Notes

Decarboxylation Studies on 3,5-Dihydroxyhomophthalic Acid Derivatives[1a]

RICHARD N. HURD*[1b] AND DINUBHAI H. SHAH

Research Department, Commercial Solvents Corporation, Terre Haute, Indiana 47808

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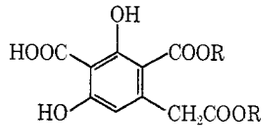
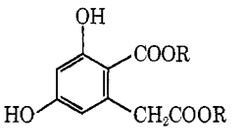
A synthetic pathway, developed for the preparation of (*R*,*S*)-zearalanone,[2] required removal of both the salicylic type and the α,β-unsaturated type of carboxyl group from polyfunctional derivatives of 3,5-dihydroxyhomophthalic acid.

Removal of the 4-carboxyl group of dialkyl 4-carboxy-3,5-dihydroxyhomophthalates has been reported on several occasions under various conditions. Poor yields generally have been experienced, which we have confirmed.

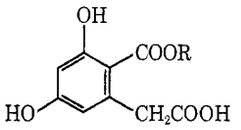
Treatment of dimethyl 4-carboxy-3,5-dihydroxyhomophthalate (**1**) with quinoline and copper powder consumed **1**, but did not yield the expected product **3**.[3] The action of hot 23% KOH on the diethyl ester **2** gave only a poor yield of crude half-ester **5**.[4] Poor



1, R = CH_3
2, R = C_2H_5



3, R = CH_3
4, R = C_2H_5



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or unreproducible yields of **3** and **4** have been obtained by treatment of **1** and **2**, respectively, with hot quinoline and copper bronze.[5-7] Similarly, hot glycerol resulted in a poor, unreproducible yield of **3** from **1**.[5]

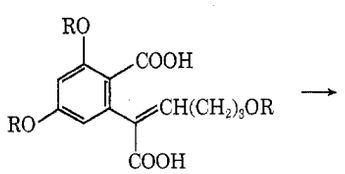
In contrast to these unproductive results, we found that an excellent, reproducible method for decarboxylation of **1** is to heat its solutions in dimethyl sulfoxide or dimethylformamide. No catalyst is necessary. Heating a solution of **1** in dimethyl sulfoxide[8] to 155° for 40–60 min consistently gave a 65–70% yield of **3**. A pure product could be obtained more readily in the same yield by refluxing a solution of **1** in dimethylformamide for 30 min.

Also, adaptation of a technique developed by Kaeding[9] for decarboxylation of salicyclic acids gave rise to a reproducible, preparative yield of diester **3** from 4-carboxy diester **1**. A mixture of **1** and magnesium benzoate in benzoic acid, when heated to 180° for 20 min, readily gave a 60% yield of recrystallized **3**. In this decarboxylation, **1** and magnesium benzoate were used in approximately 11:1 molar proportions. Doubling the relative amount of magnesium benzoate did not increase the yield. No **3** was obtained when benzoic acid was replaced with a less protic solvent, resorcinol.

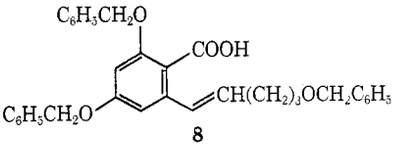
α-(4-Benzyloxybutylidene)-3,5-bis(benzyloxy)homophthalic acid (**6**), a Stobbe product,[10] proved more difficult to decarboxylate. Heating diacid **6** to 185° under nitrogen for 30 min gave a mixture of at least three unidentified products. A similar result was obtained at 185° in quinoline in the presence of copper powder.[3] Johnson and his coworkers developed a method for decarboxylation of Stobbe products from succinic esters, wherein the Stobbe product was refluxed with a 3:2:1 mixture of acetic acid, 48% hydrobromic acid, and water.[11] Under these conditions a 65% recovery of **6** was experienced after 2.5 hr of refluxing.

Aliphatic α,β-unsaturated acids, RCH=CHCOOH, have been decarboxylated to $RCH{=}CH_2$ in preparative yields by conversion to $RCHBrCH_2COONa$ and heating the latter to give the olefin.[12] This method was not applicable for **6**, however, since treatment with hydrogen bromide at 0° in chloroform chiefly promoted debenzylation to give benzyl bromide and debenzylated diacid **7**.

In contrast to the decarboxylation of **1** in dimethyl sulfoxide, we found that, in order to decarboxylate **6** into monoacid **8** in this solvent at 150°, it was necessary to use an acid salt of **6**. Pure **6** was unreactive under



6, R = $CH_2C_6H_5$
7, R = H



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(1) (a) Part of this work was presented as a paper at the 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 1969, MEDI 28. (b) G. D. Searle International Co., P. O. Box 5486, Chicago, Ill. 60680.

(2) R. N. Hurd and D. H. Shah, *J. Med. Chem.*, in press.

(3) C. Walling and K. B. Wolfstirn, *J. Amer. Chem. Soc.*, **69**, 852 (1957).

(4) D. S. Jerdan, *J. Chem. Soc.*, 808 (1899), reported a 30% yield of **5** under the same conditions. For the correct structural assignments to Jerdan's products, see ref 5 and 6.

(5) A. Kamal, A. Robertson, and E. Tittensor, *J. Chem. Soc.*, 3375 (1950).

(6) H. Nogami, *J. Pharm. Soc. Jap.*, **61**, 24 (1941).

(7) W. R. Allison and G. T. Newbold, *J. Chem. Soc.*, 2512 (1960).

(8) Tetrahalophthalic acids have been decarboxylated in excellent yield by refluxing their solutions in dimethyl sulfoxide: C.-T. Chen, S.-J. Yan, and C.-H. Wang, *Chem. Ind. (London)*, 895 (1970).

(9) W. W. Kaeding, *J. Org. Chem.*, **29**, 2556 (1964).

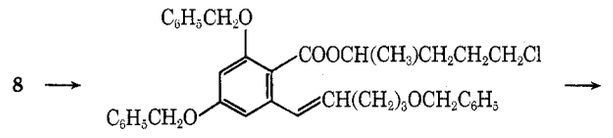
(10) R. N. Hurd and D. H. Shah, *J. Org. Chem.*, **38**, 607 (1973).

(11) W. S. Johnson, A. Goldman, and W. P. Schneider, *J. Amer. Chem. Soc.*, **67**, 1357 (1945).

(12) W. G. Young, R. T. Dillon, and H. J. Lucas, *ibid.*, **51**, 2528 (1929); S. Winstein, D. Pressman, and W. H. Young, *ibid.*, **61**, 1646 (1939).

these conditions. This acid salt,[10] which contained 0.7 g-atom of sodium per mole of **6**, underwent decarboxylation to give 80–90% yields of **8** consistently. As with **1**, we found that dimethyl sulfoxide could be replaced with dimethylformamide to give the same yield of **8**, but in a more readily purified state.

The structure shown for **8** was supported by conversion of acid **8** into ester **9** followed by debenzylation and reduction of the latter to the 6-substituted β-resorcylic ester **10**. Esterification of **8** was accomplished in 73%



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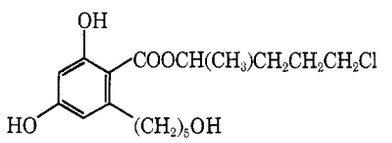

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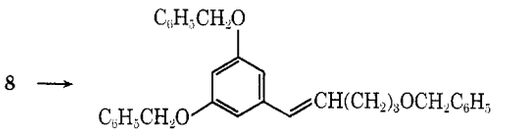
yield by intermediate formation of the acid chloride of **8**, and reaction of the acid chloride with 5-chloro-2-pentanol. Hydrogenation of **9** (Pd/C) gave **10** in 75% yield.

In contrast to the successful esterification of **8** to **9**, treatment of **8** with 5-chloro-2-pentanol in refluxing benzene, catalyzed by *p*-toluenesulfonic acid, led only to the decarboxylated resorcinol derivative **11**.



11

Carboxylate anions have been shown to be intermediates in some, and proposed in many other, first- and second-order electrophilic thermal decarboxylations.[13] The fact that **6** is not decarboxylated in DMSO as **1** is, but requires conversion to an acid salt, appears to relate to the lower acidity of **6** compared to **1**. That **6** is weaker than **1** is evident by considering two models for **6** and **1**, namely, 2-methoxybenzoic acid, pK_a = 4.09, and atropic acid, PhC(COOH)=CH$_2$, pK_a = 3.85. The nonreaction of pure **6** in DMSO agrees with Chen, Yan, and Wang's observation[8] that relatively weak acids are not decarboxylated in this manner.

Experimental Section

Infrared spectra were obtained with a Perkin-Elmer 21 spectrophotometer. Nuclear magnetic resonance spectra were obtained on a Varian A-60A spectrometer. Melting points were taken in a Thomas-Hoover capillary melting point apparatus, and are uncorrected.

Dimethyl 3,5-Dihydroxyhomophthalate (3).—A solution of dimethyl 4-carboxy-3,5-dihydroxyhomophthalate (**1**)[2,14] (50.0 g, 0.12 mol) in 150 ml of DMF was refluxed under nitrogen for 30 min. On cooling, the mixture was diluted with 1 l. of water, and the whole was extracted seven times with 250-ml portions of ether. The combined ether extracts were washed thrice with 250-ml portions of water, then dried ($MgSO_4$). Removal of ether gave 29.0 g (70%) of crude **3** which was purified by chromatographic separation on 300 g of 100–200 mesh Florisil with chloroform. This treatment resulted in 17.0 g (40%) of **3**:[7] mp 144–145°; nmr (acetone-d_6) δ 3.66 (s, 3, $-OCH_3$), 3.87 (s, 5, benzylic CH_2 and $-OCH_3$), 6.38 (s, 2, 2 aromatic H), 9.3 (broad s, 1, -OH), 11.55 (s, 1, H-bonded -OH).

Anal. Calcd for $C_{11}H_{12}O_6$: C, 55.00; H, 5.00. Found: C, 54.92; H, 5.13.

From the aqueous wash of the above ether extracts, unreacted **1** (5.00 g) was recovered.

3 was also obtained by heating to 160° a solution of **1** (6.90 g) in 40 ml of dimethyl sulfoxide for 45–60 min until CO_2 evolution stopped. On cooling, the mixture was diluted with 400 ml of water, and the whole was extracted four times with 150-ml portions of ether. After the extracts were washed and dried, and the ether was removed, 3.8 g (64%) of crude **3** was obtained. This was recrystallized from benzene–hexane to give 1.2 g of **3**, mp 144–145°.

3 was also obtained by preparing a mixture of 2.0 g of **1**, 0.174 g of magnesium benzoate, and 10.0 g of benzoic acid. This mixture was heated to 180° for 20 min under nitrogen. After cooling, the mixture was dissolved in 20 ml of ether, and the ether solution was thrice extracted with 30-ml portions of 5% $NaHCO_3$ solution. The ether solution was dried, and ether was removed to give 2.0 g of viscous red oil. Some of this oil could be separated as crystals (0.6 g), mp 144–145°, by treatment with benzene–hexane followed by trituration with chloroform.

2,4-Bis(benzyloxy)-6-(5-benzyloxy-1-penten-1-yl)benzoic Acid (8).—A solution of the acid salt of α-(4-benzyloxybutylidene)-3,5-bis(benzyloxy)homophthalic acid (**6**)[10] (6.5 g) in 40 ml of DMSO was heated to 155° under nitrogen for 30 min. The reaction mixture was worked up in the same manner as isolation of **3** from its DMSO reaction mixture. The crude, oily **8** from the ether extract residues was purified by chromatographic separation on 170 g of Silicar-CC-7 with chloroform to give 4.75 g (80%) of **8**: nmr ($CDCl_3$) δ 1.5–2.5 (m, 4, $=CHCH_2CH_2CH_2O-$), 3.5 (t, 2, $-CH_2CH_2OCH_2C_6H_5$), 4.46 (s, 2, aliphatic $-OCH_2C_6H_5$), 4.96–5.00 (d, 4, 2 aromatic $-OCH_2C_6H_5$), 6.1–6.7 (m, 4, 2 aromatic H, and $-CH=CH-$), 7.2–7.32 (d, 15, 3 $-OCH_2C_6H_5$), 9.58 (broad s, 1, -COOH).

Anal. Calcd for $C_{35}H_{32}O_5$: C, 77.95; H, 6.30. Found: C, 78.28; H, 6.47.

8 was prepared also by refluxing a solution of the acid salt of **6**[10] (0.50 g) in 10 ml of DMF for 30 min under nitrogen. The mixture was worked up in the same manner as isolation of **3** from its DMF mixture, except that chromatographic purification was unnecessary. Ether extracts were evaporated to give 0.36 g (80%) of **8** with the same physical characteristics as above.

4-Chloro-1-methylbutyl 2,4-Bis(benzyloxy)-6-(5-benzyloxy-1-penten-1-yl)benzoate (9).—To a solution of **8** (2.03 g, 4 mmol) in 20 ml of dry benzene were added thionyl chloride (0.960 g, 8 mmol) and 12 drops of pyridine. The mixture was stirred overnight. Pyridine hydrochloride was filtered off. Volatiles were removed under vacuum to give a viscous red paste. To this paste was added 5-chloro-2-pentanol[15] (1.4 g, 10 mmol) in 20 ml of dry benzene. The mixture was stirred overnight, benzene was removed under vacuum, and the thick red liquid residue was chromatographed to give 1.75 g (73%) of **9** as a red paste: nmr ($CDCl_3$) δ 1.18–1.29 (d, 3, $>CHCH_3$), 1.50–2.50 (m, 8, $-CH_2-CH_2CH_2Cl$ and $-CH_2CH_2CH_2OCH_2C_6H_5$), 3.15–3.6 (m, 4, $-CH_2-OCH_2C_6H_5$ and $-CH_2Cl$), 4.45 (s, 2 aliphatic $-OCH_2C_6H_5$), 4.95 (d, 4, 2 aromatic $-OCH_2C_6H_5$), 6.00–6.35 (m, 2, $-CH=CH-$), 6.42 (J = 2 cps, 1, aromatic H), 6.62 (J = 2 cps, 1, aromatic H), 7.3 (d, 15, 3 $-OCH_2C_6H_5$).

Anal. Calcd for $C_{35}H_{41}ClO_5$: Cl, 5.80. Found: Cl, 5.71.

4-Chloro-1-methylbutyl 2,4-Dihydroxy-6-(5-hydroxypentyl)benzoate (10).—A mixture of **9** (11.8 g, 0.02 mol) and 6.0 g of 5% Pd/C catalyst in 200 ml of ethanol was reduced with hydrogen (1 atm, 25°). After the theoretical amount of hydrogen was taken up, the catalyst was removed, and the solution was concentrated under vacuum to give 6.0 g (90%) of **10**: nmr ($CDCl_3$) δ 1.3–1.4 (d, 3, $-OCHCH_3$), 1.43–2.00 (m, 10, $-CH_2CH_2CH_2Cl$ and $-CH_2CH_2CH_2CH_2CH_2OH$), 2.55–3.1 (m, 2, benzylic CH_2), 3.4–3.9 (m, 5, $-CH_2OH$ and $-CH_2Cl$), 5.2 (broad s, 1, -COO-

(13) B. R. Brown, *Quart. Rev., Chem. Soc.*, **5**, 131 (1951).

(14) W. Theilacker and W. Schmid, *Justus Liebigs Ann. Chem.*, **570**, 15 (1950); E. Hardegger, W. Rieder, A. Walser, and F. Kugler, *Helv. Chim. Acta*, **49**, 1283 (1966).

(15) R. C. Elderfield, W. J. Gensler, F. Brody, J. D. Head, S. C. Dickerman, L. Wiederhold, III, C. B. Kremer, H. A. Hageman, F. J. Kreysa, J. M. Griffing, S. M. Kupchan, B. Newman, and J. T. Maynard, *J. Amer. Chem. Soc.*, **68**, 1579 (1946).

$CHCH_3$), 6.25 (s, 2, J = 2 cps, 2 aromatic H), 7.3 (s, 1, phenolic OH), 11.98 (s, 1, H-bonded phenolic OH).

Anal. Calcd for $C_{17}H_{25}ClO_3$: C, 59.21; H, 7.25; Cl, 10.30. Found: C, 59.01; H, 7.21; Cl, 9.79.

1-(5-Benzyloxy-1-penten-1-yl)-3,5-bis(benzyloxy)benzene (11).—A mixture of **8** (0.34 g, 0.67 mmol), 5-chloro-2-pentanol[15] (0.40 g, 3.27 mmol), and *p*-toluenesulfonic acid (0.05 g) in 75 ml of dry benzene was refluxed overnight, water being removed by a Dean-Stark receiver. On cooling, the mixture was washed with 15 ml of 5% $NaHCO_3$ and 15 ml of water, then dried ($MgSO_4$). Benzene was removed to leave a greenish liquid residue which was purified on a preparative tlc plate using chloroform to give 0.25 g (80%) of **11** as a paste. The ir spectrum of **11** showed no carbonyl absorption.

Anal. Calcd for $C_{32}H_{32}O_3$: C, 82.90; H, 6.94. Found: C, 82.40; H, 7.12.

Registry No.—**3**, 6110-30-1; **8**, 37173-19-6; **9**, 37173-20-9; **10**, 37173-21-0; **11**, 37173-22-1.

Acknowledgment.—The assistance of Mr. Carl Wassink and his staff in obtaining elemental analyses and ir spectra is gratefully acknowledged.

A Novel Furan Dimer

JOHN L. ISIDOR, M. S. BROOKHART, AND R. L. MCKEE*

Department of Chemistry, University of North Carolina, Chapel Hill, North Carolina 27514

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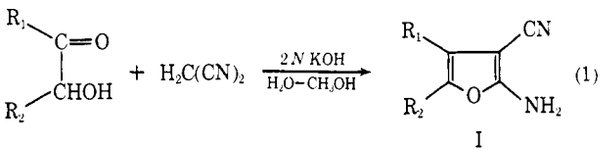
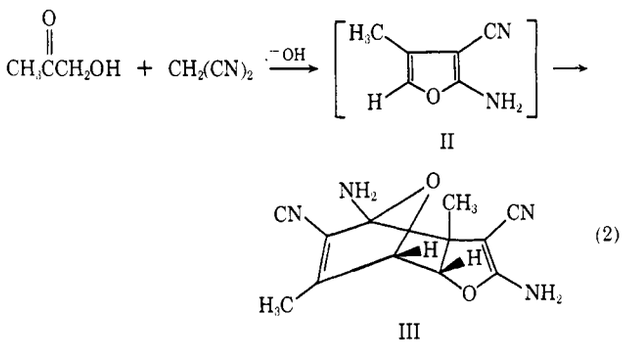
Gewald[1] has reported that the interaction of acyloins with malononitrile in aqueous base yields 2-amino-3-cyanofurans of type I (eq 1).[2] This scheme has subsequently been used to prepare a variety of such substances from readily available acyloins.



(1)

I

We would like to report that our experience with the synthesis of 2-amino-3-cyano-4-methylfuran (II), from hydroxy-2-propanone and malononitrile according to Gewald (eq 2), leads us to conclude that the product is not II but that it is 2,4-diamino-3,5-dicyano-3a,6-dimethyl-3a,4,7,7a-tetrahydro-*endo*-4,7-epoxybenzofuran (III), formed by way of a remarkable Diels–Alder cycloaddition of II with itself.



(2)

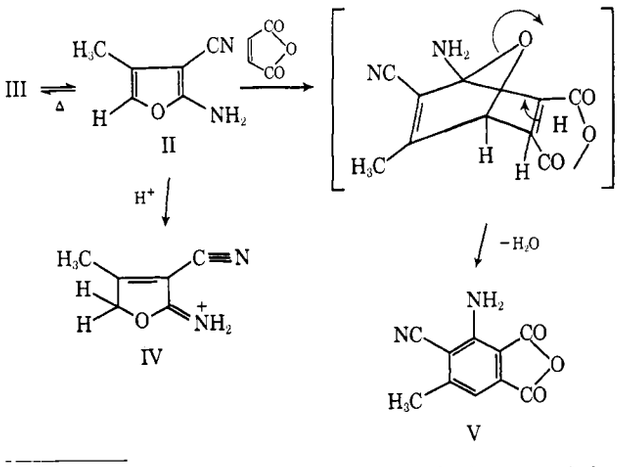
The nmr spectrum of III in pyridine-d_5 consisted of a singlet at 1.62 (3 H, 3a-CH_3), a singlet at 2.20 (3 H, 6-CH_3), an AB quartet centered at 4.37 (2 H, J = 8 Hz, $\Delta\gamma_{AB}$ = 21.6 Hz, 7-CH and 7a-CH), a broad singlet at 8.20 (2 H, 4-NH_2) and an identically broad singlet at 10.00 ppm (2 H, 2-NH_2) downfield from TMS. Upon ^{14}N double-irradiation both singlets underwent a considerable sharpening effect, and upon addition of D_2O the two broad downfield singlets collapsed immediately.

The mass spectrum (70 eV) of III using a direct-probe inlet and a relatively cold instrument (T 160°)[3] gave the following significant fragments: *m/e* (rel intensity) 244 (36, dimer molecular ion), 229 (100), 218 (21), 189 (14), 149 (20), 128 (23), 122 (52), and 93 (35). In addition, a well-resolved ir spectrum (KBr) revealed the presence of two closely spaced nitrile bands of equal intensity at 2200 and 2180 cm^{-1}.

The overall spectral evidence quite conclusively points to a dimer structure. More specifically, the two hydrogen AB pattern in the nmr indicates completely selective cycloaddition across the 4,5 double bond in the manner shown. The endo configuration is indicated by the coupling constant of 8 Hz for the AB hydrogens, which implies a dihedral angle near zero in a system such as III.[4]

Dimer III has been mentioned several times in the literature under the guise of the monomeric structure (II). Gewald[1] arrived at a clever synthesis of substituted 2-aminobenzonitriles by subjecting III and several other 2-amino-3-furonitriles to maleic anhydride in refluxing acetone, and Wie, Sunder, and Blanton[5] included III in a study of the enamine behavior of furan, pyrrole, and thiphene aminonitriles. They observed formation of IV upon treatment of III with trifluoroacetic acid. Brief mention is also made of III as structure II in Taylor and McKillop's recent monograph on *o*-aminonitriles.[6] The formation of IV and V indicate that III is quite capable of acting as a precursor for II (Scheme I).

SCHEME I



(1) K. Gewald, *Chem. Ber.*, **99**, 1002 (1966).

(2) Triethylamine in methanol gives comparable results.

(3) The mass spectrum using a Teflon slug showed only monomeric fragments.

(4) (a) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); (b) F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961); (c) K. Ramsey, D. Lini, R. Moriarty, H. Gospal, and H. G. Welsh, *J. Amer. Chem. Soc.*, **89**, 2401 (1967).

(5) C. T. Wie, S. Sunder, and C. D. Blanton, *Tetrahedron Lett.*, 4605 (1968).

(6) E. C. Taylor and A. McKillop, *Advan. Org. Chem.*, **7**, 126, 213 (1970).