acids mostly 3(α)-hydroxy-6-keto-*allo*cholanic acid, 9% of an unknown dihydroxycholanic acid, probably chenodesoxycholic acid and about 6% of a C_{27} acid, possibly a steroid sapogenin, as well as some residues not further examined.

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[CONTRIBUTION FROM THE WHITMORE LABORATORIES, SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Derivatives of Benzofuran

BY R. B. WAGNER AND JOHN M. TOME

During studies of preparative procedures for benzofuran derivatives and for their use as precursors for the biosynthesis of penicillin,[1] 2-benzofurylacetic acid[2] was prepared by the Arndt–Eistert synthesis[3] in 29% yield from α-benzofuroic acid. Catalytic rearrangement of 2-diazoacetylbenzofuran (I) prepared from the latter gave ethyl 2-benzofurylacetate in 64% yield while rearrangement to the corresponding amide gave only a 34% yield. The 2-benzofurylacetic acid was obtained by hydrolysis of the ester.

A study of the reactivity[4] of the diazoketone (I) showed that treatment with aqueous hydrochloric acid yields 2-chloroacetylbenzofuran (II), hydrolysis with aqueous sulfuric acid gives 2-hydroxyacetylbenzofuran, and reduction with hydriodic acid yields 2-acetylbenzofuran. Treatment of the diazoketone (I) with glacial acetic acid or treatment of the chloroketone (II) with sodium acetate gave 2-hydroxyacetylbenzofuran acetate.

The chloroketone (II) was characterized by degradation to α-benzofuroic acid by treatment with pyridine to form α-benzofuroylmethylpyridinium chloride followed by alkaline cleavage. This reaction has been shown to be quite general.[5,6,7] Treatment of the chloroketone (II) under conditions of the haloform degradation reaction gave the same acid. The chloroketone was coupled with mercaptoacetic acid in the presence of base to give α-benzofuroylmethylmercaptoacetic acid.

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Experimental[8]

2-Diazoacetylbenzofuran (I).—An ethereal solution of 0.92 mole of diazomethane[9] was treated by the standard procedure[3] with an ether solution of 55.5 g. (0.31 mole) of α-benzofuroic acid chloride, m. p. 52-53°, b. p. 112-123° (6 mm.), 98-100° (3 mm.) (prepared as previously described).[2,10] A yield of 42.1 g. (74%) of yellow crystals, m. p. 111-118°, was obtained by crystallization from benzene-pentane. Recrystallizations from benzene-pentane and acetone gave a constant melting point of 117-118°.

Anal. Calcd. for $C_{12}H_6O_2N_2$: N, 15.05. Found: N (Dumas), 15.00, 15.11.

Ethyl 2-Benzofurylacetate by Rearrangement of the Diazoketone (I).—To a warm ethanolic solution of 20 g. (0.107 mole) of 2-diazoacetylbenzofuran was added 9.6 g. of silver oxide by the standard procedure.[3] The volume of gas collected during the reaction was 4% below the theoretical amount. The product was fractionated to give 14.1 g. (64% yield) of colorless liquid, b. p. 147-148° (8 mm.), m. p. 18.0-18.5°, $n^{20}\text{D}$ 1.5400, d^{20} 1.140.

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.57; H, 5.93; $M\text{D}$, 56.23. Found: C, 70.75; H, 6.36; $M\text{D}$, 56.22. The calculated molecular refraction includes an exaltation correction[11] of +1.58.

The free acid, 2-benzofurylacetic acid, was obtained by refluxing for seventeen hours a solution of 8.2 g. of the ester and 14 g. of potassium hydroxide in 200 ml. of methanol. The mixture was diluted with an equal volume of water, concentrated in vacuum, and filtered. The solution was acidified to approximately *p*H 7 and the red gum which separated was discarded. The solution was then acidified to *p*H 3-5 (congo red paper) to give an orange precipitate. This precipitate was treated with activated carbon in ethanol and recrystallized first from ethanol, then from benzene-pentane to give 5.27 g. (75% yield) of white plates, m. p. 97-99° (lit.,[2] m. p. 98-99° cor.).

Anal. Calcd. for $C_{10}H_8O_3$: neut. equiv., 176. Found: neut. equiv., 179.

The amide was prepared from the 2-benzofurylacetic acid by a standard procedure,[12] giving white crystals from benzene, m. p. 163-164°. A mixed melting point determination with the amide from the rearrangement of the diazoketone (I) showed no depression.

2-Benzofurylacetamide by Rearrangement of the Diazoketone (I).—A hot solution of 5.0 g. of 2-diazoacetylbenzofuran, 50 ml. of dioxane and 50 ml. of concentrated ammonium hydroxide (sp. gr. 0.9) was treated with 27 ml. of 10% aqueous silver nitrate according to the standard procedure.[3] The volume of nitrogen collected was 6% below the theoretical amount. The product after treatment with activated carbon was recrystallized from benzene and from chloroform to yield 1.6 g. (34%) of white plates, m. p. 163.5-164.5°.

Anal. Calcd. for $C_{10}H_9O_2N$: N, 8.00. Found: N (Dumas), 8.07, 8.35.

2-Chloroacetylbenzofuran (II) by Hydrohalogenation of I.—To a solution of 2.0 g. of 2-diazoacetylbenzofuran in 7 ml. of dioxane was added 5 ml. of concentrated hydro-

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[1] Stone, Patterson and Farrell, *J. Bact.*, **51**, 598 (1946).

[2] Reichstein and Reichstein, *Helv. Chim. Acta*, **13**, 1275 (1930).

[3] Bachmann and Struve, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 38.

[4] Eistert, "Newer Methods of Preparative Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1948, p. 513.

[5] King, THIS JOURNAL, **66**, 894 (1944).

[6] Reich and Reichstein, *Helv. Chim. Acta*, **22**, 1124 (1939).

[7] Brown, *Iowa State Coll. J. Sci.*, **11**, 221 (1936).

[8] All melting and boiling points are uncorrected.

[9] Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 165.

[10] Fuson, Kneisley and Kaiser, "Organic Syntheses," Vol. 24, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 33.

[11] Auwers and Kohlhaas, *J. prakt. Chem.*, **108**, 321 (1924).

[12] Shriner and Fuson, "The Systematic Identification of Organic Compounds," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1940.

chloric acid. After warming for fifteen minutes the solution was cooled and diluted with 50 ml. of water which precipitated 1.97 g. (95% yield) of pale yellow crystals, m. p. 103–105°. Treatment with carbon black and recrystallizations from ethanol, propanol and carbon tetrachloride gave white needles with a constant melting point of 104–105°.

Anal. Calcd. for $C_{10}H_7O_2Cl$: Cl, 18.22. Found: Cl (Stepanoff), 18.21, 18.25.

The haloform degradation was carried out by a standard procedure[12] using 0.5 g. of 2-chloroacetylbenzofuran. The product was chromatographed on a 8 × 1/2" silica gel (50–200 mesh) column using anhydrous ether as the developing agent. Material from several cuts was recrystallized from aqueous ethanol and aqueous dioxane to give white crystalline α-benzofuroic acid, m. p. and mixed m. p. 189.5–193° (lit.,[10] m. p. 190–193°).

2-Hydroxyacetylbenzofuran by Hydrolysis of I.—To 1.0 g. of 2-diazoacetylbenzofuran dissolved in 15 ml. of warm purified dioxane was added 20 ml. of 2 *N* sulfuric acid and the mixture was warmed until evolution of nitrogen ceased (thirty minutes). The reaction mixture was diluted with water and the dioxane was evaporated in vacuum to precipitate a solid. This solid was treated with activated carbon and recrystallized from ethanol (needles) and acetone-pentane (plates) to give 0.46 g. (49% yield) having a constant melting point of 128–129°.

Anal. Calcd. for $C_{10}H_8O_3$: C, 68.18; H, 4.58. Found: C, 68.22; H, 4.71.

2-Acetylbenzofuran by Reduction of I.—To a solution of 1.5 g. of 2-diazoacetylbenzofuran in 15 ml. of chloroform was added 6 ml. of 47% hydriodic acid. The mixture was warmed for twenty minutes, then cooled and washed with water and 5% sodium thiosulfate. The chloroform layer was separated, dried and evaporated in vacuum. The resulting solid was treated with carbon black and fractionally crystallized from ethanol to give 1.23 g. (95% yield) of yellow crystals, m. p. 69–71° (lit.,[13] m. p. 75–76°). Subsequent repeated treatment with carbon black and recrystallization from benzene-pentane and from ethanol resulted in white plates with the same melting point.

The semicarbazone was prepared by a standard procedure[12] to yield white needles from aqueous ethanol, m. p. 217–218° (lit.,[14] m. p. 217°).

2-Hydroxyacetylbenzofuran Acetate (a).—A mixture of 1.0 g. of 2-diazoacetylbenzofuran and 10 ml. of glacial acetic acid was warmed on the steam-bath until evolution of nitrogen ceased (two hours). The mixture was diluted with 60 ml. of water and the precipitate was treated with activated carbon in hot ethanol. Crystallization from both ethanol and benzene–pentane gave 0.90 g. (81% yield) of white crystals, m. p. 86.5–87.5° (lit.,[15] m. p. 86–87°).

Anal. Calcd. for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 65.95; H, 4.65.

(b)—A mixture of 0.95 g. of 2-chloroacetylbenzofuran (II), 2.04 g. of fused sodium acetate, 1.4 ml. of 0.1 *N* hydrochloric acid and 20 ml. of ethanol-water (1:1) was treated under the conditions of Shriner and Anderson[15] to yield 0.42 g. (40% yield) of yellow crystals, m. p. 82–85°. Treatment with activated carbon and recrystallization from ethanol gave white crystals, m. p. and mixed m. p. 86.5–87.5°.

α-Benzofuroylmethylpyridinium Chloride.—A mixture of 2.58 g. of 2-chloroacetylbenzofuran and 15 ml. of dry pyridine was warmed on the steam-bath for thirty minutes with the formation of white crystals. The crystals were filtered and washed with pentane to give 3.20 g. (88% yield) of white needles, m. p. 238–241° dec. (darkening at 215°). Attempts at recrystallization lowered the melting point and raised the chlorine analysis. A qualitative nitrogen analysis by the method of Shriner and Fuson[12] was positive.

Anal. Calcd. for $C_{15}H_{12}O_2NCl$: Cl, 12.95. Found: Cl (Stepanoff), 12.85, 12.95.

Degradation by alkaline cleavage was carried out. A mixture of 52 mg. of α-benzofuroylmethylpyridinium chloride dissolved in 5 ml. of water and 7 ml. of 0.1 *N* sodium hydroxide was warmed on the steam-bath for fifteen minutes, then acidified (congo red paper) with concentrated hydrochloric acid and cooled to yield 26 mg. (78%) of pale yellow crystalline α-benzofuroic acid, m. p. and mixed m. p. 191–192.5° (lit.,[10] m. p. 190–193°).

α-Benzofuroylmethylmercaptoacetic Acid.—To a solution of 2.76 g. (0.03 mole) of mercaptoacetic acid, 1.2 g. (0.03 mole) of sodium hydroxide, and 90 ml. of dioxane was added dropwise with stirring a dioxane–water (9:1) solution of 5.0 g. (0.026 mole) of 2-chloroacetylbenzofuran. After stirring for twelve hours, a solution of 1.2 g. of sodium hydroxide in 50 ml. of dioxane–water (3:2) was added dropwise and then stirring was continued for an additional forty-one hours. The reaction mixture was refluxed for four hours, then diluted with an equal volume of water. The dioxane was evaporated in vacuum to precipitate the product which was purified by repeated transfer into and out of ether with acidic and basic washes. The acid, after treatment with carbon black, was recrystallized from ether-acetone and aqueous ethanol to yield 1.0 g. (15%) of pale yellow crystals having a constant melting point of 148.5–149.5°.

Qualitative analysis for sulfur by the methods of Shriner and Fuson[12] and Mulliken and Huntress[16] was positive.

Anal. Calcd. for $C_{12}H_{10}O_4S$: C, 57.59; H, 4.03; neut. equiv., 250. Found: C, 57.40; H, 4.24; neut. equiv., 258.

Summary

1. The Arndt–Eistert synthesis is a satisfactory means for the preparation of 2-benzofurylacetic acid. Catalytic rearrangement of the intermediate 2-diazoacetylbenzofuran (I) to ethyl 2-benzofurylacetate gives a higher yield than rearrangement to 2-benzofurylacetamide.

2. The intermediate diazoketone (I) undergoes the normal reactions of hydrohalogenation, hydrolysis, reduction and acetylation.

3. Normal products are obtained from 2-chloroacetylbenzofuran upon acetylation, haloform degradation, pyridine salt formation and mercaptan coupling.

State College, Penna. Received January 30, 1950

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[13] Stoermer and Schaffer, *Ber.*, **36**, 2863 (1903).

[14] Stoermer, Chydenius and Schinn, *ibid.*, **57B**, 72 (1924).

[15] Shriner and Anderson, This Journal, **61**, 2705 (1939).

[16] Mulliken and Huntress, "A Systematic Course of Instruction in the Identification of Organic Compounds," Lew A. Cummings Co., Cambridge, Massachusetts, 1937, p. 14.