was obtained, m. p. 138–176°. The first crop material was suitable for the preparation of dithioöxalodimorpholide.[15]

Summary

The reaction of α-tetralone with morpholine and sulfur yields 4-(2-naphthyl)-morpholine.

Dithioöxalodimorpholide has been isolated as a reaction product of sulfur and morpholine.

SALT LAKE CITY, UTAH RECEIVED MARCH 9, 1948

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

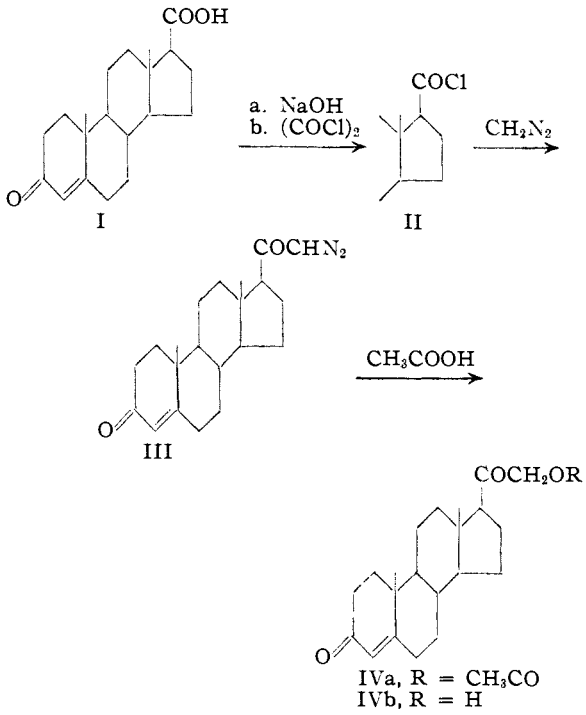
The Preparation of Desoxycorticosterone Acetate from 3-Keto-Δ^4-etiocholenic Acid

BY A. L. WILDS AND CLIFFORD H. SHUNK[1]

Desoxycorticosterone acetate (IVa) has been prepared by Reichstein and co-workers[2] from 3-acetoxy-Δ^5-etiocholenic acid by treating the acid chloride with diazomethane to form the diazoketone, followed by hydrolysis, Oppenauer oxidation of the remarkably stable diazoketone to 21-diazoprogesterone (III) and finally reaction with acetic acid. Attempts to prepare this adrenal cortical hormone from 3-keto-Δ^4-etiocholenic acid (I), thus avoiding the selective hydrolysis and oxidation of the diazoketone, have been unsatisfactory because of difficulties in preparing the acid chloride.[3,4] The α,β-unsaturated ketone grouping seems to be sensitive to reagents, such as thionyl chloride, normally used to prepare the acid chlorides. Apparently because of these difficulties, Reich and Lardon[5] developed a six-step procedure for converting 3-keto-Δ^4-steroids into the 3-acetoxy-Δ^5-derivative. This procedure was employed by von Euw and Reichstein[6] in a partial synthesis of 11-dehydrocorticosterone which necessitated re-oxidation to the 3-keto-Δ^4 derivative at a later stage.

In connection with the synthesis of certain analogs of desoxycorticosterone and progesterone lacking ring C, we have developed an improved procedure for converting unsaturated keto acids of this type into the acid chlorides and diazoketones. This procedure has proved to be quite successful with 3-keto-Δ^4-etiocholenic acid (I). The critical step is the formation of the acid chloride at low temperatures (below 15°) by reaction of the sodium salt of the acid with oxalyl chloride.[7,8] After reaction with diazomethane the diazoketone III was obtained in 81% over-all yield from the acid I. By adding the diazoketone to boiling acetic acid,[9] desoxycorticosterone acetate (IVa) was obtained in 73% yield. The over-all yield is considerably higher than those reported for the earlier syntheses.

These procedures should prove of value for similar reactions with the 11-oxygenated derivatives of I.



Experimental[10]

21-Diazoprogesterone (III).—A solution of 506 mg. of 3-keto-Δ^4-etiocholenic acid[11] in 19 ml. of 0.091 *N* sodium hydroxide was frozen and evaporated to dryness (lyophilized) under reduced pressure and the residue dried at 110° (0.1 mm.) for eight hours. After cooling, 10 ml. of dry, thiophene-free benzene and 3 drops of pyridine were added; the salt was scraped from the sides of the flask, mixed thoroughly and cooled in an ice-bath before adding 2 ml. of redistilled oxalyl chloride (b. p. 60–60.5°). There was an immediate evolution of gas which stopped after a few

(1) National Research Council Predoctoral Fellow, 1946–1948.

(2) Reichstein and v. Euw, *Helv. Chim. Acta*, **23**, 136 (1940); see also Steiger and Reichstein, *ibid.*, **20**, 1164 (1937).

(3) Private communication from Dr. Lewis H. Sarett of Merck and Co., Inc., Rahway, New Jersey.

(4) Dr. Wayne Cole of The Glidden Co., Soya Products Division, Chicago, Ill., has informed us that they have obtained this acid chloride in impure form using thionyl chloride in cold ether containing a trace of pyridine.

(5) Reich and Lardon, *Helv. Chim. Acta*, **29**, 671 (1946).

(6) v. Euw and Reichstein, *ibid.*, **29**, 1913 (1946).

(7) Adams and Ulich, THIS JOURNAL, **42**, 599 (1920).

(8) Dr. Thomas L. Johnson found this to be a superior method for preparing the acid chloride of a different type of keto acid; see Wilds and T. L. Johnson, THIS JOURNAL, **70**, 1166 (1948).

(9) Dr. Warren R. Biggerstaff has found that this procedure is superior to dissolving in acetic acid before heating.

(10) All melting points are corrected.

(11) We are indebted to the Research Dept. of The Glidden Co., Soya Products Division, for this material.

seconds. The mixture was then allowed to warm to 15° for four minutes and as no further evolution of gas was noticed the solvent was evaporated under reduced pressure. Dry air was then admitted and three 1.5-ml. portions of benzene were added and evaporated, keeping the temperature below 15° at all times. Finally the acid chloride was dissolved in 5 ml. of benzene, filtered through a dry, sintered glass funnel into a cooled receiver and diluted with an equal volume of ether. The acid chloride was added slowly to a cold (−15°) ethereal solution of diazomethane (prepared from 6 g. of nitrosomethylurea[12]), maintained at −15° for one-half hour and at 0° for one-half hour, then the solvent was evaporated under reduced pressure. Trituration of the residual oil with acetone gave a total of 439 mg. (81%) of the light yellow diazoketone which decomposed at 177–178° (reported,[2] 182–184°).

Desoxycorticosterone Acetate (IVa).—To 10 ml. of boiling, purified[13] acetic acid was slowly added 163 mg. of 21-diazoprogesterone; there was immediate evolution of nitrogen and a light yellow solution resulted. After refluxing for three minutes the acetic acid was evaporated under reduced pressure and the residual oil dissolved in acetone. On cooling long needles were obtained which changed to 109 mg. of a powder upon drying at room temperature, m. p. 155–157°. A second crop of 14 mg., m. p. 153–155°, and an additional 8 mg., m. p. 146–154°, after molecular distillation of the filtrate at 160° (0.001 mm.) brought the total yield of desoxycorticosterone acetate to 73%. Recrystallization of a sample from acetone raised the m. p. to 158–159° (reported,[2] 158–159°).

Hydrolysis of the acetate by the method of Reichstein and von Euw[14] gave desoxycorticosterone; after molecular distillation at 150° (0.001 mm.) and two recrystallizations from acetone–ether, this melted at 140–142° and showed no depression when mixed with an authentic sample.

(12) The diazomethane solution was distilled, dried for two hours over potassium hydroxide pellets, and then for one hour over sodium wire before use; see Fieser and Turner, THIS JOURNAL, **69**, 2341 (1947).

(13) The acetic acid was refluxed for six hours with 5% by weight of potassium permanganate, distilled and the distillate fractionated, collecting the last fraction, b.p. 117°.

Summary

A procedure has been developed for preparing acid chlorides from α,β-unsaturated keto acids using the sodium salt and oxalyl chloride in the cold. By means of this reaction it has been possible to convert 3-keto-Δ⁴-etiocholenic acid to 21-diazoprogesterone and desoxycorticosterone acetate in good yields.

(14) Reichstein and v. Euw, *Helv. Chim. Acta*, **21**, 1181 (1938).

MADISON 6, WISCONSIN RECEIVED MARCH 19, 1948

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF EVANS RESEARCH AND DEVELOPMENT CORPORATION]

Esters of (Carboxymethylmercapto)-succinic Acid

BY JOHN F. MULVANEY,[1a] JAMES G. MURPHY AND RALPH L. EVANS

(Carboxymethylmercapto)-succinic acid has been prepared by Fitger,[1] by Morgan and Friedmann[2] and by Larsson.[3] Larsson gives a procedure for the preparation of the *dl*-acid in excellent yield by the interaction of maleic acid and thioglycolic acid at water-bath temperature.

During an investigation of derivatives of thioglycolic acid, we prepared esters of (carboxymethylmercapto)-succinic acid of the three types indicated in Fig. 1. No attempt was made during this work to isolate any optically active forms of these esters.

Fig. 1

Type I	Type II	Type III
SCH_2COOR	SCH_2COOH	SCH_2COOR
$CHCOOR$	$CHCOOR$	$CHCOOH$
CH_2COOR	CH_2COOR	CH_2COOH

Esters of Type I.—These were prepared in the usual manner with an acid catalyst and with toluene or benzene as water-entraining agents.

The esters were purified by fractional distillation. Tne octadecyl ester was crystallized from toluene, alcohol and acetone.

The properties of the esters of Type I are listed in Table I. The *n*-propyl (b. p. 125–131° at 0.1 mm.) and isopropyl (b. p. 124–129° at 0.4 mm.) esters were prepared but were not purified for analysis.

Esters of Types II and III.—Preliminary attempts to prepare esters of Type II by the addition of thioglycolic acid to alkyl maleates gave only slow and partial reaction. The isolation of fumaric acid from the reaction mixture indicated hydrolysis and isomerization. When sodium thioglycolate was used, the reaction proceeded almost to completion at room temperatures.

$$NaOOCCH_2SH + ROOCCH{=}CHCOOR \longrightarrow \begin{matrix} SCH_2COONa \\ CHCOOR \\ CH_2COOR \end{matrix} \quad (1)$$

Similarly, it was found that thioglycolic acid esters reacted more completely with sodium maleate than with maleic acid to give esters of Type III.

$$ROOCCH_2SH + NaOOCCH{=}CHCOONa \longrightarrow \begin{matrix} SCH_2COOR \\ CHCOONa \\ CH_2COONa \end{matrix} \quad (2)$$

Experimental

In general, 0.25 mole of the acid was neutralized with 15% sodium hydroxide and an alcoholic solution of the ester (0.25 mole) was added. The mixture was allowed to stand at room temperature until titration with iodine showed that the addition was almost complete.

(1) Fitger, Diss. Lund, 1924.

(1a) Present address: General Aniline Works, General Aniline and Film Corporation, Grasselli, N. J.

(2) E. J. Morgan and E. Friedmann, *Biochem. J.*, **32**, 733 (1938).

(3) E. Larsson, *Trans. Chalmers Univ. Technol.*, **47**, 3–7 (1945).