[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF FORDHAM UNIVERSITY]

The Stereochemistry of Some Phenylfurans

BY ANTOINE KHAWAM AND ELLIS V. BROWN

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A study of diphenyl type isomerism in the phenylfuran series has been made. 3-(2-Methyl-6-nitrophenyl)-2,5-dimethyl-4-furoic, 3-(2,4-dimethyl-6-nitrophenyl)-2,5-dimethyl-4-furoic and 3-(2-nitrophenyl)-2,5-dimethyl-4-furoic acids have been successfully resolved through their quinine salts. The optically active free acids have also been isolated.

Since the resolution of 2,2′-dinitrodiphenic acid by Christie and Kenner,[1] extensive investigation has done much to elucidate the situation in the field of the optical isomerism of the diphenyls.[2] This type of isomerism has been developed to some extent in the heterocyclic series,[2] *i.e.*, phenylpyridines, dipyridyls, phenylpyrroles, dipyrryls and phenylpyrazoles, where difficulty in synthesis seriously hampered progress in the field. The present report covers a study of diphenyl type isomerism in the phenylfuran series. First, it was necessary to prepare compounds which have substituents sufficiently large to give an interference value[2] capable of restricting free rotation. In the diphenyl series (Fig. 1), the C–C bond in the rings o and o′ is 1.42

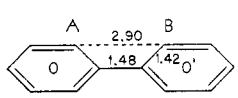


Fig. 1.

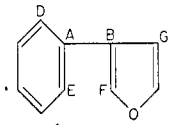


Fig. 2.

Å. The C–C bond between rings is 1.48 Å., hence the distance AB when o and o′ are coplanar is accurately known to be 2.90 Å. No such data are available in the phenylfuran series. Distances AB, DG and EF (Fig. 2) are not known. The available data for the benzene ring are given by Schomaker and Pauling[3] who found the C–C bond to be 1.39 ± 0.02 Å. and the C–H bond to be 1.08 ± 0.04 Å. while the C–C–C angle equaled 120° and the H–C–C angle equaled 120 ± 3°. The information on the furan[3] ring is summarized in Fig. 3. No data are available for phenylfurans and, therefore, before approaching the present problem, a few as-

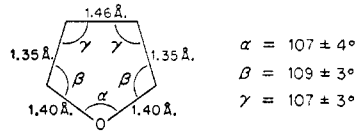
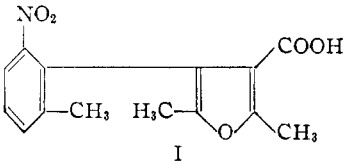


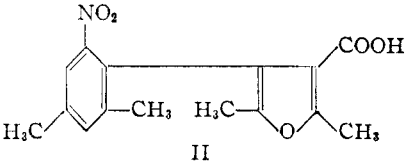
Fig. 3.

sumptions became necessary, *i.e.*, (1) that in phenylfurans the benzene and furan are coplanar, (2) that the C–C bond distance between the benzene and furan rings is approximately 1.48 Å. as in the case of diphenyl and (3) that in phenylfuran the bond angles and the bond lengths are not distorted, that is, the values of C–O, C–C and C–H as determined by Pauling[3] are not appreciably changed by forming a beta substituted phenylfuran. Hence, the distance GD (Fig. 2) when the phenylfuran molecule is drawn to scale according to the data is approximately 3.00 ± 0.05 Å.

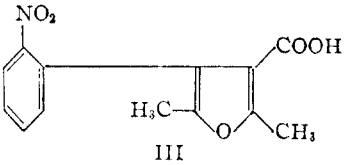
Three new substituted phenylfurans were synthesized for resolution studies.



I



II



III

3-(2-Methyl-6-nitrophenyl)-2,5-dimethyl-4-furoic acid (I), 3-(2,4-dimethyl-6-nitrophenyl)-2,5-dimethyl-4-furoic acid (II) and 3-(2-nitrophenyl)-2,5-dimethyl-4-furoic acid (III) were successfully resolved and the dextro and levo forms isolated. The rotations were measured in chloroform solution. Acids I and II were quite stable as their rotation did not change at room temperature on standing several days in chloroform solution. However, acid III racemized rapidly at room temperature. All of the acids racemized upon heating in alcohol for a short time.

It seemed desirable to attempt to calculate the interference values for the three acids, and in the light of the results re-examine our assumptions. For estimating the average interference values it is convenient as shown by Adams[2] to find half of the sum of the internuclear distances of the four substituents and subtract our calculated distance of 3.0 Å. By this method we arrive at the average interference value as 0.47 Å. for acids I and II. For acid III this average value is 0.075 Å. This low value explains the rapid racemization of acid III in chloroform at room temperature.

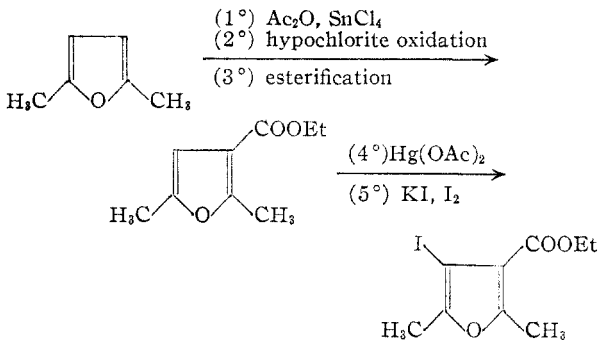
All the compounds were prepared from 2,5-dimethyl-3-iodo-4-carbethoxyfuran[4] which was synthesized from 2,5-dimethylfuran by a five-step reaction series. The phenylfurans were then prepared from this furan and the corresponding substituted bromobenzenes by means of the Ullmann reaction.

(1) G. H. Christie and J. Kenner, *J. Chem. Soc.*, **121**, 614 (1922).

(2) For a complete discussion, see H. Gilman, "Organic Chemistry," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1940, p. 347, and R. Adams and H. Yuan, *Chem. Revs.*, **12**, 261 (1933).

(3) V. Schomaker and L. Pauling, THIS JOURNAL, **61**, 1769 (1939).

(4) E. V. Brown, Thesis, Iowa State College, 1936.



Experimental

3-Acetyl-2,5-dimethylfuran.—2,5-Dimethylfuran obtained through the courtesy of the Carbide and Carbon Chemical Co. was acetylated as described by Hurd and Wilkinson.[5]

2,5-Dimethyl-3-furoic Acid (Pyrotritaric Acid).—To 310 g. of commercial HTH dissolved in 1.5 l. of warm water, a warm solution of 256 g. of K_2CO_3 and 73 g. of KOH in 750 ml. of water was added slowly with stirring. Efficient stirring was continued until the semi-solid gel which first formed became quite fluid. The suspended solid was filtered and washed with 250 ml. of hot water. The filtrate was warmed to 55°, stirring was started and 100 g. of 3-acetyl-2,5-dimethylfuran was added dropwise. An exothermic reaction began and the temperature had to be kept at 60–70° by frequent cooling. After about an hour excess hypochlorite was destroyed with $NaHSO_3$, the solution was cooled and acidified. There was obtained 85 g. of acid which after recrystallization from alcohol melted at 134–135°.

Ethyl Pyrotritarate.—The above acid (85 g.) was esterified in the conventional way with 500 ml. of absolute ethanol and 25 ml. of 100% H_2SO_4 to give 45 g. of the ester and 10 g. of unreacted acid.

Ethyl 4-Iodo-2,5-dimethyl-3-furoate.—To 120 g. of mercuric acetate dissolved in 1 l. of 45% ethanol at 50°, 42 g. of the above ester in 40 ml. of alcohol was added dropwise with stirring. Heavy white crystals formed in a few minutes but stirring at room temperature was continued for another 12 hours. The mercurial was separated and treated with KI–I_2 solution until on prolonged shaking the brown color remained. Excess iodine was destroyed with $Na_2S_2O_3$ and the iodo ester was extracted into ether. After evaporation of the ether and recrystallization from methanol, 58 g. of the iodo ester, m.p. 41–42°, was obtained.

2-Bromo-3-nitrotoluene.—2-Methyl-6-nitroaniline was prepared in two different ways from *o*-toluidine. The method described by Meisenheimer and Hesse[6] was found more suitable than of Hadfield and Kenner.[7] This compound (25 g.) was diazotized in 48% HBr at 0°, the diazonium solution was poured over cuprous bromide in 48% HBr solution[8] and steam distilled. About 30 l. was collected and, after ether extraction and distillation, there was obtained 23 g. of the bromo compound distilling at 157° at 22 mm. and melting at 37–38°.

3-(2-Methyl-6-nitrophenyl)-2,5-dimethyl-4-furoic Acid (I).—A mixture of 10 g. of 2-bromo-3-nitrotoluene and 14 g. of ethyl 2,5-dimethyl-3-iodo-4-furoate was placed in an ignition tube and stirred with a thermometer while heating in an oil-bath. When the temperature reached 200°, 45 g. of precipitated copper powder was added in small amounts over a period of 45 minutes. The reaction was highly exothermic and the temperature was maintained at 230–240° for an hour. The reaction mass was cooled and thoroughly extracted with ether. The ether extract was refluxed for half an hour with Nuchar and filtered. The ether was evaporated and the residue was refluxed for 10 hours with 250 ml. of 10% aqueous ethanolic NaOH. During the last moments of the refluxing, a few grams of charcoal was added and the solution was filtered while hot. After cooling and acidifying with 2 *N* HCl, a yellowish material was separated which was taken into 200 ml. of hot benzene and filtered, thus leaving on the filter paper a small amount of dicarboxylic acid formed during the reaction. The benzene solution was concentrated to 50 ml. and extracted with 5% NaOH. Upon acidification, pure 3-(2-methyl-6-nitrophenyl)-2,5-dimethyl-4-furoic acid separated. After three recrystallizations from ethanol and sublimation *in vacuo*, there was obtained 2.15 g. of acid, m.p. 225–226°.

Anal. Calcd. for $C_{14}H_{13}NO_5$: neut. equiv., 275; C, 61.09; H, 4.72; N, 5.09. Found: neut. equiv., 273.5; C, 60.94; H, 4.64; N, 5.20.

Resolution of 3-(2-Methyl-3-nitrophenyl)-2,5-dimethyl-4-furoic Acid.—To 800 mg. of the above acid dissolved in 300 ml. of boiling 40% ethanol, 1.05 g. of quinine was added, the solution was boiled for a few minutes with 0.5 g. of charcoal, filtered and left in an ice-box. A few pieces of ice were added daily for three days until a gummy material precipitated. After standing several more days in an ice-box, the gum solidified, was separated, pressed dry on a porcelain plate and dried two days *in vacuo*. The first crop of 835 mg. was collected in this way. After evaporation of the mother liquor to 150 ml. another 200 mg. of the quinine salt was separated giving a total of 1.035 g. of quinine salt Ia, m.p. 110–115° with previous softening at 100°. The filtrate was evaporated to dryness *in vacuo* and 525 mg. of salt Ib was collected, m.p. 110–114°. Salt Ia had $[\alpha]^{25}D$ −30.3° (*c* 0.1745 g. in 10 ml. of $CHCl_3$[9]). Salt Ib had $[\alpha]^{25}D$ −128.3° (*c* 0.0653 g. in 10 ml. of $CHCl_3$).

The salts were recrystallized from ethanol and dried over P_2O_5 at 70° for 24 hours.

Anal. Salt Ia. Calcd. for $C_{34}H_{37}O_7N_3 \cdot {}^1/_2H_2O$: C, 67.10; H, 6.25. Found: C, 67.11; H, 6.10. Salt Ib. Calcd. for $C_{34}H_{37}O_7N_3$: C, 68.11; H, 6.17. Found: C, 67.85; H, 5.88.

The two salts were decomposed by 6 *N* HCl in the cold, washed with 2 *N* HCl and an excess of water, then dried *in vacuo*. The acid from salt Ia (*l*-form) had $[\alpha]^{25}D$ −22.8° (*c* 0.1290 g. in 10 ml. of $CHCl_3$) and melted at 220–222°. The acid from salt Ib (*d*-form) had $[\alpha]^{25}D$ 22.1 (*c* 0.0760 g. in 10 ml. of $CHCl_3$) and melted at 223–224°. The chloroform solution of the acid did not change in rotation on standing one week at room temperature. Attempts to recrystallize the acid from hot ethanol cause complete loss of activity.

4-Bromo-5-nitro-1,3-xylene.—This compound was prepared from the corresponding 4-amino-5-nitro-1,3-xylene by means of the Sandmeyer reaction.[8] Diazotization at 20° as described by Spitzer and Wheland[10] gave some phenol while diazotization at 0–5° with stirring for two hours was found to be better.

3-(2,4-Dimethyl-6-nitrophenyl)-2,5-dimethyl-4-furoic Acid (II).—This acid was prepared in the same manner as acid I using the Ullmann reaction. From 8 g. of 4-bromo-5-nitro-1,3-xylene and 11.25 g. of ethyl 4-iodo-2,5-dimethyl-3-furoate there was obtained 2.65 g. of the acid, m.p. 218–220°.

Anal. Calcd. for $C_{15}H_{15}NO_5$: neut. equiv., 289; C, 62.28; H, 5.19; N, 4.84. Found: neut. equiv., 287; C, 62.07; H, 5.01; N, 5.02.

Resolution of 3-(2,4-Dimethyl-6-nitrophenyl)-2,5-dimethyl-4-furoic Acid.—The above acid (2.65 g.) was dissolved in 1 l. of boiling 45% ethanol, 3.30 g. of quinine was added and the solution filtered. After the addition of a few pieces of ice, the solution was left in the ice-box for several days. A first crop of 2.75 g. of a salt (IIa), m.p. 114–115°, was collected. The solution was evaporated to 750 ml. and left in the ice-box for three days when 2.10 g. of salt IIb, m.p. 112–114°, was collected. Salt IIa had $[\alpha]^{25}D$ 52.6° (*c* 0.1705 g. in 10 ml. of $CHCl_3$). Salt IIb, had $[\alpha]^{25}D$ −53.5° (*c* 0.1710 g. in 10 ml. of $CHCl_3$).

The salts were recrystallized from ethanol and dried over P_2O_5 at 70° for 24 hours.

Anal. Salt IIa. Calcd. for $C_{35}H_{39}O_7N_3 \cdot H_2O$: C, 66.56; H, 6.4. Found: C, 66.70; H, 6.24. Salt IIb. Found: C, 66.54; H, 6.02.

After decomposition of the salts in the usual manner, the acid from salt IIa had $[\alpha]^{25}D$ −33.6° (*c* 0.1540 g. in 10 ml. of $CHCl_3$) and melted at 206–208° with softening at 205° and the acid from salt IIb had $[\alpha]^{25}D$ +26.2° (0.1378 g. in 10 ml. of $CHCl_3$) and melted at 203–206° with softening at 198°.

(5) C. D. Hurd and K. Wilkinson, THIS JOURNAL, **70**, 739 (1948).
(6) J. Meisenheimer and E. Hesse, *Ber.*, **52**, 1171 (1919).
(7) J. H. Hadfield and J. Kenner, *Proc. Chem. Soc.*, **30**, 253 (1915).
(8) J. L. Hartwell, *Org. Syntheses* **24**, 22 (1944).
(9) In all cases decimeter tubes were used.
(10) W. C. Spitzer and G. W. Wheland, THIS JOURNAL, **62**, 2995 (1940).

The chloroform solution of the acid did not change in rotation on standing one week at room temperature. Attempts to recrystallize the acid from hot ethanol caused complete loss of activity.

3-(2-Nitrophenyl)-2,5-dimethyl-4-furoic Acid (III).—This acid was prepared from 10 g. of the iododimethylfuroate and 7 g. of *o*-bromonitrobenzene in the manner previously detailed. There was obtained 2.75 g. of the acid, m.p. 175–176°.

Anal. Calcd. for $C_{13}H_{11}NO_5$: C, 59.77; H, 4.21; N, 5.36. Found: C, 59.86; H, 4.01; N, 5.70.

Resolution of 3-(2-Nitrophenyl)-2,5-dimethyl-4-furoic Acid.—The above acid (2.75 g.) was treated with an equimolar amount of quinine as in the previous cases in dilute alcohol. The solution was evaporated to dryness and the quinine salt was dissolved in 300 ml. of boiling acetone. After cooling for several days, a first crop of crystals (IIIa) was collected. After evaporation of the mother liquor *in vacuo*, a gum was left which solidified upon cooling (IIIb). The salt IIIa, m.p. 167–168°, had $[\alpha]^{25}D$ −38° (*c* 0.1924 g. in 10 ml. of $CHCl_3$). The salt IIIb, m.p. 183–185° had $[\alpha]^{25}D$ −52° (*c* 0.0906 g. in 10 ml. of $CHCl_3$). The salts were recrystallized from ethanol and dried over P_2O_5 at 70° for 24 hours.

Anal. Salt IIIa. Calcd. for $C_{33}H_{35}O_7N_3$: C, 67.69; H, 5.98. Found: C, 68.00; H, 5.87. Salt IIIb. Calcd. for $C_{33}H_{35}O_7N_3 \cdot {}^1/_2H_2O$: C, 66.66; H, 6.06. Found: C, 66.97; H, 6.00.

The rotation of both salts was −65 and −64°, respectively, after recrystallization, indicating racemization during this process.

The acid from salt IIIa had $[\alpha]^{25}D$ −7.8° (*c* 0.1533 g. in 10 ml. of $CHCl_3$) and melted at 170–171° with softening at 162–165°. The acid from salt IIIb had $[\alpha]^{25}D$ 12.3° (*c* 0.1216 g. in 10 ml. of $CHCl_3$) and melted at 168–169° with softening at 156°. The rotation of the chloroform solution fell to zero in three hours of standing at room temperature.

NEW YORK 58, N. Y.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY, DEPARTMENT OF SURGERY OF BETH ISRAEL HOSPITAL AND HARVARD MEDICAL SCHOOL]

Synthesis of 2-Naphthyl β-D-Glucopyruronoside and 2-Naphthyl β-D-Glucofururonolactone and their Behavior toward β-D-Glucuronidase[1]

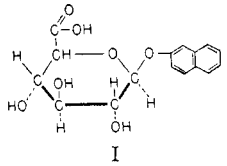
BY KWAN-CHUNG TSOU AND ARNOLD M. SELIGMAN

RECEIVED APRIL 3, 1952

Catalytic oxidation of 2-naphthyl β-D-glucopyranoside with molecular oxygen and platinum black yielded 2-naphthyl β-D-glucopyruronoside. Fusion of 2-naphthol with triacetyl-β-D-glucofururonolactone in the presence of *p*-toluenesulfonic acid yielded 2-naphthyl diacetyl-β-D-glucofururonolactone, which was converted to 2-naphthyl-β-D-glucofururonamide with dry ammonia and methanol. The amide reacted with sodium nitrite in 50% acetic acid to give 2-naphthyl β-D-glucofururonolactone rather than the acid. The pyranoside was readily hydrolyzed by β-D-glucuronidase whereas the furanoside was not. Therefore, substrates susceptible to β-D-glucuronidase activity require a pyranose ring.

In the course of a search for suitable substrates for the colorimetric and histochemical demonstration of β-D-glucuronidase activity,[2] 2-naphthyl β-D-glucopyruronoside (I) and 2-naphthyl β-D-glucofururonolactone (V) were synthesized. Hitherto I has been obtained only by isolation from the urine of man, dog,[3] rabbit[4] and rats[5] after feeding 2-naphthol. The lactone V was not known. Their synthesis and susceptibility to the hydrolytic action of β-D-glucuronidase are given in this report.

Using the procedure of Fernández-García, *et al.*,[6] with some modification, the oxidation of 2-naphthyl β-D-glucopyranoside[7] in aqueous solution with molecular oxygen in the presence of platinum black as catalyst afforded I. The product was isolated through the lead salt and regenerated with hydrogen sulfide. Its infrared spectrum in dioxane showed, in addition to the characteristic 2-naphthyl band pair at 6.11 and 6.21 μ,[7] a carbonyl band at 5.75 μ (Fig. 1) which is in the carboxyl region assigned by the Colthup chart.[8] Its *p*-toluidine salt melted at 186.5–187° (lit. m.p. 184–186°).[5] A mixed melting point of the *p*-toluidine salt of I with a sample prepared from I which we isolated from rabbit urine, showed no depression. Both I and its salt gave a positive naphthoresorcinol test[9] for glucuronide and on hydrolysis in hot 6 *N* sodium hydroxide gave 2-naphthol.



I

The chemical synthesis provides a useful chromogenic substrate for β-D-glucuronidase which should be more practical and more readily available than the tedious biosynthetic preparation of phenolphthalein monoglucuronide currently in use.[10] The latter compound has not been obtained crystalline but is only available as a crude cinchonidine salt.

Moreover, since there could be no change of the oxide ring during the catalytic oxidation of the primary alcohol group of 2-naphthyl β-D-glucopyranoside, the pyranose structure of urinary 2-naphthyl β-D-glucopyruronoside is proved. That a pyranose ring occurs in the natural products has been deduced from methylation study and the periodic acid degradation of bornyl glucuronide[11]

(1) This investigation was supported by a research grant from the National Cancer Institute of the National Institutes of Health, Public Health Service, Federal Security Agency, and by an institutional grant to Harvard University from the American Cancer Society.

(2) A. M. Seligman, M. M. Nachlas, L. H. Manheimer, O. M. Friedman and G. Wolf, *Ann. Surg.*, **130**, 333 (1949).

(3) M. Lesnik and M. Nencki, *Ber.*, **19**, 1534 (1886).

(4) F. Bergmann, *Biochem. Z.*, **267**, 296 (1933).

(5) M. Berenbom and L. Young, *Biochem. J.*, **49**, 165 (1951).

(6) R. Fernández-García, L. Amorós, H. Blay, E. Santiago, H. Soltero-Díaz and A. A. Colón, *El Crisol*, **4**, 40 (1950).

(7) K.-C. Tsou and A. M. Seligman, THIS JOURNAL, **74**, 3066 (1952).

(8) N. B. Colthup, *J. Optical Soc. Am.*, **40**, 397 (1950).

(9) B. Tollens, *Ber.*, **41**, 1788 (1908).

(10) P. Talalay, W. H. Fishman and C. Huggins, *J. Biol. Chem.*, **166**, 757 (1946).

(11) J. Pryde and R. T. Williams, *Nature*, **128**, 187 (1931); C. F. Huebner, R. Lohmar, R. J. Dimler, S. Moore and K. P. Link, *J. Biol. Chem.*, **159**, 503 (1945).