Preparation and Diels-Alder Reactions of 2,5-Dihydrofuran

By Neal O. Brace

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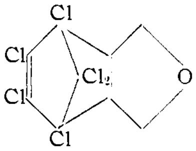
cis-2-Buten-1,4-diol (I) is one of the materials made available by the acetylene-formaldehyde reaction. Cyclodehydration of the closely-related 1,4-butanediol to tetrahydrofuran is essentially a quantitative reaction and was the basis for large-scale manufacture in Germany. In the case of I, however, dehydration is complicated by rearrangement to crotonaldehyde. Yields of 35 to 55% of 2,5-dihydrofuran (DHF) have been reported for dehydration by hot dilute acid[1,2] or anhydrous hydrogen bromide.[3] Vapor phase dehydration[4] appeared attractive, but the patented process appeared to be unnecessarily time-consuming, and published reports[4-6] differ in important details. With careful control of conditions and selection of dehydrating catalyst I gave DHF at a rapid rate and a conversion of 75% over activated alumina with very little crotonaldehyde being formed.

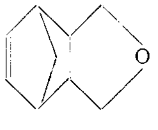
Other dehydration catalysts tried were less successful. These include two other more active aluminas, aluminum silicate and an alumina on silica gel; I was also refluxed with iodine. In each case much crotonaldehyde was formed.

DHF, unlike tetrahydrofuran, is not completely miscible at 25° with water but, like tetrahydrofuran, DHF distils from water as an azeotrope, b.p. 64-65°, containing 6.1% water.

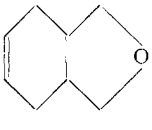
DHF undergoes the Diels-Alder reaction. Besides the known anthracene adduct,[7] addition of hexachlorocyclopentadiene[8] to DHF gave a good yield of the adduct[9] II, cyclopentadiene gave the adduct[9] III in lower yield and butadiene gave hexahydrophthalan IV in poor yield.



II



III



IV

Experimental

2,5-Dihydrofuran.—A 12 × 1 inch Pyrex glass tube (fitted with a side inlet near the top for nitrogen gas, a thermocouple well, and heated in a vertical position by an electric furnace) was filled with 100 cc. of 4-8 mesh Alcoa activated alumina "H-41" and 50 cc. of 8-mm. glass beads at the top as a pre-heat section. *cis*-2-Buten-1,4-diol (General Aniline and Film Co.; $n^{25}D$ 1.4765) was dropped in at a constant rate of 1 cc./min. using a calibrated metering pump or constant feed dropping funnel at 220-222° inside temperature (center of catalyst zone). In four hours 250 cc. (270 g.) had been added. The liquid, condensed by a water-cooled Friedrichs-type condenser, weighed 237.5 g. Distillation in a twenty-plate column at 10/1 reflux ratio gave fractions: A, b.p. 60-62.5°; $n^{25}D$ 1.4240, 25.5 g.; B, b.p. 63-68°, $n^{25}D$ 1.4260, 139.5 g.; C, b.p. 80-85°, 5.3 g. and D (water), b.p. 98-100°, 46.8 g.; liquid residue 22.3 g. The yield of 2,5-dihydrofuran (as 94% azeotrope) was 75%. When A and B were dried over anhydrous magnesium sulfate two days, the product distilled at 66-67.5°; $n^{25}D$ 1.4281 and contained 0.214% water by analysis; reported[2,3] b.p. 66.5-67.0°; $n^{25}D$ 1.4289-1.4294. The compound was colorless, and had a sharp, disagreeable odor. DHF azeotrope, b.p. 64-65°, $n^{25}D$ 1.4245, contained 6.1% water by Karl Fischer water analysis; reported[4] b.p. 60-67°; 5% water.

Other catalysts tried in the same way were Harshaw "AL0104" activated alumina, $^1/_8$ inch pellets; Alcoa activated alumina "F-1," 8-14 mesh granules; an alumina on silica gel (2.60% Al_2O_3, 5.06% H_2O) and a granular catalyst of mixed sizes made from Eimer and Amend aluminum silicate. These all gave a strongly exothermic reaction at 220°, carrying the inside temperature to above 250°. They produced crotonaldehyde in varying amounts (isolated as azeotrope, b.p. 67-86°; when dry, b.p. 100-102°, $n^{25}D$ 1.4335) and low yields of DHF.

When *cis*-2-buten-1,4-diol (180 g.) was refluxed with 1 g. of iodine under an 18-in. column packed with stainless steel protruded packing, DHF azeotrope (80.6 g., 55% yield) distilled at 130° pot temperature and a tarry solid (62.8 g.) remained after six hours heating.

Diene Additions to 2,5-Dihydrofuran. (a) **Hexachlorocyclopentadiene.**—272.8 g. of hexachlorocyclopentadiene (Hooker Electrochemical Co.) and 70 g. of 2,5-dihydrofuran (containing a trace of hydroquinone) were heated under reflux 16 hours up to 135°. When cool, the solid crystalline mass was dissolved in hot acetone, treated with charcoal and the filtered solution allowed to crystallize. Several successive crystal fractions totalling 260.7 g. were obtained (76% yield).

The first fraction (158 g.) was recrystallized from 1.8 l. of methanol and 0.2 l. of acetone, giving 108.8 g. of solid II, which sintered at 206° and melted with decomposition at 219-226°. *Anal.* Calcd. for $C_9H_6Cl_6O$: C, 31.55; H, 1.76; Cl, 62.05. Found: C, 31.55; H, 1.83; Cl, 62.05. The infrared spectrum of II showed a sharp band at 6.20 μ (double-bond) and 9.25 and 9.5 μ (ether).

(b) **Cyclopentadiene.**—In a 440-ml. silver-lined steel pressure tube was placed 68 g. of cyclopentadiene (distilled and kept at Dry Ice temperature before use), 68 g. of 2,5-dihydrofuran and 0.5 g. of barium carbonate. The tube was heated to 180° for eight hours. The liquid product (134 g.) was fractionated in a twenty-plate column. Cyclopentadiene (11.6 g.), DHF (31.0 g., 0.5 m.) and cyclopentadiene dimer, b.p. 78-80° (25 mm.), $n^{25}D$ 1.5019, 15.0 g.; and b.p. 81-85.5° (25 mm.), $n^{25}D$ 1.5020, 11.7 g., were recovered. The adduct III, b.p. 85.5-88° (25 mm.), $n^{25}D$ 1.5000, 11.0 g. and b.p. 65-70° (7.0 mm.), 12.2 g. was obtained as a liquid with a penetrating odor (28% yield on DHF used up; 16% efficiency). *Anal.* Calcd. for $C_9H_{12}O$: C, 79.4; H, 8.88. Found: C, 79.4; H, 8.82. Higher boiling fractions consisting of the solid cyclopentadiene trimer[10] and possibly higher adducts with DHF were also isolated.

(c) **Butadiene.**—Seventy-eight g. of butadiene and 70 g. of 2,5-dihydrofuran were heated together at 175-180° for eight hours to give 147 g. of liquid product which was fractionated in the twenty-plate column. About 0.7 mole of 2,5-dihydrofuran was recovered, b.p. 66-67.5°, $n^{25}D$ 1.4288; vinylcyclohexene, b.p. 30-33.5° (20 mm.), $n^{25}D$ 1.4617, 46 g. of hexahydrophthalan[11] IV, b.p. 64-70° (18-17 mm.), $n^{25}D$ 1.4881, 5.8 g. (15.6% yield based on DHF used up; 4.6% efficiency) were separated, leaving a residue of 12.0 g. *Anal.* Calcd. for $C_8H_{12}O$: C, 77.38; H, 9.74. Found (IV): C, 80.9; H, 10.3. Infrared spectrum of IV showed a double bond absorption band at 6.0 μ and ether absorption bands at 9.18 and 9.45 μ.

2,3-Dimethylbutadiene and 2,5-dihydrofuran when heated in equimolar amounts 24 hours at 150° gave, besides start-

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[1] A. Valette, *Ann. Chim.*, [12] **3**, 644 (1948); *C. A.*, **43**, 2577 (1949).

[2] R. Paul, M. Fluchaire, G. Collardeau, *Bull. soc. chim. France*, 668 (1950).

[3] A. J. Weinheimer, S. W. Kantor and C. R. Hauser, *J. Org. Chem.*, **18**, 801 (1953).

[4] British Patent 510,949.

[5] J. W. Copenhaver and M. H. Bigelow, "Acetylene and Carbon Monoxide Chemistry," Reinhold Publ. Corp., 1949, p. 142.

[6] L. H. Smith, "German Synthetic Fiber Developments," Textile Research Institute, 1946, p. 537.

[7] H. Krzikalla, E. Woldan and O. Dornheim, German Patent 736,024.

[8] E. K. Fields, This Journal, **76**, 2709 (1954).

[9] *C. A.* nomenclature of II is 1,7,8,9,10,10-hexachloro-4-oxatricyclo[5,2,1,$0^{2,6}$]-8-decene and of III is 4-oxatricyclo[5,2,1,$0^{2,6}$]-8-decene.

[10] H. Staudinger and H. A. Bruson, *Ann.*, **447**, 97 (1926).

[11] See K. Alder and W. Roth, *Ber.*, **87**, 161 (1954).

ing material, only diene dimer as condensation product, b.p. 87.5–88° (15.0 mm.).

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Confirmation of the *ortho* Substitution Rearrangement of the Benzhydryltrimethylammonium Ion by Sodium Amide

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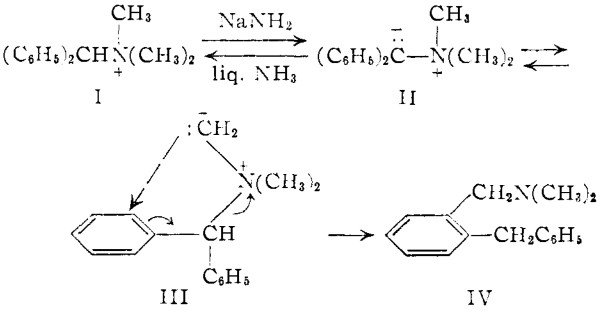
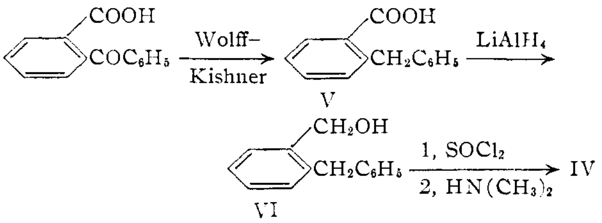
One of the *ortho* substitution rearrangements of benzyl type quaternary ammonium ions by sodium amide in liquid ammonia reported recently,[2] is that of the benzhydryltrimethylammonium ion (I) to form tertiary amine IV (88%). This example is particularly remarkable[3] since the reactive intermediate is carbanion III (an ylide),[4] not carbanion II which is presumably present in much higher concentration.



The product was assigned structure IV because, on oxidation, it produced *o*-benzyl- and *o*-benzoylbenzoic acids. We have confirmed this assignment of structure by unequivocally synthesizing tertiary amine IV from *o*-benzoylbenzoic acid, passing through intermediates V and VI, and showing that it was identical with the tertiary amine obtained from the rearrangement of I.



Experimental[5]

o-Benzylbenzoic acid (V), m.p. 114–115° (lit. m.p. 111–113°,[6] 117°[7]), was prepared in 50% yield by the reduction of *o*-benzoylbenzoic acid by the Wolff–Kishner method according to the general procedure described in "Organic Reactions."[8]

o-Benzylbenzyl Alcohol (VI).—To a stirred suspension of 2.1 g. (0.058 mole) of lithium aluminum hydride in 100 ml. of anhydrous ether was added a solution of 14 g. (0.066 mole) of *o*-benzylbenzoic acid in 50 ml. of anhydrous ether. The resulting mixture was stirred and refluxed for one hour, and the excess hydride destroyed by addition of 5 ml. of ethyl acetate. The ether solution, after washing with 10% sulfuric acid and 10% sodium bicarbonate, was dried over potassium carbonate and the solvent removed. The oily residue was crystallized from 30–60° petroleum ether to give 10.6 g. (81%) of *o*-benzylbenzyl alcohol (VI), m.p. 40–41°.

Anal. Calcd. for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.93; H, 7.05.

o-Benzylbenzyl-N,N-dimethylamine (IV).—A solution of 9.6 g. (0.049 mole) of *o*-benzylbenzyl alcohol in 10 ml. of benzene and 12 g. (0.1 mole) of thionyl chloride was boiled (after the first vigorous reaction had subsided) until the volume of the solution was 15 ml. An additional 10 ml. of benzene was added, and the volume of the solution again reduced to 15 ml. To this material was added an ice-cold solution of 14 g. (0.31 mole, 500% excess) of dimethylamine in 100 ml. of methanol, and the resulting solution allowed to stand for 30 hours. Methanol and excess dimethylamine were removed at the water aspirator and the residue taken up in water. After washing with ether, the aqueous solution was made basic with 10% sodium hydroxide and the liberated amine taken up in ether. The ether solution was dried over solid potassium hydroxide and the solvent removed. The residue was distilled under reduced pressure to yield 7.1 g. (70%) of *o*-benzylbenzyl-N,N-dimethylamine (IV), b.p. 129.5–130° at 2.3 mm., n^{25}_{D} 1.5598.

Anal. Calcd. for $C_{16}H_{19}N$: C, 85.31; H, 8.46; N, 6.22. Found: C, 85.52; H, 8.50; N, 6.33.

The picrate melted at 151–152°; reported m.p. 156–156.6°.[3]

Anal. Calcd. for $C_{22}H_{22}N_4O_7$: N, 12.33. Found: N, 12.03.

Amine IV, obtained from the rearrangement of quaternary ion I as described previously,[2] boiled at 133–135° at 2.5 mm.; n^{25}_{D} 1.5600. It gave a picrate, m.p. 151–152°, which was not depressed on admixture with the picrate (m.p. 151–152°)[2] of the amine prepared from *o*-benzoylbenzoic acid.

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[1] Carbide and Carbon Chemicals Company Fellow, 1954.

[2] S. W. Kantor and C. R. Hauser, THIS JOURNAL, **73**, 4122 (1951).

[3] The rearrangement of I to IV was first observed by M. Sommelet (*Compt. rend.*, **205**, 56 (1937)) who allowed an aqueous solution of the hydroxide of I to evaporate in sunlight. G. Wittig, R. Mangold, and G. Felletschin (*Ann.*, **560**, 116 (1948)) confirmed this result, and showed that the rearrangement may be effected, along with the Stevens 1,2-shift, by means of lithium phenyl.

[4] See G. Wittig and M. Wetterling, *Ann.*, **557**, 193 (1947).

[5] Melting points and boiling points are uncorrected. Analyses are by Clark Microanalytical Laboratory, Urbana, Ill.

[6] E. C. Horning and D. B. Reisner, THIS JOURNAL, **71**, 1036 (1949).

[7] P. H. Dirstine and F. W. Bergstrom, *J. Org. Chem.*, **11**, 55 (1946).

[8] D. Todd, "Organic Reactions," Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 385.

The Synthesis of N$^{\alpha}$-Acetyl-L-kynurenine[1]

BY R. R. BROWN AND J. M. PRICE[2]

RECEIVED FEBRUARY 12, 1955

This communication presents a convenient method for the synthesis of crystalline N$^{\alpha}$-acetyl-L-, -DL- or -D-kynurenine. Previous methods yielded only racemic non-crystalline material,[3] or depended on isolation from biological material.[4] In this method, ozonolysis of N-acetyltryptophan[5] yielded an intermediate (probably N′-formyl-N$^{\alpha}$-acetylkynurenine)[6] which was converted by mild hydrolysis to N$^{\alpha}$-acetylkynurenine as anticipated

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[1] This research supported by the Wisconsin Division of the American Cancer Society, the Elsa U. Pardee Foundation, and the American Cancer Society upon recommendation of the Committee on Growth of the National Research Council.

[2] Scholar in Cancer Research of the American Cancer Society.

[3] C. E. Dalgleish, *J. Chem. Soc.*, 137 (1952).

[4] C. Yanofsky and D. M. Bonner, *Proc. Natl. Acad. Sci. U. S.*, **36**, 167 (1950).

[5] J. L. Warnell and C. P. Berg, THIS JOURNAL, **76**, 1708 (1954).

[6] A. H. Mehler and W. E. Knox, *J. Biol. Chem.*, **187**, 431 (1950).