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The Preparation of Some Substituted 1-Dibenzofuranpropionic and -Butyric Acids

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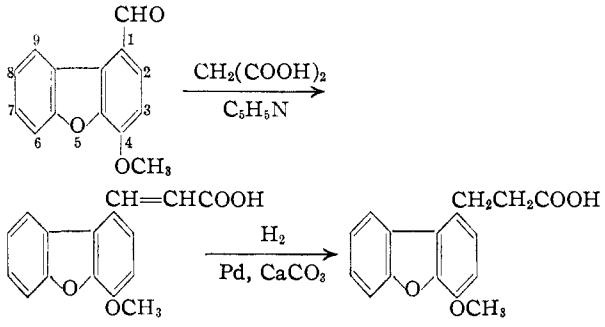
In connection with studies concerning the possible bridging of the 1- and 9-positions of dibenzofuran, we have prepared some previously unreported 1-substituted dibenzofurans. Appropriately substituted dibenzofurans were acylated by means of the Friedel–Crafts reaction employing succinic anhydride[1]; several of the keto acids have been reduced to the corresponding dibenzofuranbutyric acids. Acylation was directed to the 1-position[2] by a methoxyl group in the 4-position as well as by the use of the solvent system, nitrobenzene–tetrachloroethane.[3]

The introduction of a three-carbon side chain in the 1-position was accomplished by means of the Knoevenagel reaction with 4-methoxy-1-dibenzofurancarboxaldehyde and malonic acid. The substituted acrylic acid so formed was catalytically reduced to the dibenzofuranpropionic acid.[4]



Experimental[5]

The substituted dibenzofuroylpropionic acids (Table I) were prepared by the procedure previously described[2] for the synthesis of β-(2-dibenzofuroyl)-propionic acid.

The reductions to the corresponding dibenzofuranbutyric acids (Table II) were carried out by means of a modified Clemmensen reaction.[2] β-(2-Bromo-4-methoxy-1-dibenzofuroyl)-propionic acid was dehalogenated under conditions of the reduction and yielded γ-(4-methoxy-1-dibenzofuran)-butyric acid.

γ-(3-Nitro-4-methoxy-1-dibenzofuran)-butyric Acid.—A solution of 4.0 g. (0.014 mole) of γ-(4-methoxy-1-dibenzofuran)-butyric acid in 100 ml. of glacial acetic acid was heated on the steam-bath to 40–45°, and 4 ml. of fuming nitric acid (sp. gr., 1.50) was added with stirring. After one hour, the solution was allowed to cool, and the precipitated nitro compound was filtered off. Recrystallization from glacial acetic acid gave 2.0 g. (44%) of pure compound, m.p. 169–170°.

Procedures for Structure Determination.—(a) Oxidation of β-(4-methoxy-1-dibenzofuroyl)-propionic acid with alkaline potassium permanganate solution gave a product which did not depress the melting point when mixed with an authentic specimen of 4-methoxy-1-dibenzofurancarboxylic acid.[2]

(b) Four-tenths of a gram (0.0011 mole) of β-(2-bromo-4-methoxy-1-dibenzofuroyl)-propionic acid was suspended in 40 ml. of absolute ethanol with 1.0 g. of palladium–calcium carbonate catalyst[6] and shaken for 30 minutes at room temperature under a pressure of 35 p.s.i. of hydrogen. After filtration, water was added to the filtrate; the precipitated material melted at 224–225°, both alone and in admixture with a specimen of β-(4-methoxy-1-dibenzofuroyl)-propionic acid prepared as reported above. The yield was quantitative.

(c) Oxidation of β-(4,6-dimethoxy-1-dibenzofuroyl)-propionic acid with alkaline potassium permanganate solution yielded material melting at 297–298° which did not depress the melting point of an authentic sample of 4,6-dimethoxy-1-dibenzofurancarboxylic acid.[7]

(d) Alkaline potassium permanganate oxidation of γ-(3-nitro-4-methoxy-1-dibenzofuran)-butyric acid gave an acid melting at 269–270°. Decarboxylation[8] at 200° in the presence of copper powder and quinoline yielded material melting at 194–194.5°. A mixed melting point with an authentic sample of 3-nitro-4-hydroxydibenzofuran[9] was not depressed.

4-Methoxy-1-dibenzofurancarboxaldehyde.—A mixture of 7.0 g. (0.035 mole) of 4-methoxydibenzofuran, 9.0 g. (0.059 mole) of freshly distilled phosphorus oxychloride and 9.0 g. (0.067 mole) of N-methylformanilide was heated on the steam-bath for 90 minutes with occasional shaking. The excess phosphorus oxychloride was hydrolyzed with a 10% solution of sodium acetate. The product solidified on cooling and was filtered off. Recrystallization from a 50:50 water–methanol solution gave 5.0 g. (63%) of white needles, m.p. 104–105°.

Anal. Calcd. for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46. Found: C, 74.56, 74.57; H, 4.55, 4.51.

Neutral potassium permanganate oxidation of the aldehyde gave a 47% yield of 4-methoxy-1-dibenzofurancarbox-

TABLE I

SUBSTITUTED PROPIONIC ACIDS

-Propionic acid	Empirical formula	Yield, %	M.p., °C.	Analyses, % Calcd.	Found
β-(4-Methoxy-1-dibenzofuroyl)-	$C_{17}H_{14}O_5$	92	224–225	C, 68.45 H, 4.69	C, 68.71 H, 4.98
β-(4,6-Dimethoxy-1-dibenzofuroyl)-	$C_{18}H_{16}O_6$	91	241–242	[a]	
β-(2-Bromo-4-methoxy-1-dibenzofuroyl)-	$C_{17}H_{13}BrO_5$	71	194–195	Br, 21.22	Br, 21.36

[a] Calcd.: methoxyl, 18.90, neut. equiv., 328. Found methoxyl, 18.97; neut. equiv., 332.

TABLE II

SUBSTITUTED BUTYRIC ACIDS

-Butyric acid	Empirical formula	Yield, %	M.p., °C.	Analyses, % Calcd.	Found
γ-(4-Methoxy-1-dibenzofuran)-	$C_{17}H_{16}O_4$	81	165	C, 71.83 H, 5.63	C, 71.93 H, 5.81
γ-(4,6-Dimethoxy-1-dibenzofuran)-	$C_{18}H_{18}O_5$	42	197–198	C, 68.79 H, 5.73	C, 68.87 H, 5.89
γ-(3-Nitro-4-methoxy-1-dibenzofuran)-[a]	$C_{17}H_{15}NO_6$	44	169–170	C, 62.00 H, 4.59	C, 61.67; 61.84 H, 4.62; 4.47

[a] Calcd.: N, 4.25. Found: N, 4.10.

(1) E. Berliner in R. Adams, "Organic Reactions," Vol. V, John Wiley and Sons, Inc., New York, N. Y., 1949, Chapter 5.

(2) Dibenzofuran itself yields β-(2-dibenzofuroyl)-propionic acid on treatment with succinic anhydride and aluminum chloride; see H. Gilman, P. T. Parker, J. C. Bailie and G. E. Brown, THIS JOURNAL, **61**, 2836 (1939).

(3) Reference 1, p. 241.

(4) The dibenzofuranpropionic and -butyric acids were cyclized to give ketones in good yield. Such cyclization presumably could take place at either the 2- or 9-position. The results of studies on the structures of these cyclic ketones will be reported later.

(5) All melting points are uncorrected.

(6) M. Busch and H. Stöve, *Ber.*, **49**, 1063 (1916).

(7) H. Gilman and L. C. Cheney, THIS JOURNAL, **61**, 3149 (1939).

(8) A. F. Shepard, N. R. Winslow and J. R. Johnson, *ibid.*, **52**, 2083 (1930).

(9) H. Gilman, A. L. Jacoby and J. Swislowsky, *ibid.*, **61**, 954 (1939).

ylic acid, identified by its melting point (280–281°) and failure to depress the melting point of an authentic sample.[2]

β-(4-Methoxy-1-dibenzofuran)-acrylic Acid.—A mixture of 13.0 g. (0.058 mole) of 4-methoxy-1-dibenzofurancarboxaldehyde, 13.0 g. (0.125 mole) of malonic acid and 15 ml. of dry pyridine was heated on the steam-bath for 2.5 hours. Several minutes after heating was begun, the mixture became a homogeneous liquid, and shortly thereafter evolution of carbon dioxide commenced. The solution solidified to a yellow cake to which water was added. The insoluble material was filtered off and then dissolved in 200 ml. of a hot 5% solution of sodium carbonate. After filtration, the clear, colorless basic solution was acidified with hydrochloric acid. A pale yellow precipitate formed. Recrystallization from glacial acetic acid gave 9.5 g. (61%) of light yellow needles melting at 281–282°.

Anal. Calcd. for $C_{16}H_{12}O_4$: C, 71.64; H, 4.50; neut. equiv., 268. Found: C, 71.41, 71.57; H, 4.67, 4.61; neut. equiv., 266.

β-(4-Methoxy-1-dibenzofuran)-propionic Acid.—Solution of 1.5 g. (0.0056 mole) of β-(4-methoxy-1-dibenzofuran)-acrylic acid in 75 ml. of water was accomplished by the addition of 0.2 g. of sodium hydroxide; to this was added 2 g. of palladium–calcium carbonate catalyst.[6] The mixture was hydrogenated at 20 p.s.i. for 2 hours. The catalyst was filtered off and the product precipitated from the filtrate by addition of hydrochloric acid. The crude material weighed 1.5 g., m.p. 165–175°. Recrystallization from 95% ethanol gave 1.3 g. (86%) of thick needles, m.p. 176–178°.

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.11; H, 5.22; neut. equiv., 270. Found: C, 71.29, 71.18; H, 5.20, 5.18; neut. equiv., 265, 269.

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2,6-Dichloro-3,5-xylenol

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2,4-Dichloro-3,5-xylenol, m.p. 95–96°, was prepared by Lesser and Gad[1] by chlorination of 3,5-xylenol with sulfuryl chloride. Jones[2] obtained the same dichloroxylenol by treating 4-chloro-3,5-xylenol with N-chloroacetamide, but reported m.p. 83° for his substance after crystallization from ligroin. This difference in m.p. was apparently why Huntress[3] listed Jones' compound as the 2,4-dichloro-3,5-xylenol and that of Lesser and Gad as the 2,6-dichloro isomer.

In view of its antibacterial and antifungal properties, 2,4-dichloro-3,5-xylenol was the subject of a recent study by Gemmell.[4] He duplicated the syntheses of Lesser, Gad and Jones and found that the procedures of these workers led to the same isomer, namely, the 2,4-dichloro compound. It would seem that Jones had a mixture of 2,4-dichloro-3,5-xylenol and of some unchanged 4-chloro-3,5-xylenol.

Gemmell further mentioned that the literature contains no reference to the synthesis of the 2,6-dichloro isomer and that he was not able to prepare it. Direct chlorination of 3,5-xylenol or of 2-chloro-3,5-xylenol yields mixtures containing mostly the 2,4-dichloro derivative, but we have obtained the desired 2,6-dichloro-3,5-xylenol by an indirect method. 4-Bromo-3,5-xylenol was chlorinated to yield 4-bromo-2,6-dichloro-3,5-xylenol which was debrominated by zinc and alkali, following a procedure previously described[5] for the preparation of certain bis-phenols, to the 2,6-dichloro compound.

2,6-Dichloro-3,5-xylenol is a colorless, crystalline substance, melting at 87–88°. Its benzoate melts at 143–145°, that of the 2,4-dichloro isomer at 114–115°. Both isomers have a similar, not too pleasant odor.

It is interesting to note that 2,6-dichloro-3,5-xylenol is much less active bactericidally than the 2,4-isomer, as seen from the data of Table I. The tests were made employing the U. S. Food and Drug Administration method[6]; a plate-count modification[7] also was employed in order to get a more quantitative picture.

TABLE I

BACTERICIDAL ACTIVITY OF DICHLORO-3,5-XYLENOLS

Substance	Dilution[a]	Contact time of 10 min. at 20°: Growth in tubes	Contact time of 10 min. at 20°: Number of colonies on plates
A. Against *S. typhosa*			
2,4-Dichloro cpd.	1–1000	−[b]	0
	1–5000	−	0
2,6-Dichloro cpd.	1–1000	+	6,000[c]
	1–5000	+	10,000

B. Against *M. pyogenes* var. aureus

Substance	Dilution	Contact time of 10 min. at 20°: Tubes	10 min. at 20°: Plates	5 min. at 37°: Tubes	5 min. at 37°: Plates
2,4-Dichloro cpd.	1–1000	∓	50	−	0
	1–2500	+	180	∓	70
2,6-Dichloro cpd.	1–1000	+	7000	+	800
	1–2500	+	9000	+	2000

[a] 0.1 g. dissolved in 1 ml. of 0.5 *N* alcoholic potassium hydroxide plus 1 ml. of alcohol and diluted with distilled water. [b] −, no growth; +, growth. [c] Counts above 5,000 are estimated.

While it has been previously observed[8] that *p*-chloro-alkylphenols show somewhat greater germicidal potency than their isomers with chlorine in the ortho and alkyl in the para position, the large difference in the antibacterial activity of the two dichloroxylenols is surprising.

Experimental

4-Bromo-2,6-dichloro-3,5-xylenol.—Chlorine (150 g.) was bubbled into a moderately stirred solution of 4-bromo-3,5-xylenol[9] (78 g.) in 1,500 ml. of carbon tetrachloride at 70–75° during 10 hours. The large excess of chlorine was used since an experiment employing the theoretical amount of chlorine (56 g.) resulted in 4-bromo-2-chloro-3,5-xylenol as main product.

The orange solution was poured into water and the organic layer was separated and washed twice with water. After drying and filtering, the solvent was removed by distillation, and the yellow residue (120 g.) was extracted by refluxing it for one hour with a solution of 100 g. of sodium hydroxide in 600 ml. of water. Three more extractions of

(1) R. Lesser and G. Gad, *Ber.*, **56**, 975 (1923).

(2) B. Jones, *J. Chem. Soc.*, 275 (1941).

(3) E. H. Huntress, "Organic Chlorine Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, pp. 258 and 283.

(4) J. Gemmell, *Mfg. Chemist*, **23**, 63 (1952); *Soap, Perfumery & Cosmetics*, **25**, 1160 (1952).

(5) G. Tassinari, *Gazz. chim. ital.*, **17**, 90 (1887); W. S. Gump and J. C. Vitucci, THIS JOURNAL, **67**, 238 (1945).

(6) G. L. A. Ruehle and C. M. Brewer, U. S. Dept. of Agriculture, Circular No. 198, December 1931.

(7) A. R. Cade and H. O. Halvorson, *Soap*, **10**, [8], 17; [9], 25 (1934).

(8) E. Klarmann, V. A. Shternov and L. W. Gates, THIS JOURNAL, **55**, 2576 (1933).

(9) K. v. Auwers and E. Borsche, *Ber.*, **48**, 1715 (1915).