[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, TULANE UNIVERSITY]

The Synthesis of 3-Substituted Furans

BY HANS WYNBERG

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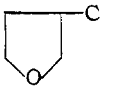
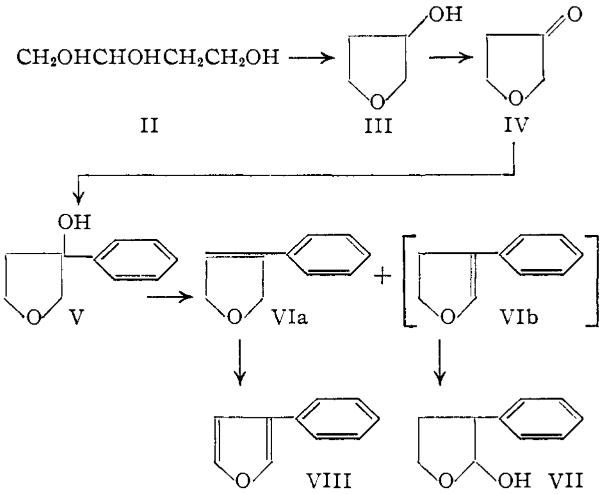
Starting with the commercially available 1,2,4-trihydroxybutane a new route to 3-substituted furans *via* 3-ketotetrahydrofurans has been investigated. The synthesis of the hitherto unknown 3-phenylfuran has been accomplished. It has been shown that pure 3-phenyl-2,5-dihydrofuran can be obtained and that dehydrogenation to the furan system can be accomplished by the use of sulfur in boiling dimethylformamide.

A variety of natural products, many of which adhere to the isoprene rule, embody the part structure I.[1] Although a few of these natural products have been synthesized,[2] it seemed worthwhile to investigate an entirely different approach to the preparation of 3-substituted furans. The synthesis of the unknown 3-phenylfuran[3] was chosen as a model study and was accomplished by the route



I



Using catalytic amounts of *p*-toluenesulfonic acid, 3-hydroxytetrahydrofuran (III) was obtained in excellent yield[4] from commercially available 1,2,4-trihydroxybutane. The ketone IV[5,6] could be obtained by a number of oxidizing procedures. However, due to the complete water miscibility of the ketone, as well as its low boiling point (138° (760 mm.)) only two procedures have proved of preparative value. The first involves low temperature chromic acid oxidation of III and produces the ketone IV in low (30%) but reproducible yield. The Oppenauer oxidation of III using aluminum isopropoxide and benzophenone furnished the ketone IV in 50–60% yields. Careful temperature control proved to be essential in order to prevent rapid further condensation of the carbonyl compounds. The reaction of 3-ketotetrahydrofuran (IV) with phenylmagnesium bromide proceeded to furnish 3-hydroxy-3-phenyltetrahydrofuran (V). Steam distillation of this carbinol from a 1% sulfuric acid solution furnished one isomer, 3-phenyl-2,5-dihydrofuran (VIa) as a low melting (m.p. 38°) stable solid in 40% yield. The bond isomer VIb apparently remained in the residue from the steam distillation as the hydrated cyclic hemi-acetal VII. The structure of VIa is based on the following observations: (1) elementary analysis[6]; (2) conversion to 3-phenylfuran in high yield; (3) no reaction with an alcoholic solution of 2,4-dinitrophenylhydrazine hydrochloride[7]; and (4) maximum absorption in the ultraviolet at 256 mμ (log ϵ 3.9).[8] When the aqueous residue from the steam distillation was treated with an alcoholic 2,4-dinitrophenylhydrazine solution an immediate orange-red precipitate appeared. This precipitate, not identical with the 2,4-dinitrophenylhydrazone of IV, darkened and decomposed rapidly upon exposure to air and light. When care was taken to isolate VII under essentially neutral conditions, treatment with 2,4-dinitrophenylhydrazine furnished a slightly more stable red precipitate.[9]

We now turn to the conversion of the dihydrofuran to the fully aromatic system (VIII). The formation of the isolated furan ring system by dehydrogenation only does not appear to have been accomplished previously. Because of the relatively low resonance energy of furan (23 kcal.) it

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[1] *Ann. Reports*, **51**, 243 (1954); A. F. Dunlop and F. N. Peters, "The Furans," Reinhold Publishing Corp., New York, N. Y., 1953, p. 29.

[2] T. Reichstein, A. Zschokke and A. Georg, *Helv. Chim. Acta*, **14**, 1370 (1931); A. J. Birch, R. A. Massy-Wintropp, S. E. Wright, K. Matsuura and H. D. Sutherland, *Chemistry & Industry*, 902 (1954); T. Kubota and T. Matsuura, *ibid.*, 521 (1956).

[3] D. M. Burness, *J. Org. Chem.*, **21**, 102 (1955), has reported recently a new synthesis of 3-methylfuran. Attempts to prepare 3-phenylfuran by this route failed however (private communication from Dr. Burness).

[4] W. Reppe, *Ann.*, **596**, 1 (1955), reports the formation of 2,5-di-(β-hydroxyethyl)-1,4-dioxane under virtually the same conditions reported for the formation of III in the same paper. In view of the proximity in b.p. of the dioxane (b.p. 90° (20 mm.)) and III (b.p. 93–95° (20 mm.)) the identity of the dioxane appears to be open to question.

[5] A. W. Johnson, U. S. Patent 2,468,881, *C. A.*, **43**, 5424 (1949), has reported the formation of this ketone directly from 1,4-butynediol. However, both in our laboratory and by a group of Russian workers (Yu. K. Yur'ev, *et al.*, *Doklady Akad. Nauk, SSSR*, **86**, 91 (1952), *C. A.*, **47**, 7478 (1953)) this could not be repeated.

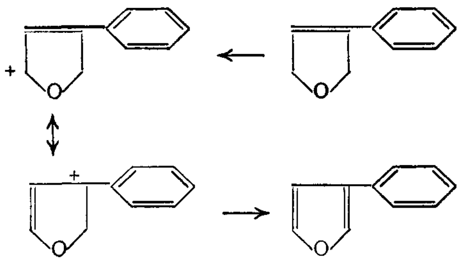
[6] The first authentic preparation of IV appears to be that reported by the Russian group (Yu. K. Yur'ev, *et al.*, *Zhur. Obshchei Khim.*, **26**, 553 (1956), *C. A.*, **50**, 13863 (1956) and previous papers cited therein) whose work became available to us during our studies.

[7] Compare the ease with which 2,3-dihydrofurans form carbonyl derivatives *via* the hydrated (cyclic hemi-acetal) form: (a) A. Lipp, *Ber.*, **22**, 1196 (1889); (b) H. Wohlgemuth, *Ann. chim.*, [9] **2**, 403 (1914); (c) W. E. Parham and H. E. Holmquist, THIS JOURNAL, **73**, 913 (1951); (d) R. Paul, M. Fluchaire and G. Collardeau, *Bull. soc. chim. France*, 668 (1950).

[8] Cinnamyl alcohol absorbs at 250 mμ (log ϵ 4.2); P. Ramart-Lucas and M. T. Hock, *ibid.*, [5] **2**, 327 (1935). The extra alkyl substituent in VIa accounts for the bathochromic shift of 6 mμ.

[9] Apparently formation of an unstable tetrahydropyridazine is involved as has also been observed in analogous cases by Wohlgemuth[7b] and Lipp.[7a]

might be anticipated that its formation from tetrahydrofuran would be approximately as difficult as the conversions butane → butene → butadiene, which have only been accomplished by catalytic means. Nevertheless, 3-phenyl-2,5-dihydrofuran was found to dehydrogenate smoothly and in high yield, even though 3-alkyl-2,5-dihydrofuran analogs decomposed prior to dehydrogenation. This difference in behavior may be due to stabilization of the transition state of the former



reaction by resonance of the benzyl type.[10] The reagent system which best accomplished this conversion was found to be a 2–3% solution of sulfur in boiling dimethylformamide. Dehydrogenation with this reagent was thus effected in homogeneous medium at 155° in 85% yield. 3-Phenylfuran obtained in this manner is a stable solid, in contrast to its position isomer, 2-phenylfuran, which is reported to be a liquid.[5] The maleic anhydride adduct of VIII formed rapidly and completely at 100°.

Acknowledgment.—A grant from the Smith, Kline and French Foundation in support of part of this investigation is gratefully acknowledged.

Experimental

3-Hydroxytetrahydrofuran (III). A.—A mixture of 318 g. (3 moles) of 1,2,4-trihydroxybutane[11] and 3 g. of *p*-toluenesulfonic acid monohydrate was distilled over a period of 2 to 3 hr. to give 300–306 g. of distillate, b.p. 85–87° (22 mm.). The colorless mixture of water and 3-hydroxytetrahydrofuran thus obtained was fractionated. Two fractions were collected: (1) 50–60 g., b.p. 42–44° (24 mm.), $n^{25}\text{D}$ 1.3343, was mainly water; and (2) 215–231 g., b.p. 82–88° (24 mm.), was pure **3-hydroxytetrahydrofuran**, $n^{26}\text{D}$ 1.4497, $d^{20}{}_4$ 1.095. The reported values are[12] b.p. 50° (1 mm.) $n^{18}\text{D}$ 1.4486, $d^{20}{}_4$ 1.090.

3-Ketotetrahydrofuran (IV). (A) **Dichromate Oxidation.**—A solution of 3-hydroxytetrahydrofuran (44.0 g. of crude distillate containing 36.0 g. of alcohol III) in 40 ml. of ether was cooled to −10°. Over a period of three hr. a cooled (0°) solution containing 50.0 g. of sodium dichromate dihydrate, 60.0 g. of concentrated sulfuric acid and 200 g. of water was added with vigorous stirring. The temperature was kept below −9° during these 3 hr. then below −5° for 4 hr. while stirring was continued. The reaction mixture was allowed to come to room temperature overnight. The ketone was separated from the aqueous layer by continuous extraction with ether, followed by drying with a saturated calcium chloride solution and anhydrous calcium chloride. Careful removal of the ether at atmospheric pressure and fractionation of the residue furnished 5.52 g. (32% based on recovered starting material), b.p. 134–142°, $n^{21}\text{D}$ 1.4358; and 18.5 g. of unchanged starting material, b.p. 145–161°, $n^{21}\text{D}$ 1.4380. Redistillation of fraction II furnished the pure ketone, b.p. 136.0–136.5° (739 mm.), $n^{21}\text{D}$ 1.4347; 2,4-dinitrophenylhydrazone, m.p. 155.5–156.2° (reported[6] b.p. 139.4–139.8° (760 mm.), $n^{20}\text{D}$ 1.4384, 2,4-DNP m.p. 155°). Although the yield of ketone is relatively low, it is reproducible within a few per cent.

(B) **Oppenauer Oxidation.**—One mole (88 g.) of freshly distilled alcohol (III), 2 moles (364 g.) of benzophenone and 10 g. of aluminum isopropoxide were mixed and heated to 150° at 35 mm. pressure. After removal of isopropyl alcohol, 59.6 g. (68%) of ketone contaminated with some starting alcohol was distilled over a period of 3 hr. Fractionation furnished 30.5 g. (50% based on recovered alcohol) of nearly pure ketone, b.p. 135–145°, $n^{25}\text{D}$ 1.4352.

3-Phenyl-2,5-dihydrofuran (VIa).—To the Grignard reagent prepared from 31.5 g. of freshly distilled bromobenzene and 4.80 g. of magnesium turnings in 400 ml. of ether was added 25.8 g. of 3-ketotetrahydrofuran in 100 ml. of ether over a period of 1 hr. The complex was decomposed with 200 ml. of saturated ammonium chloride solution and the ether, bromobenzene (3.5 g.) and diphenyl (0.2 g.) removed by steam distillation. Concentrated sulfuric acid (5 ml.) was added to the aqueous residue and steam distillation was continued until 1 l. of distillate had been collected. Upon cooling in ice, 13.04 g. (46.5%) of crystalline 3-phenyl-2,5-dihydrofuran (VIa) could be removed by filtration. Its m.p. 37–38° was not changed after distillation (b.p. 146–148° (30 mm.)); ultraviolet absorption $\lambda^{95\%\text{ alc}}_{\text{max}}$ 256; log ϵ 3.90 (reported m.p. 37–38°).

In another experiment, using 8.30 g. (0.097 mole) of ketone, 15.7 g. (0.1 mole) of bromobenzene and 2.43 g. (0.1 g. atom) of magnesium turnings in 250 ml. of ether, the Grignard complex was decomposed with ammonium chloride solution, the ether removed by steam distillation and the aqueous layer divided into two parts. One part, comprising one-third of the total, was steam distilled as described to furnish 1.93 g. of crystalline 3-phenyl-2,5-dihydrofuran, m.p. 35–37° (41% based on the total solution). The residual aqueous solution from the steam distillation was treated with an alcoholic solution of 2,4-dinitrophenylhydrazine hydrochloride. Within seconds a light red precipitate appeared. All attempts to purify this material resulted in complete resinification. The dry weight of dark resin was 0.40 g. (about 10% yield of 4-phenyl-2,3-dihydrofuran).

The other part comprising two-thirds of the total was extracted with ether, the ethereal solution dried and the ether removed leaving 3.72 g. of an oil. When 0.200 g. of this oil, 3-phenyl-3-hydroxytetrahydrofuran, was boiled for 2 min. with an alcoholic solution of 2,4-dinitrophenylhydrazine hydrochloride (0.200 g.) a dark red precipitate formed. Although this hydrazone could be kept at room temperature and exposed to air and light without apparent decomposition, slight warming (50–60°) caused complete resinification. The major portion of the oil was distilled (b.p. 205° (45 mm.)) without any dehydration. When one crystal of iodine was added to the clear distillate and the mixture warmed, dehydration occurred readily and was complete in 30 min. Distillation furnished a partly crystalline oil wnich contained only traces of the 4,5-dihydro isomer as evidenced by the fact that no appreciable precipitate was formed with 2,4-dinitrophenylhydrazine solution.

3-Phenylfuran (VIII).—A homogeneous solution containing 0.50 g. of sulfur and 2.00 g. of 3-phenyl-2,5-dihydrofuran in 50 ml. of dimethylformamide was heated under reflux for 30 min. Steam distillation produced 1.65 g. (83%) of 3-phenylfuran as glistening platelets, m.p. 56.5–58°. Sublimation at 65° (25 mm.) furnished an analytical sample, m.p. 58.5–59.0°.

Anal. Calcd. for $C_{10}H_8O$: C, 83.3; H, 5.59. Found: C, 83.04; H, 5.61.

Using only sulfur, a 74% yield of phenylfuran could be obtained, while chloranil in boiling ethylene glycol[13] furnished the aryl furan in 10% yield.

Reaction of 3-Phenylfuran with Maleic Anhydride.—When 150 mg. of VIII and 105 mg. of maleic anhydride was warmed in a test-tube at 100° the color changed from colorless → red → yellow → light amber in 5 min., while the solids liquefied. At the end of 5 min. resolidification took place. The m.p. of this crude adduct (250 mg., quantitative yield) was 114–117°. One recrystallization from methanol–benzene (4:1) furnished pure adduct as fine colorless needles, m.p. 132–132.5°, in 65% yield.

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[10] E. A. Braude, L. M. Jackman and R. P. Linstead, *J. Chem. Soc.*, 3544 (1954).

[11] Generously donated by the General Aniline and Film Corporation.

[12] C. C. Price and I. V. Krishnamurti, THIS JOURNAL, **72**, 5335 (1950).

[13] H. Wynberg, A. Logothetis and D. VerPloeg, *ibid.*, **79**, 1972 (1957).

Anal. Calcd. for $C_{14}H_{10}O_4$: C, 69.42; H, 4.16. Found: C, 69.51; H, 4.32.

Attempted **Dehydrogenation of 3-Hexyl-2,5-dihydrofuran.**—3-Hexyl-2,5-dihydrofuran prepared as described above for 3-phenyl-2,5-dihydrofuran had physical properties agreeing with those reported by Yur'ev.[6] When 1.54 g. (0.01 mole) of the olefin was heated with sulfur no hydrogen sulfide evolution at 200–250° occurred. Slow decomposition took place above this temperature and no identifiable product could be isolated from the reaction mixture. Attempts to accomplish dehydrogenation using sulfur in boiling dimethylformamide resulted in recovery (by steam distillation) of 72% of starting olefin.

NEW ORLEANS, LOUISIANA

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Bromonitro and Related Derivatives of Dibenzo-*p*-dioxin

BY HENRY GILMAN AND JOSEPH J. DIETRICH

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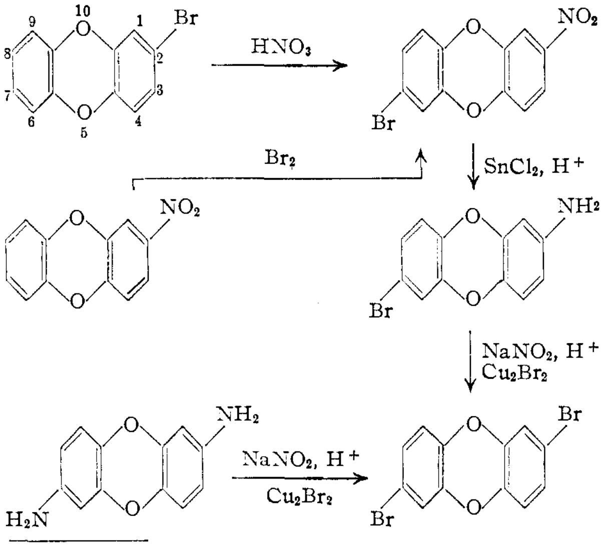
Several new derivatives of dibenzo-*p*-dioxin have been prepared while studying the directive influence of bromo and nitro substituents. Those chemically identified are 2-bromo-7-nitro-, 2-bromo-7-amino-, 2,7-diacetamido-, 2,7-dibromo- and 2,3,7,8-tetranitrodibenzo-*p*-dioxin. Infrared spectra were used to assign the structures of 2,3-dibromo-7-nitro- and 2-bromo-3,7-dinitrodibenzo-*p*-dioxin. Two compounds were designated as 2,8-dibromo-3,7-dinitro- and possibly 2,3-dibromo-7,8-dinitrodibenzo-*p*-dioxin since they are closely related to 2,3,7,8-tetrabromo- and 2,3,7,8-tetranitrodibenzo-*p*-dioxin.

In the course of studying the directive influence of various substituents on the dibenzo-*p*-dioxin nucleus, a number of interesting compounds was obtained. These have been characterized by a combination of chemical and physical methods.

The nitration of dibenzo-*p*-dioxin has been shown to proceed stepwise to yield 2-nitro-, 2,7- or 2,8-dinitro-, and finally 2,3,7-trinitrodibenzo-*p*-dioxin.[1] Bromination, in a similar manner, proceeds from the 2-bromo- to the 2,8-dibromodibenzo-*p*-dioxin in addition to a compound considered to be the 2,7-dibromo- and then to the 2,3,7,8-tetrabromodibenzo-*p*-dioxin.[2]

Nitration of 2-bromodibenzo-*p*-dioxin or bromination of 2-nitrodibenzo-*p*-dioxin resulted in the same product, the identity of which was established by reducing it to the amine and then forming the dibromo compound *via* a diazotization reaction. This dibromo compound proved to be the same as the dibromo compound obtained *via* the diazotization of 2,7-diaminodibenzo-*p*-dioxin, a known compound. Also helping to tie the above compounds together was the Beckmann rearrangement carried out on the dioxime of 2,7-diacetyldibenzo-*p*-dioxin. This reaction produced a diacetamido compound identical to that obtained by acetylating 2,7-diaminodibenzo-*p*-dioxin. A large discrepancy between the reported melting points of 2,7-dinitro-, 2,7-diaminodibenzo-*p*-dioxin[1] and the melting points, which were higher, obtained from the same compounds prepared in this Laboratory made the last sequence of reactions imperative.



A compound considered earlier to be the 2,7-dibromodibenzo-*p*-dioxin has been shown to be another isomer. This isomer may well be 2,3-dibromodibenzo-*p*-dioxin since its infrared spectrum, run in carbon disulfide, has a strong 1,2-disubstitution band at 13.3 μ, indicating that one ring was unsubstituted. When a Nujol mull was used, as in the previous paper,[2] the band at 13.3 μ was absent from the spectrum. Chemical evidence presented in the previously mentioned paper[2] is also consistent with the proposed structure.

2-Nitrodibenzo-*p*-dioxin may be brominated to yield a dibromonitrodibenzo-*p*-dioxin. Likewise, 2-bromodibenzo-*p*-dioxin may be dinitrated. Bromination[2] and nitration[1] studies fairly well limit the substituents to the 2,3,7-positions. Monobromination of 2-nitrodibenzo-*p*-dioxin and mononitration of 2-bromodibenzo-*p*-dioxin have been shown to yield the same compound. Therefore, only the position of the last group was in question. Working only with infrared data, the assignments of the two compounds in question are believed to be 2,3-dibromo-7-nitro- and 2-bromo-3,7-dinitrodibenzo-*p*-dioxin. Both compounds have a 1,2,4-trisubstitution band at 12.2 μ. This is consistent with the band found in the spectrum of 2-nitrodibenzo-*p*-dioxin at 12.2 μ but not with the band found in the spectrum of 2-bromodibenzo-*p*-dioxin at 12.4 μ. Therefore, one ring must contain the nitro group which was responsible for the band at 12.2 μ while the other ring contains the other two groups. Both assignments are theoretically sound when directive effects of the substituents already present are considered.

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[1] M. Tomita, *J. Pharm. Soc. Japan*, **55**, 1060 (1935) [*C. A.*, **31**, 6661 (1937)].

[2] H. Gilman and J. J. Dietrich, THIS JOURNAL, **79**, 1439 (1957).