Trifluoromethylfurans II

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Ethyl acetoacetate reacted with 3-bromo-1,1,1-trifluoro-2-propanone in the presence of base to give 3-carbethoxy-4,5-dihydro-4-hydroxy-2-methyl-4-trifluoromethylfuran (I). Acid catalyzed dehydration of I gave the corresponding furan (III). Saponification of III gave 2-methyl-4-trifluoromethyl-3-furoic acid which was decarboxylated to yield 2-methyl-4-trifluoromethylfuran (V) for which a structure proof is presented. Conversion of the methyl groups of III and V to formyl groups is described.

In a previous paper (1) the preparation of some 5-trifluoromethylfuran derivatives was described. This report discusses the synthesis of several 4-trifluoromethylfurans.

Addition of one equivalent of sodium ethoxide to a benzene solution of ethyl acetoacetate and 3-bromo-1,1,1-trifluoro-2-propanone gave a product (I) which was readily dehydrated under acidic conditions to give an ester, III. On saponification and decarboxylation of III a compound (V) was obtained which analyzed as a methyltrifluoromethylfuran. If the initial reaction to produce I was similar to previously reported (1,2) condensations of α-halopropanones with ethyl acetoacetate using strong base, the product, V, should have been 2-methyl-5-trifluoromethylfuran. However, comparison of the infrared and NMR spectra of V with spectra obtained from an authentic sample of 2-methyl-5-trifluoromethylfuran (1) indicated that the compounds were not the same. Examination of the NMR of V showed, in addition to the signal from the methyl group at δ 2.24, one-proton singlets at δ 6.12 and δ 7.55, a pattern which suggested that V was a 2,4-disubstituted furan. This type of product is typical of those isolated from the Feist-Benary synthesis (3) and other closely related condensations in which α-haloketoesters are condensed with β-ketoesters (4). In order to definitely establish the structure of V it was condensed with diethyl acetylenedicarboxylate to give the Diels-Alder adduct, VI. The adduct was hydrogenated over palladium on charcoal and then heated at 180°, effecting a retrograde Diels-Alder reaction. Comparison of the product with an authentic sample of diethyl 2-methylfuran-3,4-dicarboxylate (5) showed them to be identical. The formation of this compound established the structure of V as 2-methyl-4-trifluoromethylfuran.

Comparison of the NMR of V with the NMR of the acid (IV) from which it was formed showed that when the carboxyl group was present the signal due to the upfield proton on the three position of the furan ring disappeared. This observation established the structure of IV and its ethyl ester (III) as 2-methyl-4-trifluoromethyl-3-furoic acid and ethyl 2-methyl-4-trifluoromethyl-3-furoate, respectively.

These findings left only the structure of the initial condensation product, I, to be established. Dunlop and Hurd (4) were the first to question the postulate that

CHART I

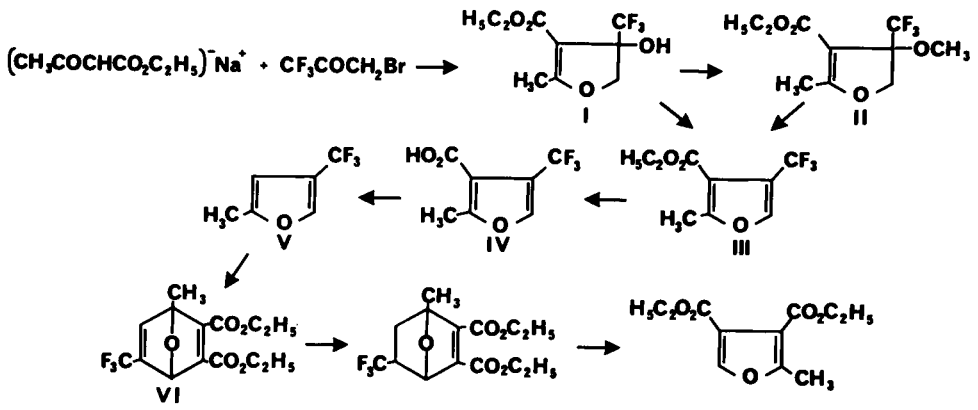
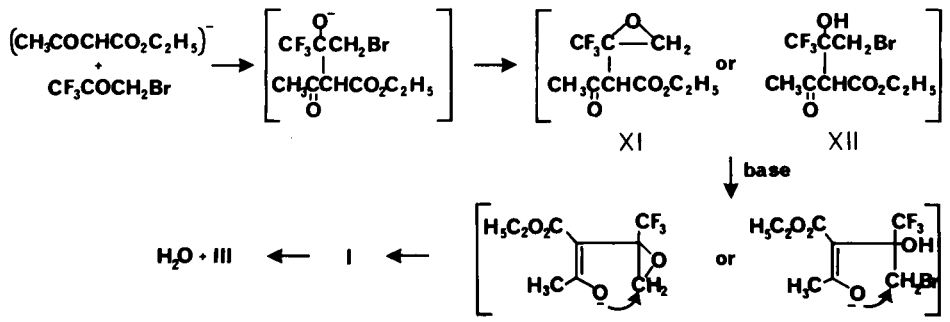


CHART II



O-alkylation was the initial step in the Feist-Benary synthesis and related reactions of α-haloketoesters with β-ketoesters. They felt that an aldol-type condensation was the initial step, giving a product which subsequently cyclized and dehydrated to give the furan. This hypothesis has been substantiated in part by the work of Cantlon, Cocker and McMurry (7) who studied the reaction of ethyl bromopyruvate with ethyl sodio-oxaloacetate and the bromination of ethyl sodio-oxaloacetate. They were able to identify the initial products from these reactions as triethyl 4,5-dihydro-4-hydroxy-2,3,4-furantricarboxylate and tetraethyl 4,5-dihydro-4-hydroxy-2,3,4,5-furantetracarboxylate, respectively. Dunlop and Hurd (4) had earlier suggested the same structures for these products. They had also suggested the epoxides, which would result if a Darzens-type reaction had occurred, as alternate possibilities for the products. Based on these considerations a reasonable sequence can be drawn for the formation of III (Chart II).

Analytical and spectral data eliminated the epoxide (XI) and the halohydrin (XII) as possibilities for the structure of I. The hydroxy dihydro-furan structure, however, fit the data quite well. The NMR spectrum of I in dimethylsulfoxide-d_6 exhibited a broad singlet at δ 6.16 and addition of deuterium oxide indicated that the proton was readily exchangeable. The signals from the two ring protons at position five appeared as an AB quartet centered at δ 4.43. The methyl group and the ethyl fragment of the ester group gave the expected signals.

Attempts to acetylate or benzoylate I met with little success; mild conditions gave no reaction and more vigorous conditions led to dehydration. However, it was possible to obtain the methyl ether (II) in 54% yield by treatment of I with methyl iodide and barium hydroxide in dimethylformamide (6). The NMR spectrum of II exhibited the expected peaks with the ring protons at position five appearing as a singlet at δ 4.53. Treatment of II with acid caused the loss of methanol and gave the furan, III.

Table I lists the infrared data obtained with compounds I and II.

TABLE I (1)

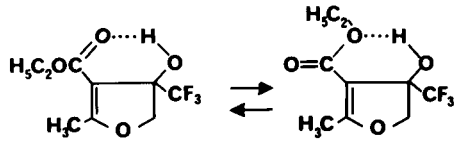
Compound	Solvent (2)	ν, C=O, μ	ν, OH, μ
I	none	5.9 (b)	2.9 (b)
	CCl_4 (3)	5.80	2.86
		5.90	2.92
	THF	5.85	3.05 (b)
		5.95 (w,s)	
	CH_3CN	5.85	2.95 (b)
		5.93 (w,s)	
II	CCl_4	5.85	
	THF	5.85	

(1) b=broad, w=weak, s=shoulder. (2) Spectra were determined at a concentration of 5-10 mg./ml. in a 1.0 mm. cell except where noted. (3) Determined over a concentration range of 3.0-50.0 mg./ml.

The spectrum obtained from I (neat) showed a broad, hydrogen bonded, O-H stretching band at 2.9 μ and a broad ester carbonyl absorption, also hydrogen bonded, at 5.9 μ. These bands are typical for intermolecularly hydrogen bonded groups (8). However, when the spectrum of I was determined in carbon tetrachloride solution, carbonyl absorption bands at 5.80 μ and 5.90 μ and hydroxyl absorption bands at 2.86 μ and 2.92 μ were observed. The positions and relative intensities of these bands were independent of concentration (3 to 50 mg./ml.) which suggested the presence of two hydrogen bonded conformations in carbon tetrachloride. In order to determine the position of the non-bonded ester carbonyl absorption of I its spectrum was determined in tetrahydrofuran (THF) and acetonitrile. Both of these solvents contain excellent hydrogen bond acceptor groups which could be expected to successfully compete with the ester group for the alcohol proton. The spectra determined in these solvents showed sharp non-bonded carbonyl absorption bands at 5.85 μ with weak, bonded bands at 5.95 μ.

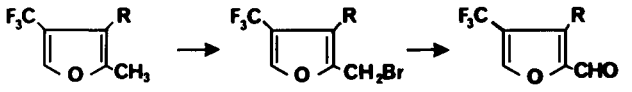
The hydroxyl bands at 3.05 μ (THF) and 2.95 μ (CH_3CN) were quite broad, indicative of strong intermolecular bonding with the solvent. The assignment of 5.85 μ to a non-bonded absorption band for the ester carbonyl agreed well with the position of the ester carbonyl absorption band (5.85 μ) obtained when the hydroxyl group of I was replaced by a methoxy group, as in compound II. Therefore, with compound I in carbon tetrachloride two intramolecularly hydrogen bonded conformations were observed; one in which the carbonyl band was shifted to a longer wave length (5.90 μ) and one where there was a shift to a shorter wave length (5.80 μ).

Hydrogen bonding to the carbonyl oxygen of an ester is well known to cause a shift of the carbonyl absorption band to longer wave lengths (8). A shift of an ester carbonyl absorption band to shorter wave lengths has only been observed in a few cases. Henbest and Lovell (9) were the first to observe this effect and ascribed it to hydrogen bonding to the "ether" oxygen of the ester function. This effect has been observed by two other groups (10). Thus, the two conformations of I present in carbon tetrachloride are probably:



This appears to be the first example of a conformational equilibrium of this type.

Because of our previously described (1) interest in trifluoromethylfurfural derivatives, compounds III and V were converted to aldehydes. Bromination of III and V with *N*-bromosuccinimide gave the bromomethyl derivatives in 67% and 78% yield, respectively. Treatment of the bromo compounds with sodium 2-propane nitronate according to the method of Hass and Bender (11) gave the desired aldehydes, IX and X.



III R = $CO_2C_2H_5$ VII R = $CO_2C_2H_5$ IX R = $CO_2C_2H_5$
V R = H VIII R = H X R = H

The semicarbazone of X was tested as an anticoccidial agent and found to be devoid of activity. An isomer of this compound, 5-trifluoromethyl-2-furfural semicarbazone, had previously shown this type of activity (1). Therefore, the trifluoromethyl group must be in the five position for biological activity, which is also the case with the corresponding nitrofurans (12).

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. The infrared spectra, unless indicated otherwise, were determined with a Beckman IR-5 infrared spectrophotometer as thin liquid films or potassium bromide pellets. GLC analyses were done with an F & M model 500 gas chromatograph equipped with a 1609 flame ionization detector using a column ¼ in. in diameter by 48 in. long packed with 5% SE-30 on Anakrom ABS. NMR spectra were recorded with a Varian A-60 spectrometer using TMS as an internal standard. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan or Galbraith Laboratories, Knoxville, Tennessee.

3-Carbethoxy-4,5-dihydro-4-hydroxy-2-methyl-4-trifluoromethylfuran (I).

Sodium (15.8 g., 0.688 mole) dissolved in 300 ml. of absolute ethanol was slowly added with stirring to a solution of 89.5 g. (0.688 mole) of ethyl acetoacetate, 131.5 g. (0.688 mole) of 3-bromo-1,1,1-trifluoro-2-propanone (13) in 350 ml. of benzene. The temperature of the reaction mixture was maintained below 10° throughout the 4 hour addition period. Next, 700 ml. of water was added and the benzene phase separated. The aqueous phase was extracted twice with ether; organic phases were then combined, dried over magnesium sulfate and the solvent evaporated. The residual oil was fractionated with a 20 cm. column packed with glass helices to give 107 g. (65% yield) of product (b.p. 48-50° at 0.06 mm.). A center cut (pure by GLC) was sent for analysis. Infrared, ν max (neat), 5.9 μ broad (C=O); 2.91 μ (OH); 8.1-8.8 μ broad (CF_3). NMR (DMSO-d_6), δ 1.23 (3H, triplet, J=7cps, CH_3CH_2O-); δ 2.25 (3H, singlet, methyl group 2 pos.); δ 4.15 (2H, quartet, J=7cps, CH_3CH_2O-); δ 4.45 (2H, AB quartet, ring protons 5 pos., overlaps with quartet at δ 4.15); δ 6.16 (1H, broad singlet, exchangeable with deuterium oxide, OH).

Anal. Calcd. for $C_9H_{11}F_3O_4$: C, 45.00; H, 4.62; F, 23.75. Found: C, 44.89; H, 4.63; F, 23.81.

3-Carbethoxy-4,5-dihydro-4-methoxy-2-methyl-4-trifluoromethylfuran (II).

A mixture of 2.0 g. (0.008 mole) of I, 15 ml. of methyl iodide, 15 g. of barium oxide, 40 ml. of dimethylformamide and 0.2 ml. of water was stirred for 2 hours. The mixture was then poured into 200 ml. of water and the resulting mixture was extracted twice with ether. The extracts were combined, dried over magnesium sulfate and evaporated to give 2.2 g. of crude oil. The crude oil was purified by preparative GLC using an F & M model 776 Prepmaster Junior. A column 3/4 in. in diameter by 80 in. long packed with 20% UCW-98 silicone rubber on Chromosorb P was used. The compound had a retention time of 4.5 minutes using a carrier gas (N_2) flow rate of 0.52 lpm. at 150°. A 54% yield (1.1 g.) of the ether was obtained. Rechromatography under the same conditions gave an analytical sample. Infrared, ν max (neat), 5.86 μ (C=O); 6.13 μ (C=C). NMR (deuteriochloroform), δ 1.33 (3H, triplet, J=7cps, CH_3CH_2O-); δ 2.39 (3H, singlet, methyl group 2 pos.); δ 3.32 (3H, singlet, -OCH_3); δ 4.30 (2H, quartet, J=7cps, CH_3CH_2O-), δ 4.52 (2H, singlet, ring protons 5 pos., overlaps with quartet at δ 4.30).

Anal. Calcd. for $C_{10}H_{13}F_3O_4$: C, 47.25; H, 5.15; F, 22.42. Found: C, 47.09; H, 5.23; F, 22.63.

Treatment of II with Acid.

A 1 g. sample of II was warmed on the steam bath for 30 minutes with a few crystals of *p*-toluenesulfonic acid. The mixture

was neutralized with aqueous sodium bicarbonate and extracted with ether. The ether extract was dried over magnesium sulfate, filtered and evaporated to give a colorless oil. The infrared spectrum and GLC retention time of the oil showed it to be ethyl 2-methyl-4-trifluoromethyl-3-furoate (III), described below.

Ethyl 2-Methyl-4-trifluoromethyl-3-furoate (III).

The dihydrofuran, I (80.0 g., 0.33 mole), was heated on a steam bath, under a slight vacuum, with 1.3 g. of *p*-toluenesulfonic acid. After one hour an additional 1.3 g. of *p*-toluenesulfonic acid was added and the heating was continued until GLC analysis indicated that the starting material was gone (approximately 30 minutes). Water (50 ml.) was added, the mixture neutralized with excess sodium bicarbonate and extracted with ether. The ether extracts were dried over magnesium sulfate and evaporated to give 72.0 g. of oil (95% pure by GLC). An analytical sample (b.p. 60°) was prepared by fractionating the material at 5 mm. using a 10 cm. column packed with Raschig rings. Infrared, ν max (neat), 5.8 μ (C=O); 6.35 μ (ring stretching); 8.4-8.9 μ (CF_3). NMR (deuteriochloroform), δ 1.36 (3H, triplet, J=7cps, CH_3CH_2O-); δ 2.59 (3H, singlet, methyl group 2 pos.); δ 4.33 (2H, quartet, J=7cps, CH_3CH_2O-); δ 7.69 (1H, singlet, ring proton 5 pos.).

Anal. Calcd. for $C_9H_9F_3O_3$: C, 48.65; H, 4.08; F, 25.65. Found: C, 48.51; H, 4.21; F, 25.56.

2-Methyl-4-trifluoromethyl-3-furoic Acid (IV).

The ester, III (60.0 g., 0.27 mole), was refluxed for 30 minutes with 10.8 g. (0.27 mole) of sodium hydroxide, 140 ml. of water and 425 ml. of ethanol. The mixture was then neutralized with hydrochloric acid and evaporated to one-third of its original volume. The solution was basified with 10% sodium hydroxide and 9 g. of unreacted starting ester was recovered by extraction with ether. The aqueous phase was re-acidified with concentrated hydrochloric acid and extracted with ether. The ether extract was dried over magnesium sulfate and evaporated to give 38.0 g. of crude acid. The unreacted starting material was hydrolyzed in the same fashion to give an additional 6.0 g. of acid to bring the total yield to 80%. Recrystallization of the acid from cyclohexane gave an analytical sample, m.p. 140-141°. Infrared, ν max (potassium bromide), 3.1-4.2 μ broad (OH); 5.95 μ (C=O); 6.35 μ (ring stretching); 8.5-8.9 μ broad (CF_3); NMR (deuteriochloroform), δ 2.69 (3H, singlet, methyl group 2 pos.); δ 7.70 (1H, singlet, ring proton 5 pos.); δ 12.0 (1H, singlet, -COO*H*).

Anal. Calcd. for $C_7H_5F_3O_3$: C, 43.29; H, 2.59; F, 29.35. Found: C, 43.13; H, 2.63; F, 29.50.

2-Methyl-4-trifluoromethylfuran (V).

The acid, IV (49.5 g., 0.255 mole), 35 ml. of quinoline and 2 g. of anhydrous cupric sulfate were placed in a flask equipped with a 10 cm. column, packed with glass helices, and an efficient condenser. The flask was heated at 230° with a Meeker burner and swept with a slow stream of nitrogen until all low boiling material had distilled. The distillate (34.3 g.) was dried over sodium sulfate and redistilled using a 10 cm. Vigreaux column to give 28.5 g. (75% yield) of pure furan, b.p. 84-85°. Infrared, ν max (neat), 6.37 μ (ring stretching); 8.4-9.1 μ broad (CF_3); NMR (deuteriochloroform), δ 2.24 (3H, singlet, methyl group 2 pos.); δ 6.12 (1H, singlet, ring proton 4 pos.); δ 7.55 (1H, singlet, ring proton 2 pos.).

Anal. Calcd. for $C_6H_5F_3O$: C, 47.97; H, 3.35; F, 37.95. Found: C, 47.78; H, 3.16; F, 37.83.

2,3-Dicarbethoxy-4-methyl-6-trifluoromethyl-7-oxabicyclo[2.2.1]-hepta-2,5-diene (VI).

A mixture of 10.6 g. (0.070 mole) of V and 12.0 g. (0.071 mole) of diethyl acetylenedicarboxylate was heated for 5.5 hours. The temperature of the heating bath was raised gradually from 125 to 160° during the heating period. The reaction mixture was fractionated at 0.1 mm. using a 10 cm. Vigreaux column. Material boiling from 75 to 85° was collected to give 15.9 g. (70% yield) of product. A center cut from the distillation, b.p. 82.5-84°, was submitted for analysis. Infrared, ν max (neat), 5.8 μ (C=O); 6.1 μ (C=C); 8.5-9.0 μ broad (CF_3). NMR (deuteriochloroform), δ 1.30 and δ 1.35 (6H, two overlapping triplets, CH_3CH_2O-); δ 1.92 (3H, singlet, methyl group 4 pos.); δ 4.28 and δ 4.38 (4H, two overlapping quartets, CH_3CH_2O-); δ 5.76 (1H, singlet, ring proton 1 pos.); δ 7.45 (1H, quartet, J=2.5cps, ring proton 5 pos.).

Anal. Calcd. for $C_{14}H_{15}F_3O_5$: C, 52.50; H, 4.72; F, 17.80. Found: C, 52.54; H, 4.88; F, 17.56.

Hydrogenation and Thermal Decomposition of VI.

A mixture of 9.6 g. (0.03 mole) of VI, 25 ml. of ethyl acetate and 0.1 g. of 10% palladium on charcoal was stirred under one atmosphere of hydrogen at room temperature. Within one hour the calculated amount of hydrogen was absorbed. The mixture was filtered and the solvent evaporated. The residual oil was heated at 180° for 15 minutes in an open flask and then fractionated at 5 mm. using a 4 cm. Vigreaux column. The material boiling at 129-131°, n^{25} 1.4683 (3.6 g., 55% yield), was collected and found to be pure by GLC analysis. The index of refraction, GLC retention time, and infrared spectrum of the material were identical with those of an authentic sample of diethyl 2-methylfuran-3,4-dicarboxylate prepared by the method of Alder and Rickert (5).

Ethyl 2-Bromomethyl-4-trifluoromethyl-3-furoate (VII).

A mixture of 103.1 g. (0.464 mole) of III, 82.6 g. (0.464 mole) of *N*-bromosuccinimide and 650 ml. of carbon tetrachloride was heated to reflux and the reaction initiated with a 275 watt sun lamp. The lamp was removed and the heating maintained until the refluxing mixture became colorless. After cooling, the mixture was filtered to remove the succinimide and the solvent distilled under reduced pressure using a 15 cm. Vigreaux column. The residual oil was fractionated at 0.05 mm. using a 20 cm. column packed with Raschig rings, to give 109.0 g. (78% yield) of product, b.p. 70°. A center cut (pure by GLC) was submitted for analysis. Infrared, ν max (neat), 5.8 μ (C=O); 6.38 μ (ring stretching); 8.3-9.0 μ (CF_3); NMR (deuteriochloroform), δ 1.49 (3H, triplet, J=7cps, CH_3CH_2O-); δ 4.40 (2H, quartet, J=7cps, CH_3CH_2O-); δ 4.83 (2H, singlet, -CH_2Br); δ 7.84 (1H, singlet, ring proton 5 pos.).

Anal. Calcd. for $C_9H_8BrF_3O_3$: C, 35.89; H, 2.68; Br, 26.54; F, 18.93. Found: C, 36.01; H, 2.80; Br, 26.43; F, 18.80.

2-Bromomethyl-4-trifluoromethylfuran (VIII).

Using the same procedure as outlined for the preparation of VII, 28.6 g. (0.19 mole) of 2-methyl-4-trifluoromethylfuran was converted to 29.2 g. (67% yield) of the bromo compound, b.p. 82.5-84° at 0.1 mm. A center cut from the fractionation was taken for analysis. Infrared, ν max (neat), 6.43 μ (ring stretching); 8.4-9.1 μ (CF_3). NMR (deuteriochloroform), δ 4.47 (2H, singlet, -CH_2Br); δ 6.58 (1H, singlet, ring proton 3 pos.); δ 7.78 (1H, singlet, ring proton 5 pos.).

Anal. Calcd. for $C_6H_4BrF_3O$: C, 31.47; H, 1.76; Br, 34.90; F, 24.89. Found: C, 31.58; H, 1.90; Br, 34.80; F, 25.00.

3-Carbethoxy-4-trifluoromethyl-2-furfural (IX).

A solution containing 7.4 g. (0.323 mole) of sodium and 36.5 g. of 2-nitropropane in 450 ml. of absolute ethanol was slowly added to a stirred solution of 97.4 g. (0.323 mole) of VII in 50 ml.

of absolute ethanol. The temperature of the reaction mixture was maintained at 50° during the three hour addition period and for one hour thereafter. One liter of water was added and the mixture extracted three times with ether. The extracts were combined, dried over magnesium sulfate, decolorized with charcoal and evaporated. The residual oil was dissolved in ether, washed with 1% sodium hydroxide solution and then water. After drying over magnesium sulfate the ether was evaporated. The residual oil was fractionated at 0.045 mm. using a 10 cm. column packed with glass helices to give 35 g. (45% yield) of aldehyde, b.p. 95-100°. An analytical sample (m.p. 55-56.5°) was prepared by recrystallizing the aldehyde from hexane. **Infrared,** ν max (potassium bromide), 5.82 μ ($CO_2C_2H_5$); 5.95 μ (CHO); 6.46 μ (ring stretching); 8.5-8.9 μ (CF_3); NMR (deuteriochloroform), δ 1.44 (3H, triplet, J=7cps, CH_3CH_2O-); δ 4.50 (2H, quartet, J=7cps, CH_3CH_2O-); δ 8.06 (1H, singlet, ring proton 5 pos.); δ 10.3 (1H, singlet, -CHO).

Anal. Calcd. for $C_9H_7F_3O_4$: C, 45.77; H, 2.99; F, 24.14. Found: C, 45.72; H, 2.85; F, 24.51.

A semicarbazone was prepared from IX in the usual fashion and recrystallized from ethanol to give material, m.p. 243-246°;

Anal. Calcd. for $C_{10}H_{10}F_3N_3O_4$: C, 40.96; H, 3.44; F, 19.44; N, 14.33. Found: C, 41.15; H, 3.40; F, 19.34; N, 14.20.

4-Trifluoromethyl-2-furfural (X).

To a cooled solution of sodium ethoxide prepared from 5.86 g. (0.255 g.-atom) of sodium and 450 ml. of absolute ethanol was added 28.0 g. of 2-nitropropane. The resulting solution was added slowly to a well stirred solution of 58.3 g. (0.255 mole) of VIII and 50 ml. of absolute ethanol maintained at 55°. Addition required 3.5 hours and the heating was continued for an additional hour. After adding 1.2 l. of water, the mixture was extracted three times with ether. The ether was evaporated and a sodium bisulfite complex was prepared by treating the residual oil with excess aqueous sodium bisulfite. The complex was collected by filtration, washed with ether and then decomposed with aqueous sodium bicarbonate. Continuous extraction of the aqueous bicarbonate solution with ether for four days yielded 14 g. (34%) of aldehyde. An analytical sample, b.p. 37-38° at 19 mm., was prepared by distillation of the aldehyde using a short path distillation apparatus. **Infrared,** ν max (neat), 3.55 μ (CHO); 5.91 μ (CHO); 6.22 μ and 6.54 μ (ring stretching); 8.2-9.0 μ (CF_3); NMR (deuteriochloroform), δ 7.51 (1H, singlet, ring proton 3 pos.); δ 8.16 (1H, singlet, ring proton 5 pos.); δ 9.85 (1H, singlet, -CHO).

Anal. Calcd. for $C_6H_3F_3O_2$: C, 43.91; H, 1.84; F, 34.74. Found: C, 43.91; H, 1.90; F, 34.96.

A semicarbazone was prepared from X in the usual fashion and recrystallized from acetonitrile to give material, m.p. 208-211°.

Anal. Calcd. for $C_7H_6F_3N_3O_2$: C, 38.02; H, 2.74; F, 25.78; N, 19.00. Found: C, 38.03; H, 2.80; F, 25.70; N, 18.86.

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