Retention of Configuration in the Wolff Rearrangement

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In the course of a synthesis under investigation in this Laboratory we have re-examined the Wolff rearrangement of optically active diazoketones of the type $\mathrm{RR'CH{-}CO{-}CHN_2}$. In this rearrangement the retention of configuration of a migrating group which contains an enolizable hydrogen was first reported by Preobrashenski and co-workers[3] in the synthesis of *d*-homopilopic acid from *d*-pilopic acid. Later, Wallis and co-workers[4-6] investigated the rearrangement of a number of optically active diazoketones and found that complete retention of configuration occurred only with compounds of the type $\mathrm{RR'R''C{-}CO{-}CHN_2}$; when the asymmetric center contained an enolizable hydrogen, complete racemization usually occurred. Lane and Wallis[5] explain this behavior by postulating an initial enolization induced by the catalyst before the rearrangement takes place, or, at higher temperatures, thermal racemization of the migrating group. While Lane and Wallis regarded this behavior as a general phenomenon, they concede that the observed retention of configuration in the synthesis of *d*-homopilopic acid may have been due to a neighboring group effect.

In 1948, Gutsche[7] reported successful Arndt–Eistert syntheses starting with both *cis*- and *trans*-2-phenylcyclohexanecarboxylic acids. While no optical activity was involved, enolization of the diazoketone would cause isomerization, which was not observed, possibly because of the careful preparation of the catalyst. Gutsche has demonstrated that the preparation of the acid chlorides with thionyl chloride at elevated temperatures was accompanied by some isomerization.

We have investigated the rearrangement of two optically active diazoketones by the method of Wilds and Meader.[8] *d*-1-Diazo-3-methylpentanone-2 was prepared from *d*-2-methylbutyric acid[9] *via* the acid chloride. The optically active diazoketone was mixed with benzyl alcohol and added dropwise to boiling *s*-collidine. Hydrolysis of the benzyl alcohol–benzyl ester mixture isolated from the reaction gave *d*-3-methylvaleric acid, $\alpha^{25}\mathrm{D}$ 6.43° (neat, 1 dm.), 78% optically pure. This shows that the total amount of racemization from both the preparation of the acid chloride and the rearrangement is not over 22%.

In the other case the diazoketone[10] from the reaction of 3β-acetoxy-Δ^5-bisnorcholenyl chloride[11] and diazomethane was dropped into a benzyl alcohol–*s*-collidine mixture heated to 160–170°. The benzyl ester was isolated in 73% of the theoretical yield; a small amount of colored impurity was removed easily by chromatography. Hydrogenolysis of the benzyl ester in ethanol with a palladium catalyst was quantitative and gave 3β-acetoxy-Δ^5-norcholenic acid in 73% of theory from the diazoketone. Only one isomer could be isolated from the reaction.

This work extends the usefulness of the Arndt–Eistert reaction, especially in those cases where more general reactions may not be applicable. No effort has been made to obtain maximum yields in the following experimental work.

Experimental

***d*-(+)-α-Methylbutyric Acid.**—(*d*)-(−)-Amyl alcohol, $\alpha^{23}\mathrm{D}$ −4.68 (neat, 1 dm.), was oxidized by the method of Doering and Aschner.[8,9] α-Methylbutyric acid, b.p. 174–175°, $\alpha^{26}\mathrm{D}$ +17.70°, was isolated in 66% yield.

***d*-(+)-α-Methylbutyryl Chloride.**—Nineteen grams of the above acid was added slowly to 24.5 g. of refluxing thionyl chloride during one hour and the mixture was allowed to stand overnight. It was then refluxed for another hour and distilled through a ten-inch Widmer column. The product, b.p. 114–116°, weighed 17.0 g. (76% yield). Redistillation gave 13.0 g., b.p. 115–115.5°.

***d*-(+)-1-Diazo-3-methylpentanone-2.**—Thirteen grams of *d*-α-methylbutyryl chloride was added dropwise during stirring to a cold ethereal solution of diazomethane prepared from 50 grams of nitrosomethylurea. The solution was allowed to stand overnight, and the ether was removed by evaporation *in vacuo*. The product, a red-brown oil, showed a positive rotation in ether solution.

***d*-(+)-3-Methylvaleric Acid.** (A).—The diazoketone from the above experiment was dissolved in 15 ml. of benzyl alcohol, and the solution was added dropwise to 20 ml. of boiling *s*-collidine. The mixture was refluxed 5 min., cooled and diluted with ether. The ether solution was washed with hydrochloric acid and water. Evaporation of the ether gave 23 g. of a mixture of benzyl alcohol and benzyl *d*-3-methylvalerate. This mixture was refluxed for 3 hr. with 12 g. of potassium hydroxide in 10 ml. of water and 80 ml. of ethanol. The alcohols were removed by dilution of the mixture with water and extraction with ether. The aqueous layer was acidified and steam distilled. The product was extracted with ether and distilled; 7.9 g. (63.5% yield), b.p. 194–196°, $n^{25}\mathrm{D}$ 1.4138, $\alpha^{25}\mathrm{D}$ +6.43° (neat, 1 dm.), was isolated.

(B).—A Grignard reagent prepared from 24.4 g. of *d*-amyl chloride was poured on crushed solid carbon dioxide and the product, 16.7 g. (62.5% yield), b.p. 110.5° at 26 mm., $\alpha^{25}\mathrm{D}$ +7.80° (neat, 1 dm.), $n^{25}\mathrm{D}$ 1.4140, was isolated in the usual way. Romburgh[12] reports $\alpha^{19}\mathrm{D}$ +8.30° (neat, 1 dm.).

3β-Acetoxy-23-diazo-Δ^5-norcholenone-22.—A solution of diazomethane in absolute ether was cooled in an ice-bath, and a solution of 25.0 g. of 3β-acetoxy-Δ^5-bisnorcholenyl chloride in 50:50 ether–benzene was added slowly during stirring. The product, 21.2 g., m.p. 260–270° dec., precipitated on standing and was collected. Concentration of the mother liquors gave an additional 0.92 g. (87%). A small portion was recrystallized from chloroform–ethanol and gave the following constants: $[\alpha]^{24}\mathrm{D}$ −54.6° (*c* 1.63, chloroform, 1 dm.), ϵ_{250} 10,500 (95% ethanol).

Anal. Calcd. for $C_{25}H_{36}O_3N_2$: C, 72.78; H, 8.80; N, 6.79. Found: C, 72.97; H, 8.57; N, 6.61.

Benzyl 3β-Acetoxy-Δ^5-norcholenate.—A mixture of 25 ml. of benzyl alcohol (Eastman Kodak Co., white label) and 25 ml. of distilled *s*-collidine was heated to 165° in a flask in an oil-bath. Twenty-one and one-half grams of the above diazoketone was added in portions over a period of about 5 min. at an internal temperature of 160–170°. After three minutes at 170°, the reaction mixture was

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[1] Procter and Gamble Co. Predoctoral Fellow, 1953–1954.

[2] The junior author gratefully acknowledges several helpful discussions with Dr. Peter Yates of Harvard University.

[3] N. A. Preobrashenski, A. M. Poljakowa and W. A. Preobrashenski, *Ber.*, **68**, 850 (1935).

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[8] A. L. Wilds and A. L. Meader, *J. Org. Chem.*, **13**, 763 (1948).

[9] W. von E. Doering and T. C. Aschner, This Journal, **75**, 393 (1953).

[10] A. Wettstein, *Helv. Chim. Acta*, **24**, 311 (1941).

[11] We wish to thank Schering Corp., Bloomfield, N. J., for a generous supply of 3β-acetoxy-Δ^5-bisnorcholenic acid.

[12] P. van Romburgh, *Rec. trav. chim.*, **5**, 219 (1886).

cooled, diluted with ether and extracted with dilute hydrochloric acid. The ether solution was washed with water, dried and concentrated. Addition of ethanol gave 19.6 g. of product, m.p. 101–103.5°. This was recrystallized from ethanol and gave 18.7 g. (73%) of yellow product, m.p. 102–104.5°. Chromatography on alumina gave a colorless product, 15.4 g., m.p. 104.4–105.5°, $[\alpha]^{25}D$ −37.1° (*c* 1.24, chloroform, 1 dm.).

Anal. Calcd. for $C_{32}H_{44}O_4$: C, 78.01; H, 9.00. Found: C, 78.13; H, 9.13.

3β-Acetoxy-Δ⁵-norcholenic Acid.—A suspension of 4.93 g. (0.01 mole) of benzyl 3β-acetoxy-Δ^5-norcholenate in 200 ml. of 95% ethanol was shaken with pre-reduced palladium (from 200 mg. of oxide) under hydrogen. At the end of 13 hr. the uptake of hydrogen ceased at 0.01 mole. The solution was filtered and evaporated to dryness *in vacuo*. The crude product, m.p. 197.5–199°, was recrystallized from acetone–petroleum ether to give 3.7 g., m.p. 197.5–198.5°, $[\alpha]^{25}D$ −42° (*c* 1.14, chloroform, 1 dm.).

Anal. Calcd. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.52: neut. equiv., 402.6. Found: C, 74.44; H, 9.37; neut. equiv., 405, 409.

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Studies on the Chemistry of Heterocyclics. XXVII.[1] α,β-Acetylenic Acids and their Esters in the Thiophene Series

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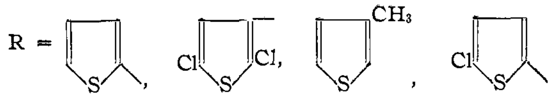
Continuing our studies on acetylenic derivatives in the thiophene series[3,4] we report in this paper the preparation of α,β-acetylenic acids and their esters. The intermediates (thienylacetylenes) were prepared according to the earlier procedure developed in this Laboratory.[5] We were able to improve the yields reported earlier. The yield for 2-thienylacetylene could be increased up to 80% while that for 2,5-dichloro-3-thienylacetylene amounted to 91%. The yield of 5-chloro-2-thienylacetylene was, however, low (28%).

The direct carbonation of the sodium salts of thienylacetylenes did not lead to any of the desired α,β-acetylenic acids. We observed that neither pressure nor different solvents had any effect on the products of the reaction. In all cases small amounts of 2-thenoic acids were isolated only. This phenomenon was observed earlier while studying γ-hydroxy-α,β-acetylenic acids. Perhaps the acetylenic acids once formed were hydrated to the keto acids. The latter on cleavage furnished the corresponding thenoic acids.

An alternate procedure *via* the α,β-acetylenic esters furnished the desired α,β-acetylenic acids in this series in satisfactory yields. The sodium salts of the thienylacetylenes were prepared by applying sodium amide in liquid ammonia as reported earlier.[4] The latter were treated with ethyl chlorocarbonate giving the corresponding esters as

$$RC{\equiv}CH \xrightarrow[NH_3]{NaNH_2}$$

$$RC{\equiv}C\cdot Na \xrightarrow[\text{Ether}]{ClCOOC_2H_5} RC{\equiv}CCOOC_2H_5$$



The previously applied method for the preparation of γ-hydroxy-α,β-acetylenic esters in this series was modified by adding a large excess of ethyl or methyl chlorocarbonate to the reaction mixture and refluxing it for several hours. Complete separation of the acetylenic esters from the accompanying acetylenes by distillation was difficult, but separation could be effected by precipitation of the acetylene as the copper salt followed by distillation of the ester *in vacuo*.

The properties and yields of the α,β-acetylenic esters are recorded in Table I.

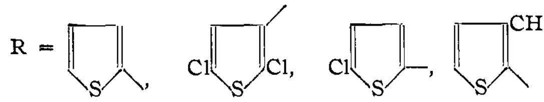
TABLE I

PROPERTIES AND YIELDS OF THE THIENYLPROPIOLIC ESTERS

Ethyl propiolate	B.p. (1 mm.), °C.	Yield, %	Analyses, % Calcd. C	H	Cl	Found C	H	Cl
2-Thienyl-	95–98	91	60	4.45	...	59.8	4.2	..
5-Chloro-2-thienyl	56–58	45	50.35	3.26	16.5	50.5	3.5	17
2,5-Dichloro-3-thienyl	92–95	80	43.37	2.41	28.59	43.5	2.3	28.3
3-Methyl-2-thienyl	65–67	70	63.5	5.29	...	63.8	5.4	..

While applying our earlier procedure for the isolation of the free γ-hydroxy-α,β-acetylenic acids[4] the free 2- and 3-thienyl-α,β-acetylenic acids were obtained in satisfactory yields according to the reaction

$$RC{\equiv}C{-}COOC_2H_5 \xrightarrow{(OH^-)} R{-}C{\equiv}C{-}COOH + C_2H_5OH$$



The properties and yield of the α,β-acetylenic acids are recorded in Table II.

TABLE II

PROPERTIES AND YIELDS OF THE THIENYLPROPIOLIC ACIDS

Propiolic acid	M.p., °C.	Yield, %	Analyses, % Calcd. C	H	Cl	Found C	H	Cl
2-Thienyl-	130–133	85	55.26	2.63	...	55.0	2.8	..
2,5-Dichloro-3-thienyl	139–141	79	38.0	0.905	32.12	37.9	1.2	32.0
5-Chloro-2-thienyl	118–120	45	45.04	1.6	19.02	44.8	2.0	18.9
3-Methyl-2-thienyl	115–118	60	57.8	3.61	...	56.0	3.8	..

Polymerization took place to a greater or lesser extent in all the reactions carried out in this series. In the case of the 5-chloro compound the polymerization was increased so far that only small yields of the desired products could be obtained. The polymerization of the acetylenic compounds in this series probably is due to the mobility of the electrons of the hetero atom.

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[1] For a comprehensive review of some recent developments in the field of thiophene see F. F. Nord, A. Vaitiekunas and L. J. Owen, *Fortschritte d. chem. Forschung*, **3**, 309 (1955).

[2] Condensed from a portion of the thesis of A. J. O. submitted to the Graduate School of Fordham University in fulfillment of the requirements of the M.Sc. degree.

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