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166. Katsura Morita, Shunsaku Noguchi, and Masamoto Nishikawa : Studies in Steroids. XIII. Formylation of Steroid Alcohols with Dimethylformamide–Phosgene Complex.

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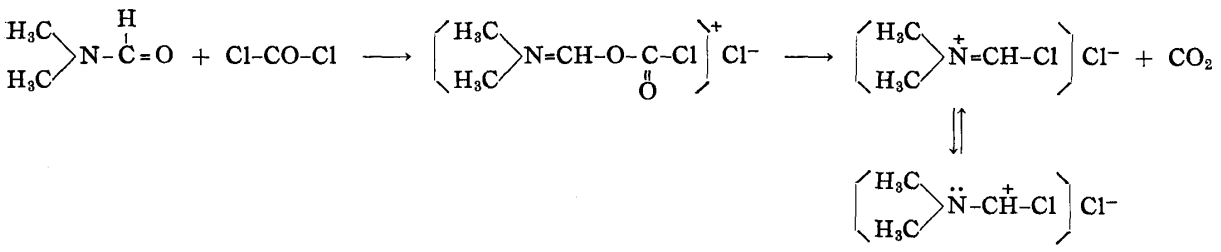
A novel method for the formylation of a number of steroidal alcohols is described in this paper.

Since the general method employing formic acid as formylating agent has to be carried out in rather strongly acid medium and hence sometimes may cause undesirable side reactions, an alternative method which can be processed in a neutral solution is an attractive one. In this connection, it is interesting to note that Stevens,[1] in his recent report, described a new procedure for the formylation of lower primary and secondary alcohols with iodine pentafluoride and dimethylformamide, although the yields were unsatisfactory.

It has been found that an equimolar complex of phosgene and dimethylformamide reacted readily with alcohols in dimethylformamide to give intermediate reaction products which, on hydrolysis with water, afforded the formyl ester of the alcohols in excellent yields. Thus, when a solution of a steroid alcohol in dimethylformamide was allowed to react with phosgene–dimethylformamide complex at room temperature, a yellow viscous solution resulted in a few minutes, which was then diluted with water to separate the formyl ester of the steroid as almost pure crystals. Instead of adding the complex to the solution, a sufficient quantity of phosgene gas can be introduced into a dimethylformamide solution of the steroid resulting in almost the same yield of the ester. Experiments somewhat parallel to the present one was reported by Roh and Kochendörfer,[2] who found that a mixture of phosgene and methylformanilide could be used as an effective formylating agent for the synthesis of substituted indole aldehydes from substituted indoles. They noticed that phosgene reacts with methylformanilide in dry benzene or other solvents with evolution of carbon dioxide gas, but no definite reaction product was isolated by these workers. It was found in this laboratory that the phosgene–dimethylformamide complex possessed the empirical formula $C_3H_7NCl_2$. The structure andthe course of formation of the complex are, therefore, assumed to be as follows :



The reaction of this resonance-stabilized cation with alcohols forms

$$\left[\text{R-O-CH=}\overset{+}{\text{N}}(\text{CH}_3)_2\right]\text{Cl}^- \rightleftharpoons \left[\text{R-O-}\overset{+}{\text{C}}\text{H-}\ddot{\text{N}}(\text{CH}_3)_2\right]\text{Cl}^-$$

which on hydrolysis affords the formyl esters.

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1) T. E. Stevens : Chem. & Ind. (London), **1958**, 1090.
2) N. Roh, G. Kochendörfer : D. R. P. 677207(1939).

After completion of the present series of experiments, a report of Arnord[3] appeared, in which he described the preparation of phosgene–dimethylformamide complex and assigned to this compound the same structure as given above.

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Experimental

Dimethylformamide-Phosgene Complex—Dimethylformamide (15 cc.) was added with stirring into a solution of phosgene (25 g.) in dry benzene (400 cc.) in a flask protected from atmospheric moisture, the temperature being kept at 10~20°. A white crystalline substance began to separate as soon as dimethylformamide was added. The reaction mixture was allowed to stand at room temperature for 1 hr., then filtered rapidly onto a sintered-glass filter, the cake was washed with petr. ether, and dried in a vacuum desiccator over P_2O_5. Yield, 26 g. *Anal.* Calcd. for $C_3H_7NCl_2$: C, 28.15; H, 5.50; N, 10.94; Cl, 55.40. Found: C, 27.72; H, 5.34; N, 10.52; Cl, 54.22.

General Procedure—One gram of dimethylformamide-phosgene complex was added to a solution of steroid (1.0~2.0 g.) in dimethylformamide (5~10 cc.) in one portion. The mixture was shaken for 5~10 min. at room temperature and then poured on crushed ice to give the formyl ester of the steroid in almost pure crystalline form. The crystals were collected, washed with water, dried, and recrystallized from a suitable solvent. Yields obtained are shown in Table I.

Table I.

Steroid	Formyl ester m.p.[a] (°C)	Formyl ester $[\alpha]_D^{20}$ [b]	Yield (%)
Cholesterol	96~97	−50°	98
5α-Cholestanol	83~84	+14°	92
Ergosterol	161~161.5	−96°	94
Tigogenin	219~220	−71°	92
Hecogenin	232~233	−8°	90
Diosgenin	210~213	−144°	95
3β-Hydroxy-5α-androstan-17-one	116~117	+59°	91
16,17-Epoxy-3β-hydroxy-5-pregnen-20-one	162~164	−27°	94
17α,21-Dihydroxy-4-pregnene-3,20-dione[c]	182~184	+136°	95
11β,17α,21-Trihydroxy-4-pregnene-3,20-dione[c]	243 (decomp.)	+130°	90
11β,17α,21-Trihydroxy-1,4-pregnadiene-3,20-dione[c]	244 (〃)	+102°	80
Testosterone	127~129	+75°	92
Methyl lithocholate	119~120	+45°	90

a) Melting points are uncorrected.
b) Rotations were measured in dioxane (c=1.0).
c) 21-Monoformyl esters of the steroids were obtained.

Summary

An equimolar complex of dimethylformamide and phosgene, which is readily formed *in situ* or in dry benzene from the components with concomitant loss of carbon dioxide, was found to be an excellent formylating agent for steroid alcohols. A mechanism of the reaction was proposed and the yield of the formyl esters are given for a number of steroids.

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3) Zdeněk Arnord, Jiří Žemlicka: Chem. listy, **52**, 2013(1958) (C. A., **53**, 4112(1959)).