions: DCC (1 mmole in dry solvent (5 ml) was added to the fatty acid (2 mmoles) in dry solvent (15 ml). After 15 hr at room temperature the DCU was collected by filtration, and the filtrate was analyzed for anhydride and DCAU. (DCU is partially soluble in pyridine and chloroform. Therefore when these solvents were used, they were removed after the reaction by evaporation, the residue was dissolved in ether, the DCU was collected by filtration and the filtrate was analyzed for anhydride and DCAU.) Anhydrides were analyzed by the hydroxamic acid test (12) and the DCAU was determined by Kjeldahl analysis of nitrogen. DCU was dried and weighed. The methyl ester prepared from oleic anhydride when tested by gas-liquid chromatography on ethylene glycol succinate polyester gave one peak with the same retention time as standard methyl oleate.

Thus, acetic anhydride is formed by the reaction of acetic acid and DCC (10). Recently (11) it was reported that DCC reacts also with formic acid to form formic anhydride, although the anhydride was not isolated. This communication deals with the study of the reaction between long-chain fatty acids and DCC and its application to the preparation of the anhydrides of these acids under mild conditions and in high yields. A thin-layer chromatographic procedure for the separation of fatty acid anhydrides, DCAU, DCC, DCU, and free fatty acids is described.



Abbreviations: DCC, dicyclohexylcarbodiimide (I); DCU, dicyclohexylurea (VI); DCAU, dicyclohexylacylurea (IV); R in the formulas being cyclohexyl.

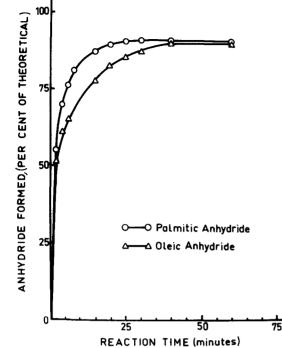


Fig. 1. Time curve of anhydride formation by the reaction of palmitic and oleic acids with DCC. The reaction was started by the addition of 1 mmole of DCC in 5 ml of CCl<sub>4</sub> to 2 mmoles of fatty acid in 15 ml of CCl<sub>4</sub>. Aliquots were taken at intervals for neutral hydroxamate determination (12). Zero-time values were obtained by subsequent addition of fatty acid and DCC to hydroxylamine.

The influence of different solvents on the course of the reaction between DCC and several fatty acids is summarized in Table 1. Carbon tetrachloride was found to be the solvent in which the highest yield of anhydride was produced. From the kinetics of the formation of oleic and palmitic anhydrides at  $25^{\circ}$  it is concluded that the reaction is complete after 40 min (Fig. 1).

The acid anhydride can be freed from the small amounts of DCAU and residual free acid by crystallization. This purification step can be omitted when the anhydride is used for acylation reactions, since the small amounts of DCAU and free acid do not interfere with these reactions.<sup>1</sup>

Synthesis of Palmitic Anhydride. A solution of DCC (10 mmoles) in dry  $CCl_4$  (50 ml) was added to a solution of palmitic acid (20 mmoles) in dry  $CCl_4$  (150 ml). The reaction mixture was kept at room temperature. After 5 hr the DCU precipitate was removed by filtration and the solvent was removed by evaporation under

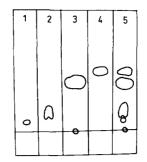


FIG. 2. Thin-layer chromatography on microchromatoplate coated with silica gel (without CaSO<sub>4</sub>) by dipping (13). Solvent: petroleum ether (bp 40-60°)-diethyl ether 8:2 (v/v). Indicator: Charring with aqueous sulfuric acid 1:1 (v/v). 7, DCAU; 2, palmitic acid; 3, DCC with small spot of DCCU at the origin; 4, palmitic anhydride; 5, mixture 1-4.

reduced pressure. The solid residue was recrystallized from acetone (125 ml) yielding 4.22 g of pure palmitic anhydride (85.4%), mp 64°. A thin-layer chromatogram of starting materials and reaction products is shown in Fig. 2.

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## WARNING

Several laboratories have reported that skin sensitivity and, later, acute respiratory difficulties may result from continual use of DCC.

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## References

- 1. Holde, D., and K. Rietz. Chem. Ber. 57 I: 99, 103, 1924.
- 2. Holde, D., and R. Gentner. Chem. Ber. 58 II: 1418, 1925.
- Wallace, J. M., and J. E. Copenhaver. J. Am. Chem. Soc. 63: 699, 1941.
- Sonntag, N. V., J. R. Trowbridge, and I. J. Krems. J. Am. Oil. Chemists' Soc. 31: 151, 1954.
- 5. Youngs, C. G. J. Am. Oil. Chemists' Soc. 35: 416, 1958.
- 6. Nicholes, J., and E. S. Schipper. Chem. Abstr. 53: 1494i, 1959.
- Staab, H. A., G. Walther, and W. Rohr. Chem. Ber. 95: 2073, 1962.
- 8. Rinderknecht, H., and V. Ma. Helv. Chim. Acta 47: 162, 1964.
- 9. Khorana, H. G. Chem. Rev. 53: 145, 1953.
- Smith, M., J. G. Moffatt, and H. G. Khorana. J. Am. Chem. Soc. 80: 6204, 1958.
- 11. Muramatsu, I., M. Itoi, M. Tsuji, and A. Hagitani. Bull. Chem. Soc. Japan 37: 756, 1964.
- Goddu, R. F., N. F. LeBlanc, and C. M. Wright. Anal. Chem. 27: 1251, 1955.
- 13. Peifer, J. J. Mikrochim. Acta no vol.: 529, 1962.

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 $<sup>^{1}</sup>$  Lapidot, Y., and Z. Selinger, manuscript submitted for publication.