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Orientation in the Furan Series. X. Anomalous Friedel–Crafts Reactions

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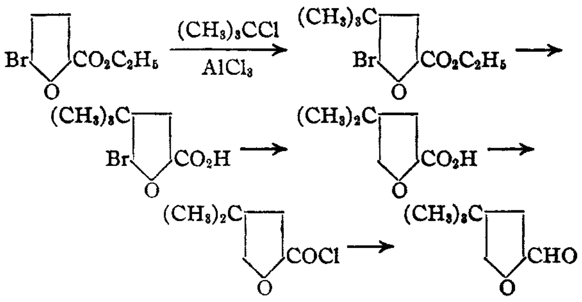
Introduction

Alkylation of 2-Furfural.—It has been shown in the preceding paper that 4-isopropyl-2-furfural results unexpectedly from a Friedel–Crafts reaction of 2-furfural and isopropyl chloride. However, when 2-furfural reacts under corresponding conditions with the next higher homologous chlorides, the butyl and amyl groups enter the 5-position. In one sense these latter reactions are normal because an entering group always tends to assume an α-position in furan if such a position be available. From another point of view the reactions are somewhat anomalous because the predominant product, and the only compound isolated, is that one having the most highly branched radical. For example, *n*-, *i*- and *t*-butyl chlorides give 5-*t*-butyl-2-furfural. This rearrangement of the radicals was observed earlier[1] in the Friedel–Crafts reaction with methyl 2-furoate: the *n*-, *i*-, *s*- and *t*-butyl chlorides giving methyl 5-*t*-butyl-2-furoate.

There is no present satisfactory explanation for the distinct differences in orientation of the isopropyl group as contrasted with the butyl and amyl groups. Because of the possibility that the isopropyl group first assumed a 5-position and then rearranged to the 4-position, 5-isopropyl-2-furfural was prepared and treated with aluminum chloride under approximately the experimental conditions used. No rearrangement was noted and the original aldehyde was recovered quantitatively. Likewise, 4-*t*-butyl-2-furfural was found not to rearrange to 5-*t*-butyl-2-furfural under corresponding conditions. The 4-*t*-butyl-2-furfural was prepared as follows



Alkylation of Benzaldehyde.—If ease of nuclear substitution be one of the criteria of aromaticity, then furan is definitely more aromatic than benzene. This is strikingly illustrated in all the usual substitution reactions, and particularly with the Friedel–Crafts reaction.[1] For example, methyl furoate but not methyl benzoate can be alkylated. Also, methyl anisate, which on the basis of ease of nuclear substitution is more aromatic than methyl benzoate, was found to undergo alkylation. This suggested that anisaldehyde might alkylate, and experiments showed this to be the case. Finally, it seemed desirable to study the alkylation of benzaldehyde. It was found that this aldehyde could be alkylated to a limited extent and at a slower rate than the alkylation of furfural. Of some significance is the observation that whereas isopropyl and *t*-butyl chlorides are oriented differently with furfural, they are oriented alike with benzaldehyde to give the *m*-isopropyl and *m*-*t*-butylbenzaldehydes.

Cleavage of Some Higher Radicals to the *t*-Butyl Radical.—In order to determine whether the 5-amyl-2-furfural (obtained by the action of *n*-amyl chloride on furfural) might have resulted from a rearrangement of 4-amyl-2-furfural, a sequence of reactions like that given previously in this paper for the synthesis of 4-*t*-butyl-2-furfural was carried out, using *n*-amyl chloride in place of *t*-butyl chloride. It was found that alkylation took place, but instead of the expected ethyl 4-amyl-5-bromo-2-furoate there was obtained ethyl 4-*t*-butyl-5-bromo-2-furoate. In short, the *n*-amyl group was cleaved and rearranged to a *t*-butyl group. A similar anomalous result was observed when ethyl 5-bromo-2-furoate was treated with *n*-hexyl bromide: ethyl 4-*t*-butyl-5-bromo-2-furoate again resulted. The study is being extended to establish the limits of the reaction and its mechanism. It is interesting to note that incidental to an examination of the fragments cleaved from the higher radicals, Mr. J. A. V. Turck, Jr., has obtained a 46% yield of ethyl 4-*t*-butyl-5-bromo-2-furoate from ethyl 5-bromo-2-furoate and *n*-octadecyl bromide ($C_{18}H_{37}Br$).

The cleavage reactions cited appear to be novel. However, related cleavages with alkylated cyclohexanes show a conversion of an ethyl

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[1] Gilman and Calloway, THIS JOURNAL, **55**, 4197 (1933).

group to dimethyl groups and of a propyl group to trimethyl groups as in the conversion of propylcyclohexane to 1,3,5-trimethylcyclohexane.[2a] A related observation was reported recently by Ipatieff and Komarewsky.[2b] More particuarly, benzene and diamylene gave a mixture of benzene homologs, the side chains being mainly butyl, amyl and hexyl.[2c]

Experimental Part

5-Isopropyl-2-furfural.—5-Isopropyl-2-furoic acid[1] was converted to 5-isopropyl-2-furoyl chloride (b. p. 117–121° (16 mm.)) by means of thionyl chloride. A Rosenmund reduction of the acid chloride gave a 35% yield of 5-isopropyl-2-furfural; b. p. 91° (11 mm.); $n^{25}\text{D}$ 1.5085; $d^{25}{}_{25}$ 1.0330. The aldehyde gave a positive aniline acetate test, and the semicarbazone of the aldehyde melted at 159° after crystallization from a water–ethanol solution.

Anal. Calcd. for $C_9H_{15}O_2N_2$: C, 54.79; H, 7.66. Found: C, 54.40; H, 7.28.

A solution of 2.7 g. of the aldehyde in carbon disulfide was added dropwise with stirring to a suspension of 3.2 g. of aluminum chloride in carbon disulfide. After attempted reaction the mixture was worked up in the usual manner to give a quantitative recovery of the aldehyde. For extra confirmatory purposes the aldehyde so recovered was characterized by conversion to the previously prepared semicarbazone.

5-*t*-Butyl-2-furfural.—A solution of 48 g. (0.5 mole) of furfural and 40 g. (0.5 mole) of *t*-butyl chloride was added dropwise with stirring at room temperature and over a one and one-half hour period to a suspension of 80 g. (0.6 mole) of aluminum chloride in 500 cc. of carbon disulfide. Stirring was continued for an additional ten minutes and the mixture was then worked up in accordance with the procedure employed in the preparation of 4-isopropyl-2-furfural. Thirty grams of furfural was recovered, and the yield of pure 5-*t*-butyl-2-furfural was 4 g.; b. p. 93–95° (13 mm.); $n^{25}\text{D}$ 1.5001; $d^{25}{}_{25}$ 1.001. The semicarbazone of the aldehyde melted at 205° when crystallized from a water–ethanol solution.

Anal. Calcd. for $C_{10}H_{15}O_2N_3$: C, 57.42; H, 7.17. Found: C, 57.05; H, 7.59.

Alkaline silver oxide oxidation of the aldehyde gave 5-*t*-butyl-2-furoic acid, the identity of which was established by comparison with an authentic specimen.[1] The same acid was obtained by oxidizing the aldehydes obtained from furfural with *n*-butyl chloride and furfural with *i*-butyl chloride.

The identities of the several aldehydes were further established by converting the corresponding acids to the amides, each of which melted at 121° when crystallized from a water–ethanol solution and then from petroleum ether (b. p. 75–115°). Mixed melting point determinations were made of the several amides.

Anal. Calcd. for $C_9H_{13}O_2N$: C, 64.67; H, 7.78; N, 8.38. Found: C, 65.01; H, 8.08; N, 8.09.

Because of the anomalous Friedel–Crafts reaction it seemed desirable to obtain additional confirmatory evidence for the reaction products. Accordingly, the acids were decarboxylated to the corresponding 2-*t*-butylfurans and comparisons with the physical constants of an authentic specimen showed no differences. Finally, the 2-*t*-butylfurans were mercurated to 5-*t*-butyl-2-furylmercuric chloride, and the several mercurials were shown to be identical with one another and with the mercurial obtained by replacing the carboxyl group in 5-*t*-butyl-2-furoic acid by a chloromercuri group.[1] The mercurial melts at 174–175°.

Anal. Calcd. for $C_8H_{11}OClHg$: Hg, 55.87. Found: Hg, 56.19 and 55.95.

The 5-*t*-butyl-2-furfural was also prepared by the following sequence of reactions: 5-*t*-butyl-2-furoic acid ⟶ 5-*t*-butyl-2-furoyl chloride ⟶ 5-*t*-butyl-2-furfural, the last transformation being effected by the Rosenmund reduction. The aldehyde prepared in this manner was identical with that obtained from furfural and *t*-butyl chloride, and the corresponding semicarbazones were the same.

There was no evidence of a rearrangement when 5-*t*-butyl-2-furfural in carbon disulfide was treated with aluminum chloride. The aldehyde was recovered quantitatively, and identified by its semicarbazone (mixed m. p.).

4-*t*-Butyl-2-furfural.—The aldehyde was prepared in order to determine whether it might rearrange to the isomeric 5-*t*-butyl-2-furfural.

A solution of 162 g. (0.74 mole) of ethyl 5-bromo-2-furoate and 68.4 g. (0.74 mole) of *t*-butyl chloride was added dropwise with stirring at room temperature to a suspension of 196.8 g. (1.68 moles) of aluminum chloride in 1450 cc. of carbon disulfide. After stirring for twenty-four hours the mixture was worked up in the customary manner to yield 6 g. or 3% of ethyl 4-*t*-butyl-5-bromo-2-furoate which distilled at 148–152° (13 mm.). The low yield is in sharp contrast with that obtained in the alkylation of the same ester with isopropyl chloride, and the differences in yield may be associated with steric influences. Hydrolysis by alcoholic potash gave 4-*t*-butyl-5-bromo-2-furoic acid which melted at 164° after crystallization from petroleum ether (b. p. 75–115°) and then from a water–ethanol solution. *Neutral equivalent.* Calcd., 247; found, 246.7.

Anal. Calcd. for $C_9H_{11}O_3Br$: Br, 32.59. Found: Br, 32.10.

A dilute ammoniacal solution of the 4-*t*-butyl-5-bromo-2-furoic acid (2.2 g.) was treated with zinc dust to give 4-*t*-butyl-2-furoic acid quantitatively. The acid melted at 89° when crystallized from a water–ethanol solution. *Neutral equivalent.* Calcd., 168; found, 168.4.

By customary procedures, the acid was converted to the acid chloride, and the acid chloride was reduced to 4-*t*-butyl-2-furfural, which distilled at 93–95° (13 mm.). The semicarbazone of the aldehyde melted at 187°.

Anal. Calcd. for $C_{10}H_{15}O_2N_3$: C, 57.42; H, 7.17. Found: C, 57.27; H, 6.98.

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(2) (a) Grignard and Stratford, *Bull. soc. chim.*, [4] **35**, 931 (1924) [*Chem. Zentr.*, **100**, *II*, 1285 (1929) has a review of the thesis]; see, also, Pictet and Lerczynska, *Bull. soc. chim.*, **19**, 326 (1916); (b) Ipatieff and Komarewsky, THIS JOURNAL, **56**, 1926 (1934); (c) Tilicheev and Kuruindin, *Neftyanoe Khozyaistvo*, **19**, 586 (1930) [*C. A.*, **25**, 3469 (1931)]; see, also, Copisarow, *J. Chem. Soc.*, **119**, 1806 (1921) and Lacourt, *Bull. soc. chim. Belg.*, **38**, 1 (1929) [*C. A.*, **23**, 2431 (1929)].

There was no evidence of rearrangement when the aldehyde was treated with aluminum chloride.

5-Amyl-2-furfural.—From 48 g. (0.5 mole) of furfural, 52.3 g. (0.5 mole) of *n*-amyl chloride, 80 g. (0.6 mole) of aluminum chloride and 500 cc. of carbon disulfide there was obtained, in addition to a 25 g. recovery of furfural, 4.3 g. of 5-amyl-2-furfural; b. p. 95–98° (15 mm.); n^{25}_{D} 1.4870; d^{25}_{25} 0.9204. The semicarbazone of the aldehyde melted at 196°.

Anal. Calcd. for $C_{11}H_{17}O_2N_3$: N, 18.83. Found: N, 18.89.

The aldehyde was oxidized by alkaline silver oxide to 5-amyl-2-furoic acid which resisted crystallization. Accordingly, the acid was converted, through the acid chloride, to the 5-amyl-2-furo-α-naphthalide which melted at 201° and showed no depression in a mixed melting point determination with the naphthalide prepared in like manner from an authentic specimen of 5-amyl-2-furoic acid.[1]

Anal. Calcd. for $C_{20}H_{21}O_2N$: C, 78.18; H, 6.84. Found: C, 77.94; H, 6.96.

The amyl radical in these several derivatives is almost certainly *t*-amyl on the basis of the tendency of all four butyl radicals to give the *t*-butyl derivatives in the Friedel–Crafts reactions with furans.

Anisaldehyde and Isopropyl Chloride.—From 13.6 g. (0.1 mole) of anisaldehyde, 7.8 g. (0.1 mole) of isopropyl chloride, 26.6 g. (0.2 mole) of aluminum chloride and 200 cc. of carbon disulfide there was obtained 4 g. or a 22.4% yield of 3-isopropyl-4-methoxybenzaldehyde: b. p. 146–150° (16 mm.); n^{25}_{D} 1.5491; d^{25}_{25} 1.054.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.16; H, 7.92. Found: C, 74.45; H, 7.69.

In this Friedel–Crafts reaction the mixture was heated until the evolution of hydrogen chloride ceased, and the mixture was then allowed to stand overnight.

The aldehyde (1 g.) was characterized by oxidizing to the corresponding acid by means of silver oxide in sodium carbonate. Purification of the 0.5 g. of acid gave 3-isopropyl-4-methoxybenzoic acid, the identity of which was established by a mixed melting point determination with an authentic specimen.

Benzaldehyde and Isopropyl Chloride.—From 21.2 g. (0.2 mole) of benzaldehyde, 15.6 g. (0.2. mole) of isopropyl chloride, 53.2 g. (0.4 mole) aluminum chloride and 400 cc. carbon disulfide there was obtained 2.2 g. of *m*-isopropylbenzaldehyde; b. p. 95–97° (2 mm.); n^{25}_{D} 1.5370. The reaction was carried out at room temperature, and subsequent to addition the mixture was stirred for twelve hours. Fifteen grams of benzaldehyde was recovered. The semicarbazone of *m*-isopropylbenzaldehyde melted at 172°.

Anal. Calcd. for $C_{11}H_{15}ON_3$: N, 20.49. Found: N, 20.62.

Inasmuch as alkaline silver oxide oxidation gave an oil which resisted crystallization, the oil was oxidized by heating in a sealed tube with 25 cc. dilute nitric acid (2 vols. of water to one of concd. nitric acid) at 170–180° for twenty hours. The white crystalline isophthalic acid was converted, through the acid chloride, to dimethyl isophthalate, which was shown to be identical with an authentic specimen.

The yield of *m*-isopropylbenzaldehyde is not significantly improved by extending the reaction period to seventy-two hours.

Benzaldehyde and *t*-Butyl Chloride.—This reaction was carried out under the conditions of the benzaldehyde–isopropyl chloride experiment. About 10 g. of a resinified material remained in the distilling flask; 35 g. of benzaldehyde was recovered; and 2.8 g. of crude *m*-*t*-butylbenzaldehyde, distilling at 140–150° (13 mm.), was obtained. Alkaline silver oxide oxidation of the aldehyde yielded a gummy crystalline solid, a part of which was crystallized from petroleum ether and then sublimed under reduced pressure to give a crystalline acid melting at 123°. A *m*-butylbenzoic acid obtained by Kelbe and Pfeiffer[3] melts at 127° and has been described as *m*-isobutylbenzoic acid. The remainder of the crude acid was oxidized by nitric acid to give isophthalic acid which was characterized by a mixed melting point determination of its dimethyl ester with an authentic specimen.

Acetylation of Benzene by Means of Stannic Chloride.[4]—Benzene has been used as a solvent in acylation reactions of thiophene[5] and furan.[6] In view of the other studies described in this report it appeared reasonable to expect that benzene might be acetylated to a small extent by means of acetic anhydride and stannic chloride. A mixture of 25 cc. of benzene, 10.2 g. (0.1 mole) of acetic anhydride and 52 g. (0.2 mole) of stannic chloride was heated at 60° for eight days. One gram of acetophenone was isolated, and this was characterized by a mixed melting point determination of its semicarbazone with an authentic specimen. It has been reported that benzene does not react with acid chlorides in the presence of stannic chloride.[5]

Acylation of Furans by Means of Various Condensing Agents.[4]—The ready acylation of furan[1,6] suggested experiments with a miscellany of condensing agents. It was found that furan and propionyl chloride reacted to give 2-furyl ethyl ketone when the following condensing agents were used: (1) zinc, (2) tin, (3) titanium tetrachloride and (4) mercuric chloride. Under corresponding conditions no ketone was obtained from furan with propionyl chloride and furan with propionic anhydride, no condensing agent being used in either case. It is interesting to note that Wertyporoch[7] observed no *alkylation* of benzene when titanium tetrachloride, mercuric chloride and stannic chloride were used.

From furan, chloroacetyl chloride and aluminum chloride there was obtained a 21% yield of 2-furyl chloromethyl ketone; b. p. 127–129° (27 mm.); n^{25}_{D} 1.5091; n^{25}_{25} 1.340. The compound is a powerful lachrymator and burns the skin without blistering.

Anal. Calcd. for $C_6H_5O_2Cl$: Cl, 24.56. Found: Cl, 24.99.

2,5-Dimethylfuran, acetic anhydride and stannic chloride give 2,5-dimethyl-3-furyl methyl ketone[1] in yields exceeding 50%. It appears that a very general and approximate order of decreasing usefulness of condensing agents in acylations of furans is: stannic chloride, ferric

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[3] Kelbe and Pfeiffer, *Ber.*, **19**, 1723 (1886).

[4] These experiments were carried out by N. O. Calloway.

[5] Stadnikoff and Goldfarb, *Ber.*, **61**, 2341 (1928).

[6] Reichstein, *Helv. Chim. Acta*, **13**, 356 (1930).

[7] Wertyporoch, *Ber.*, **66**, 1232 (1933).

chloride, aluminum chloride and titanium chloride. In alkylations of furans the order appears to be: aluminum chloride, ferric chloride and stannic chloride.

Ethyl 5-Bromo-2-furoate and *n*-Amyl Chloride.—A solution of 27 g. (0.123 mole) of ethyl 5-bromo-2-furoate and 13.7 g. (0.123 mole) of *n*-amyl chloride was added dropwise with stirring at room temperature to a suspension of 33.2 g. (0.25 mole) of aluminum chloride in 200 cc. of carbon disulfide. The mixture was stirred for twenty hours and then worked up in the customary manner. There was obtained 16.5 g. of the unchanged ester and 4.5 g. of ethyl 4-*t*-butyl-5-bromo-2-furoate distilling at 152–155° (13 mm.). Hydrolysis of the alkylated bromo ester by alcoholic potash gave 4-*t*-butyl-5-bromo-2-furoic acid, the identity of which was established by the method of mixed melting points. *Neutral equivalent.* Calcd., 246.9; found, 244.5. The 4-*t*-butyl-5-bromo-2-furoic acid when treated with zinc dust and ammonium hydroxide (to replace bromine by hydrogen) gave 4-*t*-butyl-2-furoic acid which was identified by comparison with an authentic specimen.

This Friedel–Crafts reaction was checked and rechecked.

Ethyl 5-Bromo-2-furoate and *n*-Hexyl Bromide.—From 26 g. (0.12 mole) of ethyl 5-bromo-2-furoate, 19.8 g. (0.12 mole) of *n*-hexyl bromide, 33.2 g. (0.25 mole) of aluminum chloride and 250 cc. of carbon disulfide there was obtained 2 g. of crude ethyl 4-*t*-butyl-5-bromo-2-furoate and 9.5 g. of the initial ethyl 5-bromo-2-furoate. Hydrolysis of the alkylated bromo-ester gave 4-*t*-butyl-5-bromo-2-furoic acid which was purified by crystallization from petroleum ether and then by sublimation under reduced pressure. The usual zinc-ammonium hydroxide treatment gave 4-*t*-butyl-2-furoic acid. Mixed melting point determinations were made with both the alkylated bromo-acid and the alkylated acid.

This Friedel–Crafts reaction was checked and rechecked.

Identification of *n*-Amyl Chloride and *n*-Hexyl Bromide.—The unusual results with *n*-amyl chloride and *n*-hexyl bromide warranted identification of these alkyl halides. First, it was shown that the halides used agreed in boiling point, refractive index and density with the values currently accepted. Second, each halide was characterized by an appropriate derivative.

n-Amyl chloride was converted to *n*-amylmagnesium chloride and this Grignard reagent was treated with α-naphthyl isocyanate to give a practically quantitative yield of the *n*-capro-α-naphthalide melting at 94.5–95°. This was shown to be identical with the naphthalide prepared from *n*-caproyl chloride and α-naphthylamine.

Anal. Calcd. for $C_{16}H_{19}ON$: C, 79.67; H, 7.88. Found: C, 79.60 and 79.83; H, 8.01 and 8.19.

In like manner, *n*-hexyl bromide was converted to *n*-hepto-α-naphthalide (melting at 88°) which was identical with the α-naphthalide prepared from *n*-heptoyl chloride and α-naphthylamine.

Anal. Calcd. for $C_{17}H_{21}ON$: C, 80.0; H, 8.23. Found: C, 80.19 and 80.07; H, 8.31 and 8.39.

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Summary

1. In the Friedel–Crafts alkylation of 2-furfural, *n*-, *i*- and *t*-butyl chlorides give 5-*t*-butyl-2-furfural.

2. In the alkylation of 2-furfural with *n*-amyl chloride, the alkyl group is introduced in the 5-position. However, in a corresponding reaction the isopropyl group enters the 4-position.

3. Benzaldehyde can be alkylated, and both the isopropyl and the butyl groups go *meta*.

4. In the alkylation of ethyl 5-bromo-2-furoate the *n*-, *i*- and *t*-butyl halides give ethyl 4-*t*-butyl-5-bromo-2-furoate. The *same* product is obtained when ethyl 5-bromo-2-furoate is alkylated by *n*-amyl chloride, *n*-hexyl bromide and *n*-octadecyl bromide. That is, the higher alkyl groups studied are cleaved and rearranged to give *t*-butyl groups.

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