

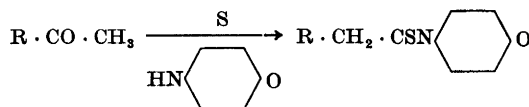
Preparation of 3-Reteneacetic Acid by the Willgerodt-Kindler Reaction

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3-Reteneacetic acid has been prepared through the Willgerodt-Kindler reaction. By hydrolysis of the crude thiomorpholide two by-products, retene-3-carboxylic acid and retene-3-glyoxylic acid were isolated. The precursor of these byproducts, 3-reteneglyoxylmorpholide has been isolated by chromatography of the crude thiomorpholide. 3-Reteneacetomorpholide can be obtained by partial hydrolysis of the thiomorpholide.

In a synthetic program 3-reteneacetic acid was required as starting material and as 3-acetylretene can be prepared in good yield ^{1,2}, the Willgerodt reaction seemed promising. The Kindler procedure ^{3,4} in the Schwenk-Bloch modification ⁵ using morpholine as the amine was selected. The main reaction product then is the thiomorpholide:



The mole ratios applied were 1:2.5:2 for ketone, sulphur and morpholine, respectively, in accordance with King and McMillan ⁶.

In a preliminary experiment the crude reaction product was hydrolyzed directly in a mixture of acetic acid and sulfuric acid. The purification of the reteneacetic acid met, however, with great difficulties. Next, a recrystallization of the thiomorpholide from alcohol was tried. When cooling the hot solution an oil separated at first, but by careful work a 75—80 % yield of light yellow crystals could be obtained. The melting point of this material was, however, far from sharp, even after several recrystallizations.

Next, hydrolysis of the thiomorpholide by means of alcoholic potassium hydroxide was tried. After boiling for a short time much crystalline material separated in the reaction mixture. The substance was colourless and contained no sulphur. It could be hydrolyzed to 3-reteneacetic acid and was thus shown to be the morpholide of this acid.

Under suitable conditions the partial alkaline hydrolysis gave a satisfactory yield of almost pure morpholide, and for the purpose of preparation of pure 3-reteneacetic acid it is advantageous to isolate the morpholide and afterwards bring the hydrolysis to completion. It turned out, that it was unnecessary to recrystallize the crude Willgerodt reaction product. Partial alkaline hydrolysis of this material gave an about 70 % yield of almost pure morpholide. The second step in the hydrolysis was most advantageously carried out by means of a solution of potassium hydroxide in *n*-propanol. By this procedure an overall yield of 60 % of 3-reteneacetic acid could be obtained.

By examination of the alkaline mother liquor from partial hydrolysis of the crude thiomorpholide two by-products were isolated and identified, *viz.* 3-retenecarboxylic acid and 3-reteneglyoxylic acid. The latter acid could not be obtained in quite pure condition but could be identified by conversion to the phenylhydrazone and the methyl ester, which was characterized through the dinitrophenylhydrazone.

In order to isolate the precursors of these by-products in the Willgerodt reaction and to isolate the thiomorpholide in pure condition, the crystalline product from the Willgerodt reaction was chromatographed on alumina. In this way 3-retenethioacetomorpholide could be isolated as a pure white compound composing the bulk of the crystalline product, but two other substances which were stronger adsorbed than the thiomorpholide were isolated as white compounds constituting about 10 % of the impure thiomorpholide. One of these compounds could be identified as 3-reteneacetomorpholide. The other substance was a neutral compound, which contained no sulphur.

The ultraviolet absorption spectrum was quite different from the spectra of 3-retenethioacetomorpholide and 3-reteneacetomorpholide, which were very similar and showed a typical retene structure, while the spectrum of the by-product showed a broad absorption band at 320—340 $m\mu$. Hydrolysis of this product with alcoholic potassium hydroxide gave 3-retenecarboxylic acid and 3-reteneglyoxylic acid. As the spectrum of methyl-3-reteneglyoxylate is almost identical with that of the by-product, it is reasonable to assume, that the by-product is 3-reteneglyoxylmorpholide. The elementary analysis supports this assumption.

EXPERIMENTAL

3-Acetylretene was prepared by the method of Dodd, Schramm and Elderfield² with the modification, that acetic anhydride was used instead of acetyl chloride in the Friedel-Crafts reaction. The yield of pure 3-acetylretene was 61 %.

Willgerodt-Kindler reaction. A mixture of 3-acetylretene (24.0 g, 0.087 mole), sulphur (7.05 g, 0.22 g-atom) and morpholine (15.2 ml, 0.174 mole) was heated under gentle reflux for 5 h, during which time a considerable amount of hydrogen sulphide was evolved. The dark coloured viscous product was poured in hot alcohol (200 ml) and left standing overnight. Crystals and oily material had now separated in the solution. The solution and the main part of the crystalline material was decanted from the oil, which was redissolved in alcohol. On cooling, some substance at first separated as an oil but later crystalline material separated. By warming the solution gently, more of the oil crystallized. The solution with the crystalline material was again decanted from residual oil and by repeating this process twice, 23 g of crystalline light yellow material was isolated, melting point 110—114°, yield 75 % calculated as pure 3-retenethioacetomorpholide.

3-Reteneacetomorpholide. The crystalline thiomorpholide (23 g) was dissolved in hot alcohol (100 ml), and a solution of potassium hydroxide (17.1 g) in water (17 ml) was added. The solution turned immediately black and subsequently red. The solution was refluxed. After 4 min boiling much precipitate suddenly separated in the reaction mixture. The precipitate was filtered by suction and washed with alcohol. Yield of 3-reteneacetomorpholide 17.1 g (78 %, calc. from the thiomorpholide), m. p. 184.5–185.5°. Recrystallization from *n*-propanol gave white crystals, m. p. 187–188.5°. (Found: C 79.5; H 7.55; N 3.90. Calc. for $C_{24}H_{27}NO_2$ (361.5): C 79.7; H 7.53; N 3.88.) U.V. absorption (in ethanol): λ_{\max} 260.5 (log ϵ 4.81); 282 (4.13); 291 (4.01); 303.5 (4.13); 329 (2.41); 335.5 (2.51); 352 $m\mu$ (2.19). λ_{\min} 234; 278; 287.5; 297; 325; 331.5; 341–345 (shoulder); 349.5 $m\mu$.

Alkaline hydrolysis of 3-reteneacetomorpholide. The morpholide (1.8 g, 0.005 mole) was dissolved in *n*-propanol (10 ml). To the warm solution was added a solution of potassium hydroxide (1.4 g, 0.025 mole) in water (1–2 ml). The mixture was refluxed for 5.5 h. After dilution with water (200 ml) the clear solution was acidified with hydrochloric acid. A white precipitate separated (1.4 g, m. p. 209–213°). The product was recrystallized from *n*-propanol (15 ml) giving 3-reteneacetic acid 1.15 g (78.8 %), m. p. 210–212.5° (subl.). (Found: Equiv.wt.: 293.3; C 82.1; H 6.84. Calc. for $C_{20}H_{20}O_2$ (292.4): C 82.2; H 6.90.)

Synthesis of 3-reteneacetic acid. A mixture of 3-acetylretene (41.4 g, 0.15 mole), sulphur (12.03 g, 0.375 g-atom) and morpholine (26.1 ml, 0.3 mole) was heated under gentle reflux for 5 h. The dark reaction mixture was dissolved in alcohol (150 ml). To the warm mixture was added a solution of potassium hydroxide (20 g) in water (10 ml) and alcohol (20 ml). The solution was refluxed for 8 min and then cooled. The precipitate was filtered by suction and washed with alcohol. The alkaline filtrate was further boiled for 15 min and left overnight. A second crop of morpholide was obtained. The crude morpholide was treated twice with boiling water. Yield of crude morpholide 38.1 g (70.2 % calc. from 3-acetylretene), m. p. 177–184°.

The morpholide (38.1 g) was dissolved in hot *n*-propanol (200 ml), and potassium hydroxide (17.7 g) in water (12 ml) was added. The mixture was boiled under reflux for 4 h. The slightly soluble potassium salt separated in the mixture. Water (300 ml) was added, and propanol was removed by distillation. The aqueous solution was boiled with charcoal, filtered and acidified. 3-Reteneacetic acid separated as colourless crystals (30.3 g). The crude product was recrystallized from a mixture of alcohol and acetone. Yield 26.8 g (61.2 % calc. from 3-acetylretene), m. p. 209–212.5° (subl.).

3-Retenecarboxylic acid. To the dark brown alkaline mother liquor from the partial hydrolysis of the crude Willgerodt reaction product was added potassium hydroxide (10 g), and the solution was refluxed for 2 h. The main part of the alcohol was removed by distillation *in vacuo*. To the residue was added water, and the solution was acidified with hydrochloric acid. A brown precipitate separated (7.5 g) and was dissolved in hot benzene. On cooling crystalline material separated (1 g). Two further recrystallizations from benzene gave 3-retenecarboxylic acid (0.3 g), m. p. 242–244° (subl.); gives no depression when mixed with an authentic specimen. (Found: C 82.1; H 6.45. Calc. for $C_{16}H_{18}O_4$: C 82.0; H 6.52.)

3-Reteneglyoxylic acid. The aqueous filtrate, resulting from digestion of the crude morpholide with hot water, was yellowish and gave on cooling a precipitate of a potassium salt. Acidification gave a yellow precipitate (2 g), which was recrystallized from a mixture of benzene and hexane and gave yellow crystals (1 g), m. p. 144–148.5°. One further recrystallization from benzene-hexane gave 3-reteneglyoxylic acid (0.8 g), m. p. 147–150°. (Found: C 78.8; H 6.15. Calc. for $C_{20}H_{18}O_3$ (306.3): C 78.4; H 5.92.)

Phenylhydrazone of 3-reteneglyoxylic acid. The keto acid (0.4 g) was dissolved in alcohol (7 ml). To the solution was added phenylhydrazine hydrochloride (0.3 g) and potassium acetate (0.2 g). The mixture was refluxed for one hour and cooled. The precipitate was washed several times with hydrochloric acid, recrystallized from glacial acetic acid. The phenylhydrazone (0.1 g) formed yellow crystals m. p. 166–168.5°. (Found: Equiv.wt. 403; N 6.9. Calc. for $C_{28}H_{24}N_2O_2$ (396.5): N 7.1.)

Methyl ester of 3-reteneglyoxylic acid. 3-Reteneglyoxylic acid (0.6 g) in methanol (25 ml) and concentrated sulfuric acid (0.1 ml) was refluxed for 8 h. The excess of methanol was distilled off and the residue dissolved in ether-benzene. The solution was washed with water, potassium bicarbonate and saturated sodium chloride. After drying with anhydrous calcium chloride the solvent was distilled off and the residue dissolved in hot

alcohol. After some time crystalline light yellow material had separated. Recrystallized from alcohol the methyl-3-reteneglyoxylate (0.08 g) had m. p. 101–102°. (Found: C 78.7; H 6.12. Calc. for $C_{21}H_{20}O_3$ (320.4): C 78.7; H 6.29.) U.V. absorption (in cyclohexane): λ_{\max} 248.5 (log ϵ 4.61); 264 (4.58); 289–92 (shoulder) (3.82); 336 $m\mu$ (4.18); λ_{\min} 223 (4.13); 256 (4.56); 299 $m\mu$ (3.74).

Dinitrophenylhydrazone of methyl-3-reteneglyoxylate. 2,4-Dinitrophenylhydrazine (0.2 g) and alcohol (10 ml) was heated to boiling. To the hot solution was gradually added concentrated sulfuric acid until clear solution. To this solution was added a solution of the keto ester (0.2 g) in alcohol (5 ml). A reddish orange precipitate at once separated. The dinitrophenylhydrazone (0.2 g) was recrystallized from xylene. Yield 0.1 g, m. p. 293–294.5°. (Found: C 64.3; H 4.85; N 10.9. Calc. for $C_{27}H_{24}N_4O_6$ (500.5): C 64.8; H 4.83; N 11.2.)

Chromatography of the crude thiomorpholide. From the Willgerodt-Kindler reaction of 3-acetylretene (16.6 g, 0.06 mole) 18.4 g of crystalline light yellow material was isolated, consisting of several fractions with the main fraction melting at 110–114°. As purification through fractional crystallization was unsuccessful, a fraction (11 g, m. p. 105–116°) was chromatographed on a column (21 × 6.5 cm) of alumina, solvent petroleum ether (600 ml) + carbon tetrachloride (400 ml).

The chromatogram was developed by the same solvent containing increasing amounts of carbon tetrachloride, and subsequently with carbon tetrachloride.

The surface of the column became strongly coloured. Next came a light yellow zone gradually changing to light grey. Next followed a broad pure white zone containing the thiomorpholide and finally a narrow yellow layer.

The column was fractionally eluted by washing with benzene. In the filtrate 3-retene-thioacetomorpholide could be isolated by evaporation of the solvent and recrystallization of the residue. Yield: 7.2 g, m. p. 119.5–122°. Two further recrystallizations gave white crystals, m. p. 120–121.5°. (Found: C 76.6; H 7.18; N 3.70; S 8.44. Calc. for $C_{24}H_{27}NSO$ (377.5): C 76.4; H 7.21; N 3.71; S 8.49.) U.V. absorption (in ethanol): λ_{\max} 261.5 (log ϵ 4.83); 282 (4.46); 303.5 (4.19); 329 (2.51); 335.5 (2.60); 352.5 $m\mu$ (2.37) λ_{\min} 233.5; 278; 299; 325.5; 331.5; 341–345 (shoulder); 350 $m\mu$.

From the column the surface layer was discarded, and the rest of the column was divided into two nearly equal parts, which were eluted separately with boiling alcohol. The eluate from the upper half was stronger yellow than that from the lower half of the column. From these two eluates two white crystalline neutral substances could be isolated. One of these, isolated from the lower half of the column, has been identified as 3-reteneacetomorpholide, yield 0.2 g, m. p. 186.5–188.5°; gives no depression, when mixed with an authentic specimen, prepared by alkaline desulphurization of 3-retene-thioacetomorpholide.

The eluate from the upper half of the column was concentrated. From the yellow solution crystalline material separated (1 g), m. p. 147.5–152°. Fractional crystallization of this fraction gave a white compound (0.4 g), m. p. 175–178°. One further recrystallization from alcohol gave 3-reteneglyoxylmorpholide, m. p. 176–178°. (Found: C 76.6; H 6.79; N 3.77. Calc. for $C_{24}H_{25}NO_3$ (375.5): C 76.8; H 6.71; N 3.73.) U.V. absorption (in cyclohexane): λ_{\max} 248 (log ϵ 4.59); 264.5 (4.60); 289–92 (shoulder) (3.93); 334 $m\mu$ (4.18). λ_{\min} 223 (4.19); 254 (4.57); 300 $m\mu$ (3.84).

Alkaline hydrolysis of 3-reteneglyoxylmorpholide. A mixture of 3-reteneglyoxylmorpholide (0.3 g) potassium hydroxide (0.2 g) and alcohol (15 ml) was refluxed for about one hour. The potassium salt of 3-reteneglyoxylic acid partly separated in the boiling liquid and more was obtained on cooling. The salt was filtered off and washed with ether. On acidification of an aqueous solution of the salt, a yellow product was obtained, which after recrystallization from benzene-hexane had m. p. 148–151°, yield 0.1 g. (Found: Equiv. wt. 301.5. Calc. for $C_{20}H_{18}O_3$: 306.3.) The acid, which was not quite pure, was shown to be 3-reteneglyoxylic acid by conversion to the methyl ester.

After filtration of the potassium salt the alkaline filtrate was evaporated to dryness. The residue was dissolved in boiling water and the solution acidified. The brownish precipitate was dissolved in benzene. On cooling a small white precipitate separated. One further recrystallization from benzene gave 3-retenecarboxylic acid, m. p. 239.5–242°; gives no depression in m. p. when mixed with an authentic specimen.

Analyses and U.V. spectra were performed in this laboratory by miss B. Møller.

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