Trifluoromethylfurans

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The preparation of 5-trifluoromethylfurfural and some of its derivatives is described. Biological activity of the derivatives is reported.

It has been known for some time that compounds possessing a 5-nitrofurfurylidene moiety usually exhibit antibacterial activity and in some cases also antiprotozoal activity (2). It was felt that replacement of the nitro group, in this type of compound, with another electronegative group might yield products with similar biological activity. The trifluoromethyl moiety was chosen as the replacement group.

The first step of the synthesis involved the alkylation of the sodium salt of ethyl trifluoroacetoacetate with chloroacetone which gave 3-carbethoxy-1,1,1-trifluorohexane-2,5-dione (I) in 64% yield. The conditions employed were essentially those used by Dann, Distler and Merkel (3) in alkylating the sodium salt of ethyl acetoacetate with chloroacetone. The infrared spectrum of I showed no absorption in the O-H stretching region and the NMR spectrum exhibited a clearly defined doublet at 6.74 τ which integrated for two protons. These data indicate that the diketo ester, I, is not significantly enolized, neat or in chloroform solution.

It was reported by Dann, *et al.* (3), that 3-carbethoxyhexane-2,5-dione was readily converted to 2,5-hexanedione on treatment with base. When this reaction was attempted with the diketo ester, I, a reverse acetoacetic ester condensation occurred yielding ethyl levulinate and presumably trifluoroacetic acid (not isolated). Apparently the trifluoromethyl group of I activates the adjacent carbonyl group for nucleophilic attack to such an extent that it is attacked by the base in preference to the carbethoxy group.

On attempted acid hydrolysis, ring closure of I occurred to form ethyl 5-methyl-2-trifluoromethyl-3-furoate (III). The optimum conditions for the formation of III from I involve refluxing the latter with toluene and *p*-toluenesulfonic acid using a Dean-Stark apparatus for azeotropic removal of the water formed in the reaction.

Hydrolysis of the furoate ester, III, gave the free acid, IV, in 86% yield. This acid was readily decarboxylated in boiling quinoline to give 2-methyl-5-trifluoromethylfuran (V) in 90% yield.

Bromination of the furoate ester, III, with one equivalent of *N*-bromosuccinimide gave ethyl 2-bromomethyl-5-trifluoromethyl-3-furoate (VI) in 77% yield. When two equivalents of *N*-bromosuccinimide were employed a mixture was obtained. Fractional distillation of the mixture gave a 34% yield of monobromo derivative, VI, and a 28% yield of dibromo derivative, VII.

When 2-methyl-5-trifluoromethylfuran (V) was brominated with one equivalent of *N*-bromosuccinimide the major product (65% yield) was the monobromo derivative, VIII. A small amount (4.7% yield) of dibromo compound, IX, was also isolated.

Both dibromo compounds, VII and IX, were readily converted to the corresponding aldehydes by mild, basic hydrolysis in 86% and 61% yields, respectively. However, since the monobromo derivatives, VI and VIII, were more easily synthesized they were used in the preparation of the corresponding aldehydes. The Sommelet method was unsatisfactory for the conversion of 2-bromomethyl-5-trifluoromethylfuran to the aldehyde. Although the yield of hexamethylenetetramine salt was nearly quantitative, attempts to hydrolyze it gave poor yields of aldehyde. The method found to be most useful for the preparation of the desired aldehydes was that of Hass and Bender (4). Thus, treatment of VI and VIII with sodium 2-propanenitronate according to their procedure gave the desired aldehydes, X and XI, in yields of 71% and 48% respectively.

Since the compounds of the 5-nitrofuran series having important biological activity generally possess a $\geq C=N-$ function in the two position, the aldehydes X and XI were converted to derivatives of this type for biological evaluation. These derivatives are listed in Table I together with the yields obtained in their preparation.

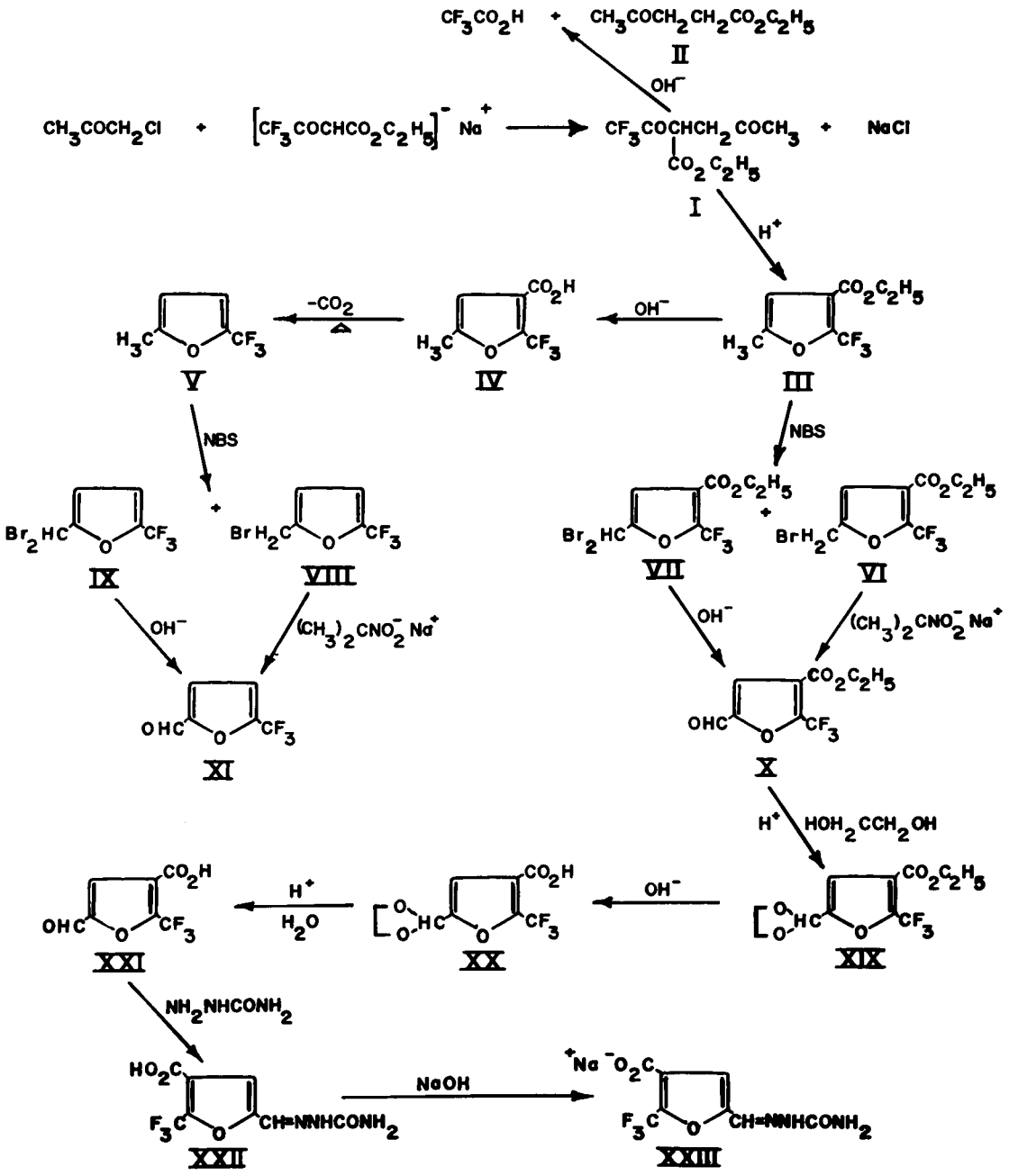
None of the derivatives listed in Table I are significantly water soluble. In order to make a water soluble 5-trifluoromethyl-2-furfural derivative available for biological testing the following sequence of reactions was carried out: 4-carbethoxy-5-trifluoromethyl-2-furfural (X) was converted to the ethylene acetal, XIX, which was hydrolyzed to give the acid-acetal, XX. Hydrolysis of XX

gave the free aldehyde, XXI, which was converted to the semicarbazone, XXII. Neutralization of XXII with the calculated amount of base gave the desired water soluble sodium salt, XXIII.

The trifluoromethylfurfural derivatives listed in Table I were tested for chemotherapeutic activity in the following screening programs: *in vitro* and *in vivo* antibacterial, *in vivo* anticoccidial and *in vivo* anthelmintic tests. Only in the anticoccidial test was any evidence of interesting chemotherapeutic action found.

The anticoccidial test involved feeding chickens infected with *Eimeria tenella* the test compound mixed with the daily food ration. In this test 5-nitrofurfural-*N*-acetylhydrazone gives 100% protection at a level of 75-100 g./ton in the feed. Table II lists the trifluoromethylfuran derivatives found active at 500 g./ton or less.

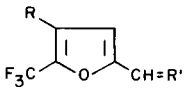
CHART I

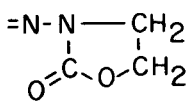


The most active compound, XV, listed in Table II has approximately 1/5 of the activity of 5-nitrofurfural-*N*-acetylhydrazone.

It is interesting that replacement of the nitro group of 5-nitrofurfural derivatives with a trifluoromethyl group has resulted in compounds that retain antiprotozoal activity but exhibit no antibacterial activity. If one assumes that the antibacterial and antiprotozoal activity of the nitrofurans are closely related biochemically, then it would seem likely that the antiprotozoal activity of trifluoromethyl derivatives reported in Table II is due to a completely different biochemical mechanism, although differences in transport phenomena could be the cause.

TABLE I



	R	R′	Yield
XII	$CO_2C_2H_5$	=N-NH-C(=O)-NH_2	79%
XIII	$CO_2C_2H_5$	=N-OH	71%
XIV	$CO_2C_2H_5$	=N-NH-C(=S)-NH_2	32%
XV	H	=N-NH-C(=O)-NH_2	84%
XVI	H	=N-OH	67%
XVII	H	=N-NH-C(=S)-NH_2	32%
XVIII	H		97%

EXPERIMENTAL

All melting points were taken in open capillary tubes with a calibrated thermometer, using a Thomas-Hoover melting point apparatus. The infrared spectra were determined as thin liquid films or as potassium bromide wafers with a Beckman IR-5 spectrophotometer. GLC analyses were carried out with an F & M model 500 gas chromatograph equipped with a 1609 flame ionization detector using a 4 ft. long, 1/4 in. diameter column packed with 5% SE-30 on Gas-Chrom Z. NMR spectra were recorded in deuteriochloroform solution, unless otherwise noted, by Simon Research Laboratory, Elgin, Ill., with a Varian A-60 spectrometer. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan.

3-Carbethoxy-1,1,1-trifluorohexane-2,5-dione (I).

To a stirred slurry of 8.6 g. (0.2 mole) of a 56% oil dispersion of sodium hydride in 200 ml. of anhydrous benzene was slowly added 36.8 g. (0.2 mole) of ethyl trifluoroacetoacetate. The mixture was stirred until hydrogen evolution had ceased. The benzene was removed by distillation under reduced pressure and 200 ml. of dry acetone was added to the residual sodium salt. Next, 0.4 g. of potassium iodide and 21 g. (0.23 mole) of chloroacetone were added and the resulting mixture was refluxed, with stirring, for 68 hours. At the end of the reflux period the *p*H of the mixture approached neutral. The mixture was then poured into 500 ml. of water and extracted three times with 200 ml. portions of ether. The extracts were combined, dried over magnesium sulfate and evaporated under reduced pressure. The residual oil was distilled at 0.25 mm. using a 4 in. Vigreaux column to give 30.7 g. (64% yield) of material boiling at 60-70°. GLC analysis of the produce indicated a purity of greater than 99%. A center cut from the distillation, N^{25} 1.4010, was submitted for analysis; infrared, ν max (neat), 5.75 μ broad (C=O); 8.0-8.8 μ

TABLE II

	Compound	Level Fed g./ton	Died/ Tested (a)	% Survival
XV	5-Trifluoromethyl-2-furfural semicarbazone	500	1/20	95%
		300	6/20	70%
XIII	4-Carbethoxy-5-trifluoromethyl-2-furfural oxime	500	6/10	40%
XVIII	3-(5-Trifluoromethyl-2-furfurylideneamino)-2-oxazolidinone	500	5/10	50%
XVII	5-Trifluoromethyl-2-furfural thiosemicarbazone	500	7/10	30%

(a) Mortality of untreated controls ranges from 80-100%.

broad (CF_3); NMR, 5.5-5.9 τ (3H, complex multiplet, -COC*H*CO_2- & CH_3CH_2O-); 6.74 τ (2H, doublet, J=7cps, $CHCH_2CO$-); 7.80 τ (3H, singlet, CH_3CO-); 8.72 τ (3H, triplet, J=7cps, CH_3CH_2O-).

Anal. Calcd. for $C_9H_{11}F_3O_4$: C, 45.0; H, 4.62; F, 23.7. Found: C, 45.2; H, 4.74; F, 23.8.

Treatment of I with Base.

A mixture of 120 g. (0.5 mole) of I, 20.0 g. (0.5 mole) of sodium hydroxide and 500 ml. of water was refluxed, with stirring, for one hour. The mixture was allowed to cool and the *p*H was adjusted to 3 with 10% aqueous hydrochloric acid. The mixture was saturated with sodium chloride and extracted three times with 100 ml. portions of ether. The extracts were combined and dried over magnesium sulfate. The drying agent was removed by filtration and the filtrate evaporated under reduced pressure. The residual oil was fractionated with a 4 in. Vigreaux column at 9.0 mm. pressure. There was obtained 58.5 g. (69.5% yield) of material boiling from 86-96° which analyzed as approximately 95% pure by GLC analysis. The material was shown to be ethyl levulinate by comparison of its infrared spectrum with that of an authentic sample and by a mixed melting point experiment of its semicarbozone with the semicarbazone of ethyl levulinate.

Ethyl 5-Methyl-2-trifluoromethyl-3-furoate (III).

In a flask fitted with a Dean-Stark water separator were placed 400 ml. of toluene and 5.0 g. of *p*-toluenesulfonic acid monohydrate. The mixture was refluxed until the water from the acid had been collected. Next, 65 g. (0.27 mole) of I was added and the mixture was refluxed for 17 hours during which time the theoretical amount of water was collected. The solution was cooled and an excess of sodium bicarbonate was added. The mixture was then washed with water and dried over sodium sulfate. The drying agent was separated by filtration and the toluene was removed by distillation under reduced pressure. The residual oil was fractionated at 0.35 mm. using a 12 in. Vigreaux column. The material boiling from 45-49° was collected, wt. 44.5 g. (74% yield). A center cut, N^{25} 1.4184, was submitted for analysis; infrared, ν max (neat), 5.75 μ (C=O); 6.35 μ (ring stretching); 8.4-8.9 μ (CF_3); NMR, 3.52 τ (1H, singlet, furan ring proton); 5.65 τ (2H, quartet, J=6.5cps, CH_3CH_2O-); 7.64 τ (3H, singlet, -CH_3); 8.65 τ (3H, triplet, J=6.5cps, CH_3CH_2O-).

Anal. Calcd. for $C_9H_9F_3O_3$: C, 48.7; H, 4.08; F, 25.7. Found: C, 48.5; H, 4.14; F, 25.9.

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

A mixture of 18.0 g. (0.0813 mole) of III, 170 ml. of ethanol, 3.52 g. of sodium hydroxide (0.088 mole) and 36 ml. of water was refluxed for 45 minutes. The mixture was then evaporated to dryness and approximately 100 ml. of water was added. The *p*H of the solution was adjusted to 2 with concentrated hydrochloric acid and the precipitated furoic acid collected by filtration. The acid was washed with water and air dried, wt. 13.5 g. (86%); m.p. 122-125°. Recrystallization of the acid from cyclohexane gave an analytical sample, m.p. 124-126°; infrared, ν max (potassium bromide), 3.1-3.7 μ (CO_2H); 5.86 μ (C=O); 6.35 μ (ring stretching); 8.5-8.7 μ (CF_3); NMR, -0.6 τ (1H, singlet, -CO_2H); 3.4 τ (1H, singlet, ring proton 4 pos.); 7.6 τ (3H, singlet, -CH_3).

Anal. Calcd. for $C_7H_5F_3O_3$: C, 43.3; H, 2.59; F, 29.4. Found: C, 43.5; H, 2.63; F, 29.5.

2-Methyl-5-trifluoromethylfuran (V).

A distillation assembly employing a 4 in. column packed with glass helices, a distillation flask fitted with a nitrogen inlet, and an efficient condensing system was used in the decarboxylation. In the distillation flask were placed 35 ml. of quinoline, 2.0 g. of anhydrous cupric sulfate and 20 g. of 5-methyl-2-trifluoromethyl-3-furoic acid. The mixture was then heated rapidly to approximately 220° with an oil bath preheated to 230° while nitrogen was bubbled gently through the mixture to sweep out the decarboxylated material. After the evolution of decarboxylated material had ceased (approximately 10 minutes) the distillation flask was cooled and the process was repeated. In this fashion 167.4 g. of acid was decarboxylated. The distillate was taken up in ether and dried over magnesium sulfate. The drying agent was removed by filtration and the filtrate fractionated with a 6 in. column packed with glass helices to give 116.5 g. (90.0%) of 2-methyl-5-trifluoromethylfuran boiling at 81-82°, N^{25} 1.3685. A GLC analysis of the product indicated the material was greater than 99% pure; infrared ν max (neat), 6.38 μ (ring stretching); 8.4-9.1 μ (CF_3); NMR, 3.30 τ (1H, doublet, J=3cps, ring proton 3 pos.); 3.92 τ (1H, doublet, J=3cps, ring proton 4 pos.); 7.68 τ (3H, singlet, -CH_3).

Anal. Calcd. for $C_6H_5F_3O$: C, 48.0; H, 3.36; F, 38.0. Found: C, 48.2; H, 3.36; F, 37.9.

Ethyl 5-Bromomethyl-2-trifluoromethyl-3-furoate (VI).

In a flask fitted with a stirrer and a condenser were placed 150 ml. of carbon tetrachloride, 22.2 g. (0.10 mole) of V and 18.0 g. (0.10 mole) of *N*-bromosuccinimide. The mixture was stirred and refluxed while being illuminated by a 275 watt sun lamp for 1.5 hours. The mixture was then cooled, filtered, and the filtrate concentrated under reduced pressure. The residual oil (lachrymator!) was fractionated at 0.06 mm. with a 6 in. Vigreaux column. The fraction boiling from 72-74° (23.4 g., 77% yield) was found to be >99% pure by GLC analysis; infrared, ν max (neat), 5.75 μ (C=O); 6.36 μ (ring stretching); 8.3-8.8 μ (CF_3); 8.08 μ (CH_2Br wag); NMR, 3.01 τ (1H, singlet, ring proton 4 pos.); 5.42 τ (2H, singlet, -CH_2Br); 5.58 τ (2H, quartet, J=7.5cps, CH_3CH_2O-).

Anal. Calcd. for $C_9H_8BrF_3O_3$: C, 35.9; H, 2.71; Br, 26.5; F, 18.9. Found: C, 36.0; H, 2.60; Br, 26.4; F, 18.8.

Ethyl 5-Dibromomethyl-2-trifluoromethyl-3-furoate (VII).

A mixture of 44.4 g. (0.20 mole) of V, 400 ml. of carbon tetrachloride and 72.0 g. (0.40 mole) of *N*-bromosuccinimide was stirred and refluxed for 12 hours. During the reflux period the reaction mixture was illuminated with a 275 watt sun lamp. The mixture was cooled and filtered to remove the succinimide. The filtrate was evaporated and the residual oil fractionated at 0.05 mm. using a 4 in. column packed with glass helices. Three fractions were obtained and subjected to GLC. The first (b.p. 82-87°; wt. 20.7 g., 34%) was found to be pure VI. The second (b.p. 87-92°; wt. 15.1 g.) was a mixture containing approximately 50% VI and 50% dibromo compound. The third fraction (b.p. 92-95°; wt. 21.1 g., 28%) was pure ethyl 5-dibromomethyl-2-trifluoromethyl-3-furoate; infrared, ν max (neat), 5.75 μ (C=O); 6.41 μ (ring stretching); 8.3-8.8 μ (CF_3).

Anal. Calcd. for $C_9H_7Br_2F_3O_3$: C, 28.4; H, 1.86; Br, 42.1; F, 15.0. Found: C, 28.5; H, 1.99; Br, 42.1; F, 15.1.

Treatment of 2-Methyl-5-trifluoromethylfuran with *N*-Bromosuccinimide.

To 64 g. (0.43 mole) of V dissolved in 500 ml. of carbon tetrachloride was added 83.0 g. (0.46 mole) of *N*-bromosuccinimide. The mixture was stirred and heated to the reflux temperature and 0.2 g. of dibenzoylperoxide was added. After a reflux period of approximately 2 hours, all the *N*-bromosuccinimide had reacted and the mixture was cooled and filtered. The filtrate was fractionated under reduced pressure using a 6 in. Vigreaux column.

After the bulk of the carbon tetrachloride had been removed the pressure was reduced to 14 mm. Two fractions were obtained at this pressure. The first, b.p. 55-56°, wt. 44.3 g., was shown by GLC analysis to be one component, 2-bromomethyl-5-trifluoromethylfuran (VIII); infrared, ν max (neat), 6.41 μ (ring stretching); 8.2-9.0 μ (CF_3); NMR, 3.17 τ (1H, doublet, J=3cps, ring proton 4 pos.); 3.48 τ (1H, doublet, J=3cps, ring proton 3 pos.); 5.48 τ (2H, singlet, -CH_2Br).

Anal. Calcd. for $C_6H_4BrF_3O$: C, 31.5; H, 1.76; Br, 34.9; F, 24.9. Found: C, 31.2; H, 1.82; Br, 35.2; F, 24.8.

The second fraction, b.p. 56-75°, wt. 33.6 g., was shown by GLC analysis to contain two major components. This material was refractionated at 9 mm. using a 4 in. column packed with glass helices. Three fractions were obtained. The first fraction (b.p. 50-58°; wt. 19.1 g.) proved to be the pure monobromo compound and brought the total yield of this product to 63.4 g. (65%). The second fraction (b.p. 58-73°; wt. 4.4 g.) was found to be a mixture of two components. The third fraction (b.p. 73-74°; wt. 6.2 g.), one component by GLC analysis, proved to be the dibrominated product, 2-dibromomethyl-5-trifluoromethylfuran (IX); infrared, ν max (neat), 6.40 μ (ring stretching); 8.3-8.9 μ (CF_3); NMR, 3.18 τ (1H, singlet, ring proton 4 pos.); 3.27 τ (1H, singlet, ring proton 3 pos.); 3.38 τ (1H, singlet, -CHBr$_2$).

Anal. Calcd. for $C_6H_3Br_2F_3O$: C, 23.4; H, 0.98; Br, 52.0; F, 18.5. Found: C, 23.3; H, 1.12; Br, 52.0; F, 18.5.

4-Carbethoxy-5-trifluoromethyl-2-furfural (X).

To 3.1 g. (0.135 mole) of sodium dissolved in 130 ml. of absolute ethanol was added 15.1 g. of 2-nitropropane. Next, 39.9 g. (0.132 mole) of VI was added over a period of 10 minutes while the temperature was maintained at 25-35°. The mixture was stirred overnight and evaporated under reduced pressure to remove the ethanol. Water (approx. 200 ml.) was added and the resulting mixture was extracted three times with an equal volume of ether. The ether extracts were combined and dried over magnesium sulfate. The mixture was filtered and the ether evaporated. The residual oil was fractionated with a 4 in. Vigreaux column at 0.3 mm. pressure. The material boiling between 70-90° was collected giving 22.1 g. (70.9% yield) of aldehyde. A GLC analysis indicated the material was approximately 95% pure and satisfactory for synthetic work. However, an acceptable analysis was not obtained. An analytical sample was obtained by washing an ethereal solution of the material with 5% sodium hydroxide solution, drying the ether phase over magnesium sulfate and finally fractionating the residual oil. Using a 4 in. column packed with glass helices, material was obtained which boiled from 66-68° at 0.4 mm. and had an N^{25} of 1.4495; infrared ν max (neat), 3.54 μ (CHO); 5.75 μ ($CO_2C_2H_5$); 5.87 μ (CHO); 6.25 μ (ring stretching); 8.3-8.5 μ (CF_3); NMR, 0.10 τ (1H, singlet, -CHO); 2.26 τ (1H, singlet, ring proton 3 pos.); 5.56 τ (2H, quartet, J=7cps, CH_3CH_2O-); 8.57 τ (3H, triplet, J=7cps, CH_3CH_2O-).

Anal. Calcd. for $C_9H_7F_3O_4$: C, 45.8; H, 2.99; F, 24.1. Found: C, 45.7; H, 3.04; F, 24.0.

This aldehyde was also prepared from VII by boiling the latter with an aqueous slurry of calcium carbonate. In this manner an 86% yield of crude aldehyde was obtained. The material was identified by its infrared spectrum and its GLC retention time. It was also converted to a semicarbazone which was identical with the one obtained from X synthesized by the nitropropane method.

5-Trifluoromethyl-2-furfural (XI).

To 5.3 g. (0.24 mole) of sodium dissolved in 300 ml. absolute alcohol was added 30 g. (0.33 mole) of 2-nitropropane and the mixture was stirred for 30 minutes. At this point the system was flushed with nitrogen and maintained under nitrogen for the duration of the reaction. To the solution was next added, with stirring, 55.3 g. (0.24 mole) of VIII. The temperature of the mixture was maintained at 65-75° throughout the reaction. After three hours the *p*H of the mixture had dropped to 7.5-7.8 and it was evaporated under reduced pressure to remove the ethanol. Water was added to the residue and the resulting mixture extracted with ether. The ether extracts were combined, washed twice with equal volumes of 5% aqueous sodium hydroxide and dried over magnesium sulfate. The mixture was filtered and the ether removed by distillation. Fractionation of the residual oil at 40.0 mm. pressure using a 4 in. column packed with glass helices gave 18.8 g. (48%) of 5-trifluoromethyl-2-furfural boiling at 66-68°. A center cut from the fractionation (N^{25} 1.4256) was submitted for analysis; infrared, ν max (neat), 3.53 μ (CHO); 589 μ (CHO); 6.24 μ (ring stretching); 8.2-8.9 μ (CF_3); NMR, 0.12 τ (1H, singlet, -CHO); 2.53 τ (1H, doublet, J=4cps, ring proton 3 pos.); 2.88 τ (1H, doublet, J=4cps, ring proton 4 pos.).

Anal. Calcd. for $C_6H_3F_3O_2$: C, 43.9; H, 1.84; F, 34.7. Found: C, 43.4; H, 1.84; F, 34.6.

This compound was also prepared from IX by hydrolyzing it with aqueous calcium carbonate. A 61% yield of crude aldehyde was obtained which was shown to be identical with XI by its infrared spectrum and by converting it to a semicarbazone identical with that obtained from XI.

The following derivatives of the aldehydes X and XI were prepared by standard procedures and only the recrystallization solvent, melting point and elemental analyses are given.

4-Carbethoxy-5-trifluoromethyl-2-furfural Semicarbazone (XII).

From ethanol, m.p. 199-201°.

Anal. Calcd. for $C_{10}H_{10}F_3N_3O_4$: C, 41.0; H, 3.44; N, 14.3; F, 19.4. Found: C, 40.8; H, 3.28; N, 14.3; F, 19.5.

4-Carbethoxy-5-trifluoromethyl-2-furfural Oxime (XIII).

From petroleum ether (b.p. 90-100°), m.p. 99-102°.

Anal. Calcd. for $C_9H_8F_3NO_4$: C, 43.0; H, 3.21; N, 5.58; F, 22.7. Found: C, 43.1; H, 3.22; N, 5.61; F, 22.6.

4-Carbethoxy-5-trifluoromethyl-2-furfural Thiosemicarbazone (XIV).

From benzene, m.p. 187-188°.

Anal. Calcd. for $C_{10}H_{10}F_3N_3O_3S$: C, 38.8; H, 3.26; F, 18.4; N, 13.6; S, 10.4. Found: C, 39.0; H, 3.43; F, 19.0; N, 13.6. S, 10.4.

5-Trifluoromethyl-2-furfural Semicarbazone (XV).

From isopropyl alcohol, m.p. 209-210°.

Anal. Calcd. for $C_7H_6F_3N_3O_2$: C, 38.0; H, 2.74; N, 19.0; F, 25.8. Found: C, 38.0; H, 2.88; N, 18.8; F, 25.7.

5-Trifluoromethyl-2-furfural Oxime (XVI).

By vacuum sublimation, m.p. 119.5-121°.

Anal. Calcd. for $C_6H_4F_3NO_2$: C, 40.2; H, 2.25; N, 7.83. Found: C, 40.3; H, 2.41; N, 7.90.

5-Trifluoromethyl-2-furfural Thiosemicarbazone (XVII).

From benzene, m.p. 162-164°.

Anal. Calcd. for $C_7H_6F_3N_3OS$: C, 35.4; H, 2.55; N, 17.7. Found: C, 35.6; H, 2.69; N, 17.7.

3-(5-Trifluoromethyl-2-furfurylideneamino)-2-oxazolidinone (XVIII).

This compound was prepared according to the method used by Gever to prepare *N*-[1-(5-nitro-2-furyl)ethylidene]-3-amino-2-oxa-

zolidinone (5). From isopropyl alcohol, m.p. 149-151°.

Anal. Calcd. for $C_9H_7F_3N_2O_3$: C, 43.6; H, 2.84; F, 23.0; N, 11.3. Found: C, 43.8; H, 3.00; F, 23.0; N, 11.2.

Ethyl 2-(1,3-Dioxolan-2-yl)-5-trifluoromethyl-3-furoate (XIX).

To a solution of 14.3 g. (0.06 mole) of 4-carbethoxy-5-trifluoromethyl-2-furfural and 5.5 g. (0.09 mole) of ethylene glycol in 84 ml. of dry benzene was added 0.5 g. of *p*-toluenesulfonic acid. The mixture was refluxed, using a Dean-Stark apparatus, until water evolution had ceased (about 3 hours). The solution was cooled and solid sodium bicarbonate was added to neutralize the *p*-toluenesulfonic acid. Filtration of the mixture and concentration of the filtrate under reduced pressure gave an oil which was fractionated at 0.3 mm. using a 4 in. Vigreaux column yielding 13.4 g. (80%) of the acetal, b.p. 89-90°. GLC analysis of the product indicated a high degree of purity.

Anal. Calcd. for $C_{11}H_{11}F_3O_5$: C, 47.1; H, 3.96. Found: C, 47.1; H, 3.91.

2-Formyl-5-trifluoromethyl-3-furoic Acid (XXI).

A solution of 13.1 g. (0.047 mole) of XIX and 3.1 g. (0.047 mole) of potassium hydroxide (85%) in 100 ml. of 50% aqueous ethanol was refluxed for 2 hours. The reaction mixture was cooled and evaporated and the crystalline residue dissolved in 20-30 ml. of water. Acidification of the solution gave 11.8 g. (99.4% yield) of the ketal-acid (XIX), m.p. 90-96°.

The ketal-acid (10.0 g., 0.04 mole) was dissolved in 100 ml. of 50% aqueous ethanol and 2 ml. of 10% hydrochloric acid was added. After refluxing the resulting solution for one hour it was evaporated to one-third of its original volume and the solid which precipitated was collected by filtration, wt. 7.3 g. (89% yield). Recrystallization of the acid from benzene gave an analytical sample, m.p. 137-140°.

Anal. Calcd. for $C_7H_3F_3O_4$: C, 40.4; H, 1.45; F, 27.4. Found: C, 40.5; H, 1.57; F, 27.3.

2-Formyl-5-trifluoromethyl-3-furoic Acid Semicarbazone (XXII).

The formyl furoic acid, XXI, was converted to the semicarbazone in the usual fashion and recrystallized from glacial acetic acid to give an analytical sample, m.p. 268-270° (70% yield).

Anal. Calcd. for $C_8H_6F_3N_3O_4$: C, 36.2; H, 2.28; N, 15.8. F, 21.5. Found: C, 36.1; H, 2.35; N, 15.8; F, 21.6.

Sodium 2-Formyl-5-trifluoromethyl-3-furoate Semicarbazone (XXIII).

The free acid was converted to its sodium salt by carefully neutralizing a solution of the acid in aqueous alcohol with the calculated amount of sodium hydroxide. Evaporation of the solution afforded a crystalline material which on drying under vacuum analyzed as the monohydrate of the desired salt.

Anal. Calcd. for $C_8H_5F_3N_3O_4Na\cdot H_2O$: C, 31.5; H, 2.31; F, 18.7; N, 13.8; Na, 7.53. Found: C, 31.5; H, 2.32; F, 18.7; N, 13.7; Na, 7.44.

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REFERENCES

(1) Present address: Parke, Davis & Company, Holland, Michigan.

(2) H. E. Paul and M. F. Paul, "The Nitrofurans--Chemotherapeutic Properties," in *Experimental Chemotherapy, Vol. II*, R. J. Schnitzer and F. Hawking, Eds., Academic Press, New York, 1964, pp. 307-359.

(3) O. Dann, H. Distler and H. Merkel, *Chem. Ber.*, 85, 457-461 (1957).

(4) H. B. Hass and M. L. Bender, *J. Am. Chem. Soc.*, 71, 1767-1769 (1949).

(5) Gabriel Gever, U. S. Patent, 2,847,416.

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