TABLE I

THE COMPOSITION AND PHYSICAL CONSTANTS OF THE ETHYL ESTERS

R =	Yield, %	Boiling point, °C.	Mm.	n^{25}_D	Formula	Composition, % Theoretical Carbon	Theoretical Hydrogen	Found Carbon		Found Hydrogen	
2-Benzoyl-	73.5[a]	180–181	3	1.5330	$C_{18}H_{22}O_3$	75.49	7.74	75.73	75.48	7.50	7.34
2-[2',4'-Dimethylbenzoyl]-	85	193–193.5	3	1.5305	$C_{20}H_{26}O_3$	76.40	8.33	76.37	76.23	8.45	8.45
2-[4'-Methoxybenzoyl]-	80	211–212	3	1.5430	$C_{19}H_{24}O_4$	72.12	7.65	72.06	71.99	7.64	7.44

[a] In every case there was a small fraction which boiled slightly higher but on saponification only the starting acid was recovered.

with four times their weight of a solution of absolute ethanol containing sulfuric acid (15% by weight). The reaction mixtures were poured into water, extracted in ether and after washing the ether extracts with water were dried over anhydrous sodium sulfate. After removal of the solvent the esters were distilled under reduced pressure. The analyses and physical constants for these esters are listed in Table I.

Saponification of the ester adducts with ethanolic potassium hydroxide (10% by weight) gave almost quantitative yields of the original acid adducts and no isomeric products could be detected.

***cis*-2-Benzoyl-4,5-dimethyl-Δ⁴-tetrahydrobenzoic Acid.**—A solution of 14.0 g. of 4,5-dimethyl-Δ⁴-tetrahydrophthalic anhydride (m. p. 78–78.5°) in 300 cc. of sodium-dry benzene was added dropwise over a period of 3 hours to a well-stirred and cooled (7–8°) suspension of 23.0 g. of aluminum chloride in 200 cc. of dry benzene. The reaction mixture was allowed to stand seven days at 10–12° and then decomposed in ice and water containing 50 cc. of concentrated hydrochloric acid. The organic layer was separated, the benzene removed by steam distillation and the residual oil dissolved in sodium bicarbonate solution, decolorized (Norit) and acidified. The resulting solid (m. p. 70–80°) was predominantly 4,5-dimethyl-Δ⁴-tetrahydrophthalic anhydride. The major portion of this unchanged starting material was removed in boiling petroleum ether. Several crystallizations of the residual oil from ether and petroleum ether gave 1.0 g. of the acid, melting at 147–148°. When mixed with the low melting adduct (m. p. 141–142°) it melted at 126–127° with previous softening.

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.61, 74.42; H, 7.17, 6.99.

The above solid was recovered unchanged from the action of a 100% excess of an ethereal solution of diazomethane. The methyl ester (m. p. 108–110°) was obtained by the portionwise addition of methyl sulfate and sodium hydroxide to this product at 80°.

Conversion of the *cis* Ester to the *trans* Acid (m. p. 141–142°).—The methyl ester (0.5 g.) was refluxed with ethanolic sodium ethylate (0.1 g. of sodium and 2.0 cc. of absolute ethanol) for four hours. The reaction mixture, when cold, was diluted with water and acidified. The resulting solid when crystallized from ether–petroleum ether mixture gave 0.1 g. of cubic crystals, which melted alone or on admixture with *trans*-2-benzoyl-4,5-dimethyl-Δ⁴-tetrahydrobenzoic acid at 139–141°.

Acknowledgments.—We wish to acknowledge our indebtedness to Professor L. F. Fieser for the use of his analytical samples which made a direct comparison with our products possible.

Summary

An examination of the isomeric adducts resulting from the reaction of β-benzoylacrylic acid with 2,3-dimethylbutadiene has revealed that the isomer melting at 141–142° is *trans*-2-benzoyl-4,5-dimethyl-Δ⁴-tetrahydrobenzoic acid. The *cis* isomer (m. p. 147–148°) has been prepared and isomerized, through its methyl ester, to the *trans* form (m. p. 141–142°). The isomer, melting at 189°, probably results from the migration of the double bond from the normal position in the adduct to one of conjugation with some other center of unsaturation.

SASKATOON, SASKATCHEWAN RECEIVED MARCH 21, 1947

2-Hydroxyacetylfuran

BY FRANK KIPNIS, HAROLD SOLOWAY AND JOHN ORNFELT

The preparation of 5-nitro-2-hydroxyacetylfuran has been reported by Stillman and Scott.[1] During work in progress at this Laboratory, we have been interested in the preparation of furan ketols, and, in view of the appearance of the above patent, we wish to announce the synthesis of 2-hydroxyacetylfuran and the furoic acid ester thereof.

Diazoacetylfuran has been prepared[2] by the interaction of furoyl chloride with diazomethane. On treatment of the diazoketone with 2 *N* sulfuric acid, nitrogen was evolved, and, by working up the mixture in the usual manner, hydroxyacetylfuran was obtained in good yield. When the diazoketone was heated with furoic acid in benzene, 2-furoyloxyacetylfuran was produced.

Experimental

2-Hydroxyacetylfuran.—Ten and one-half grams (0.077 mole) of diazoacetylfuran[2] was mixed with 150 ml. of 2 *N* sulfuric acid and 60 ml. of dioxane. A vigorous evolution of nitrogen occurred, and the temperature rose spontaneously to 45°. The mixture was stirred and maintained at that temperature (water-bath) for four hours, at the end of which time the temperature was allowed to drop to 25°. After neutralization with solid potassium carbonate, the solution was filtered and distilled from the steam-bath at reduced pressure, removing all of the dioxane and some of the water. The residue was cooled, salted with sodium chloride and extracted six times with 30 ml. of ether. The solvent layer was dried with calcium sulfate, filtered and stripped, finally under reduced pressure, leaving a crystalline residue. This material was recrystallized three times

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[1] Stillman and Scott, U. S. Patent 2,416,235 (February 18, 1947).

[2] Burger and Harnest, THIS JOURNAL, 65, 2382 (1943); Burger, U. S. Patent 2,400,913 (May 28, 1946).

from hexane to give 7.2 g. (74% yield) of material melting at 81–82°.[3] Fehling solution was reduced by the ketol.

Anal.[4] Calcd. for $C_6H_6O_3$: C, 57.14; H, 4.80. Found: C, 57.23; H, 4.88.

2-Furoyloxyacetylfuran.—Eleven grams (0.081 mole) of diazoacetylfuran was refluxed for four hours with 11 g. (0.099 mole) of furoic acid in 40 ml. of anhydrous, thiophene-free benzene. The solvent was removed under reduced pressure, and the crystalline residue was triturated with saturated sodium bicarbonate solution, and then with water, and finally recrystallized from aqueous methanol (Darco) and then from much hexane to give 8.1 g. (50% yield) of a product melting at 95°.

Anal. Calcd. for $C_{11}H_8O_5$: C, 59.73; H, 3.85. Found: C, 60.00; H, 3.66.

Summary

2-Hydroxyacetylfuran and 2-furoyloxyacetylfuran have been prepared by the interaction of 2-diazoacetylfuran with dilute sulfuric acid and furoic acid, respectively.

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RECEIVED AUGUST 12, 1947

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[3] Melting points taken with Fisher–Johns apparatus.

[4] Analyses by Oakwold Laboratories, Alexandria, Virginia.

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Aliphatic Ketones and Amines Containing the Trifluoromethyl Group

BY REUBEN G. JONES

It is well known that the introduction of fluorine atoms into aliphatic molecules has a profound effect upon the physical and chemical properties. In order to ascertain the effect of fluorine on the pharmacological properties of typical aliphatic compounds, it was of particular interest to prepare some ketones, amines, and alcohols containing the trifluoromethyl group. The compounds reported at this time were derived from trifluoroacetic acid.

Two methods were examined for the preparation of trifluoromethyl benzyl ketone. Trifluoroacetonitrile was allowed to react with benzylmagnesium chloride to produce the desired ketone in 38% yield.

$$CF_3CN + C_6H_5CH_2MgCl \xrightarrow{H_2O} CF_3COCH_2C_6H_5$$

The more convenient reaction of trifluoroacetyl chloride with benzyl zinc chloride gave a 54% yield of the ketone.

$$CF_3COCl + C_6H_5CH_2ZnCl \longrightarrow CF_3COCH_2C_6H_5$$

Both methods would appear to be quite generally applicable to the preparation of trifluoromethyl ketones. Trifluoromethyl phenyl ketone (trifluoroacetophenone[1]) was obtained readily in a yield of 61% by the reaction of trifluoroacetyl chloride with diphenylcadmium.

The pharmacology of these trifluoromethyl compounds will be reported elsewhere. However, it is of interest to note at this time that the acute toxicities were relatively low.

Experimental

Trifluoromethyl Benzyl Ketone.—A. Trifluoroacetonitrile was prepared from 56 g. (0.5 mole) of trifluoroacetamide by the method of Gilman and Jones.[2] The gaseous nitrile was led from the generating flask through glass tubing and introduced below the surface of a stirred solution of benzylmagnesium chloride prepared from 80 g. (0.63 mole) of benzyl chloride and 17 g. of magnesium in a total of 300 ml. of dry ether. When the reaction was complete, the brown ether solution was poured into a mixture of 150 g. of ice and 100 ml. of concentrated hydrochloric acid. The ether layer was separated, washed with water and dilute sodium bicarbonate solution and dried over magnesium sulfate. After evaporation of the ether the residual liquid was distilled through an eighteen-inch packed column under reduced pressure, and 36 g. (38.4% yield) of trifluoromethyl benzyl ketone was obtained as a colorless liquid; b. p. 73–73.5° (20 mm.), 163–163.5° (741 mm.): $n^{25}D$ 1.4625.

Anal. Calcd. for $C_9H_7F_3O$: C, 57.45; H, 3.75. Found: C, 57.05; H, 3.92.

B. Trifluoroacetyl chloride was prepared by the method of Tinker[3] from 57 g. (0.5 mole) of trifluoroacetic acid and 200 ml. of benzoyl chloride. The gaseous trifluoroacetyl chloride was led through a glass tube into a reaction flask containing benzylzinc chloride which was made by adding slowly, with the exclusion of air, 800 ml. of ether solution containing 1.0 mole of benzylmagnesium chloride to 136 g. (1.0 mole) of freshly fused, powdered zinc chloride. The reaction flask was provided with a Dry Ice condenser and the mixture was rapidly stirred. After several hours, the mixture was decomposed with ice and dilute hydrochloric acid. The ether layer was separated, the aqueous layer was washed with three 100-ml. portions of ether, and the combined ether solution was dried over magnesium sulfate. The ether was removed by distillation through a small packed column. From the mid fractions, distilling between 36 and 105°, was obtained 8 g. (14%) of trifluoroacetic acid (isolated as the ammonium salt), and 51 g. (54.3% yield) of trifluoromethyl benzyl ketone was collected at 160–165° (740 mm.); $n^{25}D$ 1.4621.

Trifluoromethylbenzylcarbinol.—A solution of 23.5 g. (0.125 mole) of trifluoromethyl benzyl ketone in 50 ml. of anhydrous ether with 5 g. of 5% palladium–charcoal catalyst was hydrogenated under 60 lb. pressure. The theoretical quantity of hydrogen was taken up in about twenty minutes with evolution of heat. The solution was filtered and distilled to yield 23.0 g. (98%) of trifluoromethylbenzylcarbinol; b. p. 204–204.5° (740 mm.); $n^{25}D$ 1.4678.

Anal. Calcd. for $C_9H_9F_3O$: C, 56.84; H, 4.75. Found: C, 56.74; H, 4.76.

Trifluoromethyl Benzyl Ketoxime.—A solution of 23.5 g. (0.125 mole) of trifluoromethyl benzyl ketone in 100 ml. of methanol was treated with 28 g. (0.4 mole) of powdered hydroxylamine hydrochloride followed by 30

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[1] Simons and Ramler, THIS JOURNAL, **65**, 389 (1943).

[2] Gilman and Jones, *ibid.*, **65**, 1458 (1943); Swarts, *Bull. sci. acad. roy. Belg.*, **8**, 343 (1922) [*C. A.*, **17**, 769 (1923)].

[3] Tinker, U. S. Patent 2,257,868, Oct. 7, 1941; [*C. A.*, **36**, 495 (1942)].