[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Preparation of Some Substituted β-Phenylisovaleric Acids

BY JOSEPH CORSE[1] AND EWALD ROHRMANN

β-Phenylisovaleric acid was prepared by Hoffman[2] by the haloform oxidation of 4-methyl-4-phenyl-2-pentanone, a substance readily prepared by the reaction of benzene and mesityl oxide with aluminum chloride as catalyst. The acid has also been prepared by the carbonation of neophylmagnesium chloride.[3]

We have carried out the synthesis of a number of substituted β-phenylisovaleric acids which were desired in connection with some antibiotic studies. These were prepared either from the corresponding substituted ketones by haloform oxidation or from the parent unsubstituted β-phenylisovaleric acid.

A number of substituted benzenes were subjected to reaction with mesityl oxide and aluminum chloride. The reaction was found to proceed well with benzene and with fluoro-, chloro- and bromobenzenes. We were unable to effect reaction with anisole and mesitylene, while complex mixtures resulted with toluene, *o*-xylene and tetralin. Eijkman[4] noted a similar failure of toluene to add to β,β-dimethylacrylic acid, in contrast to the behavior of benzene. Reaction of thiophene with mesityl oxide could not be satisfactorily effected with either aluminum chloride or stannic chloride.

Both Eijkman[4] and Hoffman[2] reported the preparation of the nitro derivative of β-phenylisovaleric acid by direct nitration of the acid. We have reduced this nitro acid catalytically to β-(*p*-aminophenyl)-isovaleric acid, which was diazotized and treated in the usual ways to give the *p*-arsono, *p*-arsenoso, *p*-bromo and *p*-hydroxy substituted phenylisovaleric acids. The bromo acid prepared by the Sandmeyer reaction from the amine was identical with that derived from 4-methyl-4-*p*-bromophenyl-2-pentanone and sodium hypochlorite. This indicates that the nitration of phenylisovaleric acid occurs largely in the para position, as one might expect.

β-(*p*-Iodophenyl)-isovaleric acid was made by the direct iodination of β-phenylisovaleric acid.[5]

We wish to thank Mr. W. L. Brown and Mr. H. L. Hunter of these Laboratories for the analyses.

Experimental

4-(*p*-Halophenyl)-4-methyl-2-pentanones.[2]—These were prepared by the aluminum chloride catalyst condensation of the *p*-halobenzene and mesityl oxide in carbon disulfide solution, essentially as described by Hoffman[2] for benzene. The organic layer was separated, dried and distilled *in vacuo*.

4-*p*-Fluorophenyl-4-methyl-2-pentanone.—B. p. 66° (0.1 mm.); $n^{28}D$ 1.4911; yield, 38.0 g. (70%).

Anal. Calcd. for $C_{12}H_{15}OF$: C, 74.19; H, 7.78. Found: C, 74.33; H, 8.03.

4-*p*-Chlorophenyl-4-methyl-2-pentanone.—B. p. 169–171° (16 mm.); $n^{24.5}D$ 1.5228; yield, 102.5 g. (95%).

Anal. Calcd. for $C_{12}H_{15}OCl$: C, 68.40; H, 7.17. Found: C, 68.35; H, 7.58.

4-*p*-Bromophenyl-4-methyl-2-pentanone.—B. p. 128–130° (0.6 mm.); $n^{28}D$ 1.5392; yield, 52 g. (41%).

Anal. Calcd. for $C_{12}H_{15}OBr$: C, 56.48; H, 5.92. Found: C, 56.38; H, 5.85.

Haloform Oxidation of 4(*p*-Halophenyl)-4-methyl-2-pentanones.—The haloform reactions were run with sodium hypochlorite according to the directions of Newman and Holmes[6] to yield the corresponding β-substituted phenylisovaleric acids. The yields varied from 51 to 74% of theoretical.

β-(*p*-Fluorophenyl)-isovaleric acid.—M. p. 60–62°.

Anal. Calcd. for $C_{11}H_{13}O_2F$: C, 67.23; H, 6.67. Found: C, 66.76; H, 6.45.

β-(*p*-Chlorophenyl)-isovaleric acid.—M. p. 65–67°.

Anal. Calcd. for $C_{11}H_{13}O_2Cl$: C, 62.11; H, 6.16. Found: C, 62.24; H, 5.68.

β-(*p*-Bromophenyl)-isovaleric acid.—M. p. 60–61°.

Anal. Calcd. for $C_{11}H_{13}O_2Br$: C, 51.38; H, 5.09. Found: C, 51.66; H, 4.77.

β-(*p*-Iodophenyl)-isovaleric acid.—This acid was prepared by the method of Plati, *et al.* (*cf.* ref. 5(b)). The crude acid was purified by conversion to the ethyl ester which was fractionally distilled. That portion boiling at 145–146° (0.9 mm.) proved to be the desired ester; yield, 34.6 g. (53%), $n^{28}D$ 1.5501.

Anal. Calcd. for $C_{13}H_{17}O_2I$: C, 46.99; H, 5.16. Found: C, 46.51; H, 4.80.

The acid was prepared by saponification with potassium hydroxide; m. p. 76–78°.

Anal. Calcd. for $C_{11}H_{13}O_2I$: C, 43.43; H, 4.31. Found: C, 43.32; H, 4.49.

β-(*p*-Nitrophenyl)-isovaleric Acid.—One hundred and forty grams of β-phenylisovaleric acid was added with stirring, over a period of one hour, to 250 ml. of fuming nitric acid cooled to −30° in a Dry Ice-bath. The temperature was then allowed to rise during another hour to +5°, and stirring was maintained an additional two hours at 0 to 5°. The solution was poured onto cracked ice and the product was collected on a filter and washed well with water. The product was recrystallized from alcohol–benzene; m. p. 172–175°.

Anal. Calcd. for $C_{11}H_{13}O_4N$: N, 6.28. Found: N, 6.63.

β-(*p*-Aminophenyl)-isovaleric acid.—Catalytic reduction of the above nitro acid in methanol solution on the Adams machine, using Raney nickel catalyst or platinum oxide at 3 atmospheres pressure, gave the *p*-amino substituted acid in almost quantitative yield. After being twice recrystallized from methanol–ether the melting point was 135°.

Anal. Calcd. for $C_{11}H_{15}O_2N$: N, 7.24. Found: N, 7.31.

(1) Present address: University of California at Los Angeles, California.

(2) Hoffman, THIS JOURNAL, **51**, 2542 (1929).

(3) Whitmore, *et al.*, *ibid.*, **65**, 1469 (1943).

(4) Eijkman, *Chem. Weekblad.*, **5**, 655 (1909); *C. A.*, **3**, 779 (1909); *Chem. Zentr.*, **79**, II, 1100 (1908).

(5) (a) Varma and Panickar, *J. Indian Chem. Soc.*, **7**, 503 (1930); *C. A.*, **24**, 5740 (1930); (b) Plati, Strain and Warren, THIS JOURNAL, **65**, 1273 (1943).

(6) "Organic Syntheses," Collective Vol. II, John Wiley and Sons, New York, N. Y., 1943, p. 428.

β-(*p*-Arsonophenyl)-isovaleric acid.—This acid was prepared from β-(*p*-aminophenyl)-isovaleric acid by the diazonium salt replacement reaction with arsenic trioxide. The crude acid was purified by recrystallization from hot water; yield, 56 g. (75%).

Anal. Calcd. for $C_{11}H_{15}O_5As$: As, 24.85. Found: As, 24.38, 24.35.

β-(*p*-Arsenosophenyl)-isovaleric acid.—Forty grams of the above arsono acid was dissolved in a solution of 100 ml. of concentrated hydrochloric acid and 100 ml. of water. A small crystal of potassium iodide was added, and sulfur dioxide was passed through the solution for four and one-half hours. The solid which formed was collected and dissolved in sodium bicarbonate solution. Careful acidification with 10% hydrochloric acid precipitated the acid, which was collected and washed several times with cold water; yield, 9.2 g. The material was hygroscopic and analyzed for the hydrate.

Anal. Calcd. for $C_{11}H_{15}O_4As$: As, 26.14. Found: As, 26.83, 26.81.

β-(*p*-Hydroxyphenyl)-isovaleric Acid.—This acid was prepared from β-(*p*-aminophenyl)-isovaleric acid by the diazonium salt replacement reaction. Purification was best done by esterifying the crude acid with ethanol and sulfuric acid and taking advantage of the alkali solubility of the ester. Subsequent saponification and recrystallization of the acid from ethanol–ether–petroleum ether gave a white crystalline product melting at 146–148°.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 68.04; H, 7.08.

Summary

The Friedel–Crafts addition of three halogenated benzenes to mesityl oxide to give 4-methyl-4-halogen substituted phenyl-2-pentanones is described.

A number of β-(*p*-substituted phenyl)-isovaleric acids are described.

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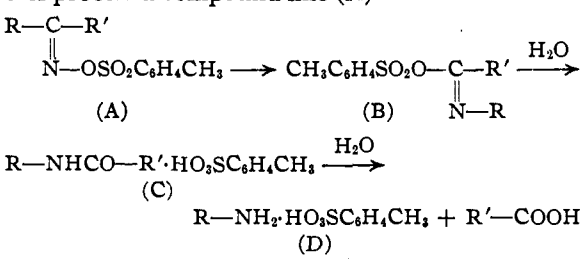
Studies on Furan Compounds. I. Conversion of 2-Acetofuran to Hexen-2-dion-4,5-acetal-1 and Pyrocatechol

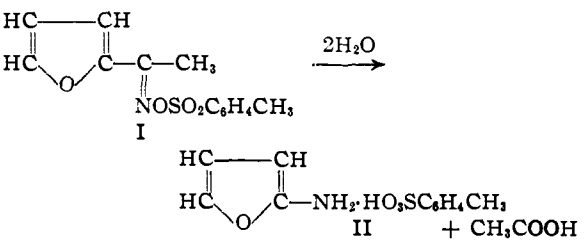
BY L. VARGHA, J. RAMONCZAI AND P. BITE

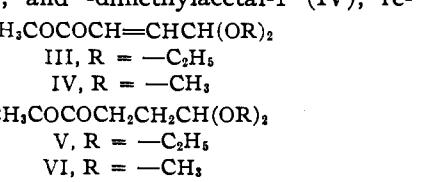
Several workers have already tried to synthesize 2-aminofuran. However, hydrolysis experiments on furan-2-ethylurethan[1] and on 2-benzyl- and 2-propionylaminofuran[2] have only resulted in the formation of ammonia and tar-like products, probably because 2-aminofuran decomposes very rapidly. We have thought that a milder procedure, such as the reaction discovered by Neber and v. Friedolfsheim[3] on the *p*-toluenesulfonyl derivatives of certain aromatic ketoximes (A) might lead to the desired goal. According to this process a compound like (A)



when shaken with ethanol at room temperature, undergoes first a Beckmann rearrangement, then the intermediate (B) suffers hydrolytic cleavage (C) under the influence of traces of water with the eventual formation of an amine (D).[3,4]

However, on shaking *p*-toluenesulfonyl 2-acetofuran oxime (I) with ethanol, not the expected toluenesulfonic acidic salt of 2-aminofuran (II) was obtained. Rather, we isolated, in addition to ammonium *p*-toluenesulfonate, a yellowish-green, strongly reducing liquid, which was free of nitrogen. Although very sensitive to heat, the liquid can be distilled *in vacuo* at constant temperature without being decomposed. The analysis and determination of molecular weight gave the elementary formula $C_{10}H_{16}O_4$ (III). Methanol, instead of ethanol, gave rise to a very similar substance with the formula $C_8H_{12}O_4$ (IV). These substances were found to represent *cis*-hexen-2-dion-4,5-diethylacetal-1 (III), and -dimethylacetal-1 (IV), re-





$CH_3COCOCH{=}CHCH(OR)_2$

III, R = $-C_2H_5$

IV, R = $-CH_3$

$CH_3COCOCH_2CH_2CH(OR)_2$

V, R = $-C_2H_5$

VI, R = $-CH_3$

spectively, as the end-products of the over-all reaction

$$C_6H_6O{-}NOSO_2C_6H_4CH_3 + H_2O + 2ROH = CH_3C_6H_4SO_3(NH_4) + \text{III or IV}$$
(I)

Proof of the structures of III and IV rests on the following experimental facts.

With maleic anhydride no adduct originated[5] from III; therefore, the latter could not possess the furan nucleus. On catalytic hydrogenation

(1) Leimbach, *J. prakt. Chem.*, [2], **65**, 20 (1902).
(2) Singleton and Edwards, THIS JOURNAL, **60**, 540 (1938).
(3) Neber and v. Friedolfsheim, *Ann.*, **449**, 109 (1926).
(4) Neber and Huh, *ibid.*, **515**, 292 (1935).
(5) Alder and Schmidt, *Ber.*, **76**, 18 (1943).