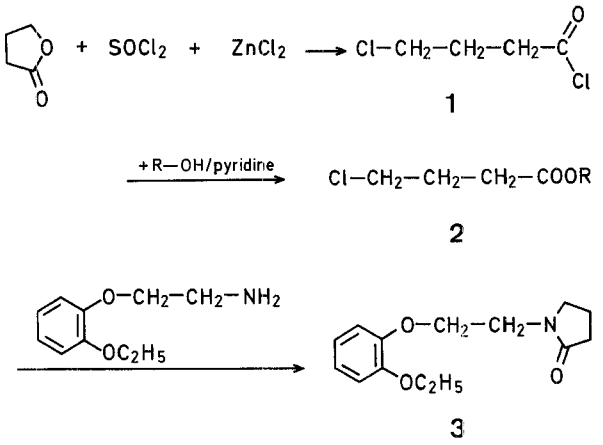
The Synthesis of 4-Chlorobutyric Acid Esters from γ-Butyrolactone

O. P. GOEL and R. E. SEAMANS

Department of Pharmaceutical Research and Development, Research and Development Division, Parke, Davis & Co., Detroit Michigan 48232, USA

γ-Butyrolactone is a convenient starting substance for the synthesis of 4-halogenated butyric acid esters (**2**). Its reaction with alcohols in presence of hydrogen chloride gas is reported[1] to produce the corresponding 4-chlorobutyric acid esters in good yield. However, in our hands, mixtures of low purity were obtained which were difficult to separate by fractional distillation, the main contaminant being the lactone. We have found that the reaction of 4-chlorobutanoyl chloride (**1**) with alcohols in presence of pyridine gave excellent yields of the corresponding esters (**2**) of high purity. 4-Chlorobutanoyl chloride, in turn, was prepared by reaction of γ-butyrolactone with thionyl chloride and anhydrous zinc chloride as catalyst[2] in 65–70% yield. It is not necessary, however, to isolate the intermediate 4-chlorobutanoyl chloride prior to reaction with alcohols. The results are summarized in the table.

Each of the esters **2** upon reaction with 2-(2-ethoxyphenoxy)-ethylamine gave the known 1-[2-(2-ethoxyphenoxy)-ethyl]-2-oxopyrrolidine[3] **3** in the yield reported in the table.



4-Chlorobutanoyl Chloride (1):

To a stirred solution of thionyl chloride (65.5 g, 0.55 mol) and anhydrous zinc chloride (3 g), γ-butyrolactone (43.05 g, 0.5 mol) was added in a rapid stream causing the temperature to rise to 45°. The reaction mixture was heated with stirring at 55° for 22 hr. The dark clear solution was subjected to vacuum distillation to give a fraction b.p. 69–85°/14 torr. Redistillation gave a colorless liquid; yield: 44 g; b.p. 69–74°/14 torr; n_D^{20}: 1.4615 (Ref.[2], b.p. 76–77°/18 torr; Ref.[4], n_D^{20}: 1.4609).

Preparation of Alkyl 4-Chlorobutanoates (2); General Procedure:

4-Chlorobutanoyl chloride (0.1 mol) was added, over 15 min, to a cooled stirred mixture of pyridine (0.1 mol) and alcohol (0.125 mol). The slurry was stirred for 18 hr at room temperature. Then 11 *N* sulfuric acid (50 ml) was introduced causing an oil to separate. The oil was isolated, the aqueous layer extracted with ether (30 ml), and the ether extract combined with the oil. The organic solution was washed with water and dried with sodium sulfate. The ether was removed in vacuo and the residual oil subjected to vacuum distillation.

When undistilled 4-chlorobutanoyl chloride was used directly from the reaction between γ-butyrolactone and thionyl chloride, a 60% yield of methyl 4-chlorobutanoate was isolated by reaction with methanol.

Table. Alkyl 4-Chlorobutanoates (**2**) and 1-[2-(2-Ethoxyphenoxy)-ethyl]-2-oxopyrrolidines (**3**) obtained from 4-Chlorobutanoyl Chloride (**1**) and Alcohols

Esters **2**[a]					Lactams **3**
R	Yield[b] (%)	b.p./torr	n_D^{20}	Purity (%) (G.L.C.)	Yield[c] (%)
CH_3	97.5	50–52°/2–3	1.4323	99.4	52
C_2H_5	89	55–60°/3.5–4.5	1.4321	91.9, 8.0(—CH_3)	65
n-C_3H_7	86	62–67°/2.5–3.0	1.4342	99.4	51
i-C_3H_7	87	49–55°/2.3	1.4286	99.7	57
n-C_4H_9	92	70–76°/2.2	1.4366	99.5	63
t-C_4H_9	52	56–65°/2–4	1.4307	96.8	17
C_6H_5—CH_2—	93.5	87–97°/0.1–0.3	1.5196	96.1	—

[a] Identification was made by I. R. and by refractive index comparison with literature values[1].

[b] Distilled 4-chlorobutanoyl chloride was used in these reactions and yields reported are of distilled products.

[c] Yield is that of isolated crystalline product.

1-[2-(2-Ethoxyphenoxy)-ethyl]-2-oxopyrrolidine (3):

A solution of 2-(2-ethoxyphenoxy)-ethylamine[3] (0.1 mol) and an alkyl 4-chlorobutanoate (0.05 mol) in dry toluene (62 ml) was heated under reflux under a blanket of nitrogen for 24 hr. The insoluble 2-(2-ethoxyphenoxy)-ethylamine hydrochloride was filtered off and toluene removed under vacuum. The residual oil on vacuum distillation gave the lactam **3** as a colorless oil which solidified on standing; b.p. 162°/0.04 torr; m.p. 48–54.5° (from benzene/petroleum ether).

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[1] J. Falbe, R. Paatz, F. Korte, *Chem. Ber.* **98**, 2312 (1965).

[2] H. Kaltschmitt, A. Tartter, *German Patent (DBP.)* 804567 (1951), BASF; *C.A.* **45**, 8031 (1951).
The combination of thionyl chloride and zinc chloride gave the best results among the many other halogenating agents investigated.

[3] R. W. Fleming, F. P. Hauck, *U.S. Patent* 3412154 ≡ *Belgian Patent* 668124 (1964), Parke, Davis & Co.; *C.A.* **65**, 3800 (1966).

[4] C. J. Pouchert, *The Aldrich Library of Infrared Spectra*, Aldrich Chemical Company, 1970.