[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE RICE INSTITUTE]

ALPHA-FURFURYL CHLORIDE AND ITS DERIVATIVES. II

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The recent preparation and isolation of α-furfuryl chloride[1] has greatly simplified the synthesis of α-furfuryl compounds and it is now possible, by using this reagent, to prepare compounds which were in many cases previously obtainable only by more or less indirect methods which usually started with furfural and involved several steps in the procedure. By the use of α-furfuryl chloride, which contains a highly reactive chlorine atom, we have prepared the following new compounds, which are listed in Table I, together with their physical constants.

TABLE I

NEW FURYL DERIVATIVES

No.	Name	B. p., °C.	Press., mm.	M. p., °C.	Yield, %	d_4^{20}	n_D^{20} (Abbé)	Molecular refraction	
								Calcd.	Obs.
1	Ethyl α-furfurylmalonic ester	135.5–136.5°	5	....	67	.....	....	....	....
2	Ethyl α-furfurylbarbituric acid	....	..	144.5–145	51	.....	....	....	....
3	α-Furfuryl-acetoacetic ester	111–111.5°	4	....	61	1.10366	1.4718	53.172	53.290
4	α-Furfuryl nitrile	74–75°	27	....	90	1.04627	1.4833	30.571	29.236
5	α-Furylacetic acid	....	..	108.5–109.5	43	.....	....	....	....
6	α-Furfuryl thiocyanate	111.5–112.5°	27	....	70	1.18709	1.5614	36.083	37.971
7	α-Furfuryl ethyl sulfide	90.5–91°	28	....	80	1.04958	1.5140	41.005	40.773

We have also prepared the following known substances (Table II) by simple replacement reactions, whereas their previous preparation started with furfural and was accomplished by more or less roundabout methods.

TABLE II

SUBSTANCES PREPARED

No.	Name	B. p., °C.	Press., mm.
1	α-Furfurylmalonic ester	125.5–127	4
2	α-Furfurylbarbituric acid	....	..
3	2-α-Furfurylacetic acid	....	..
4	α-Furfuryl acetone	....	..
5	α-Furfuryl acetone semicarbazone	....	..
6	α-Furfuryl mercaptan	84	65

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[1] Kirner, THIS JOURNAL, 50, 1955 (1928).

TABLE II (*Concluded*)

No.	M.p., °C.	Yield, %	d^{20}_4	n^{20}_D (Abbé)	Molecular refraction Calcd.	Obs.
1	....	76	1.10999	1.4591	59.433	59.152
2	186–187.5	37	.....	....	....	....
3	56.5–58	75	.....	....	....	....
4	....	12	.....	....	....	....
5	140–141	..	.....	....	....	....
6	....	33	1.13186	1.5329	31.489	31.302

In most of these reactions it was not considered necessary to use the pure distilled furfuryl chloride so the ethereal solution obtained directly from the reaction mixture was treated with the desired reagent. The main objection to this procedure is that it does not permit of an accurate method of determining the yield of product theoretically obtained in the various reactions. However, by assuming that the crude reaction product was formed in 70% yield (since a 63% yield of distilled product can be obtained), an approximate idea is obtained of the percentage yields in the various reactions.

The furfuryl-ethyl-barbituric acid is of special interest because of the possibility of its possessing a physiological activity analogous to that of Veronal. We are indebted to Professor A. M. Hjort of the Dartmouth Medical School for his investigation of the action of this substance in producing hypnosis. A more detailed report of the physiological action will be published elsewhere.

Experimental

α-Furfurylmalonic Ester.—This substance was first prepared by Sandelin[2] by condensing furfural with malonic acid, yielding furfuralmalonic acid which was then reduced to furfurylmalonic acid and esterified; b. p. 171–173° at 33 mm.; 265–267° at atmospheric pressure. It was described as a light yellow oil with a weak fruity odor. This ester was also prepared by Ojiyama, Hasegawa and Matsumura.[3] Only the abstract of their article was available in which no details were given but their method is obviously complicated.

We obtained this ester by the usual malonic ester condensation using thoroughly anhydrous alcohol prepared according to the method of Smith.[4] In this one case distilled furfuryl chloride was used and was added in a solution of Grignard ether. The yield of distilled product was 76%; b. p. 125.5–127° at 4 mm. The product was a colorless oil with an odor resembling that of malonic ester; d^{20}_{20} 1.11196; d^{20}_4 1.10999; n^{20}_D 1.4591; M_D (calcd.) 59.433; M_D (obs.) 59.152.

Anal. Subs., 0.2033: CO_2, 0.4457; H_2O, 0.1283. Calcd. for $C_{12}H_{16}O_5$: C, 59.98; H, 6.72. Found: C, 59.79; H, 7.06.

Ethyl-α-furfurylmalonic Ester.—This is a new compound. It was made by ethylating the above furfurylmalonic ester in the usual manner using ethyl iodide. The

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[2] Sandelin, *Ber.*, **33**, 490 (1900).

[3] Ojiyama, Hasegawa and Matsumura, *J. Pharm. Soc. Japan*, **533**, 597 (1926); *C. A.*, **21**, 2251 (1927).

[4] Smith, *J. Chem. Soc.*, 1288 (1927).

purification of the compound was found difficult due to the continued appearance of iodine during the vacuum distillation. This was finally all removed by several extractions with sodium thiosulfate solution. The boiling point was 135.5–136.5° at 5 mm.; yield, 67%. This substance was not analyzed but was used directly for the preparation of the furfuryl-ethylbarbituric acid.

α-Furfurylbarbituric Acid.—This substance was first prepared by Ojiyama, Hasegawa and Matsumura.[3] They gave the melting point as 193°. We prepared it according to the directions given by Dox and Yoder,[5] using furfurylmalonic ester, urea and sodium ethylate made from special anhydrous alcohol. In the isolation of the compound it was found that it was quite sensitive to the action of mineral acids and therefore should be left in contact with them over as short a period as possible and at a low temperature. The yield was 37%; m. p. 186–187.5°.

Anal. Subs., 0.2511: N_2, 30.00 cc. at 26° and 762.3 mm. Calcd. for $C_9H_8O_4N_2$: N, 13.46. Found: N, 13.53.

Ethyl-α-furfurylbarbituric Acid.—This is a new compound and was made in precisely the same manner as the substance just described above; yield, 51%; m. p. 144.5–145°.

Anal. Subs., 0.1168: N_2, 13.15 cc. at 23.6° and 760.1 mm. Calcd. for $C_{11}H_{12}O_4N_2$: N, 11.86. Found: N, 12.41.

α-Furfurylacetoacetic Ester.—This new substance was prepared by the usual acetoacetic ester condensation using specially dehydrated alcohol, the crude furfuryl chloride being added in a solution of dry ether. The product was purified by distillation in a vacuum; b. p. 111.0–111.5° at 4 mm.; yield, 61%; d^{20}_{20} 1.10562; d^{20}_{4} 1.10366; n^{20}_{D} 1.4718; M_D (calcd.) 53.172; M_D (obs.) 53.290.

Anal. Subs., 0.1993: CO_2, 0.4556; H_2O, 0.1193. Calcd. for $C_{11}H_{14}O_4$: C, 62.83; H, 6.71. Found: C, 62.34; H, 6.70.

2-α-Furfurylacetic Acid (3-α-Furylpropanoic Acid).—Baeyer[6] and also Marckwald[7] made this acid by first carrying out a Perkin's synthesis on furfural, yielding furfurylacrylic acid, which was then reduced. They give the melting point as 50–51°. Marckwald[8] also obtained it by preparing furfurylmalonic acid, which was heated and thus made to lose carbon dioxide. Sandelin[9] prepared furfuralmalonic ester, which was converted to furylsuccinic acid; this on loss of carbon dioxide yielded the furfurylacetic acid. He gave the melting point as 58.5°.

We obtained this acid by the usual acid splitting of the acetoacetic ester using very concentrated alkali for the hydrolysis according to the conditions given by v. Euler and Ölander.[10] We obtained in this way a 75% yield of crude product which was twice recrystallized from water; m. p. 56.5–58°.

α-Furfurylacetone (1-α-Furylbutanone-3).—This substance has been made by carrying out a Claisen condensation between furfural and acetone, yielding furfuralacetone, which on reduction with sodium amalgam gives the saturated ketone.[11] We obtained the ketone as a by-product in the acid splitting of the acetoacetic ester;

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[5] Dox and Yoder, THIS JOURNAL, **44**, 1141 (1922).

[6] Baeyer, *Ber.*, **10**, 357 (1877).

[7] Marckwald, *ibid.*, **20**, 2812 (1887).

[8] Marckwald, *ibid.*, **21**, 1083 (1888).

[9] Sandelin, *ibid.*, **31**, 1122 (1898).

[10] v. Euler and Ölander, *Z. anorg. Chem.*, **147**, 304 (1925).

[11] Harries and Kaiser, *Ber.*, **32**, 1320 (1899); Fujita, *J. Pharm. Soc. Japan*, **519**, 456 (1925); *C. A.*, **20**, 412 (1926); Kasiwagi, *Bull. Chem. Soc. Japan*, **1**, 90 (1926); *C. A.*, **20**, 3005 (1926).

yield of crude product, 12%. It was converted into the semicarbazone which melted at 140–141°. Harries gave the melting point as 143°.

α-Furfuryl Nitrile.—This is a new compound. It was prepared by treating a very concentrated aqueous solution of sodium cyanide dropwise with furfuryl chloride, the mixture being heated to about 70°. When the addition was complete, the mixture was heated just to the boiling point and cooled. Two layers separated. The oily layer was removed, the aqueous solution extracted with ether and the combined layers dried over anhydrous sodium sulfate. The crude yield was 90%. It was found difficult to obtain the compound in a pure state. Four systematic vacuum fractionations were carried out, yielding a colorless liquid possessing a very sweet odor; b. p. 74–75° at 27 mm.; d^{20}_{20} 1.04813; d^{20}_{4} 1.04627; n^{20}_{D} 1.4833; M_D (calcd.) 30.571; M_D (obs.) 29.236.

Anal. Subs., 0.1528: N_2, 16.82 cc. at 765.3 mm. and 25°. Calcd. for C_6H_5ON: N, 13.08. Found: N, 12.57.

α-Furylacetic Acid.—This new acid was obtained by hydrolyzing the above nitrile using a 25% solution of potassium hydroxide. The hydrolysis went rapidly after heating the mixture for only four to five minutes, the oily layer disappearing; heating was continued for one hour. The alkaline solution was extracted with ether to remove unhydrolyzed impurities, then cooled to 10°, decolorized and filtered. The filtrate was treated with excess concentrated hydrochloric acid; crystallization of the acid started immediately on cooling; yield, 43%; m. p. 108.5–109.5°.

Anal. Subs., 0.1813: CO_2, 0.3802; H_2O, 0.0776. Calcd. for $C_6H_6O_3$: C, 57.13; H, 4.80. Found: C, 57.19; H, 4.79.

α-Furfuryl Thiocyanate.—This new substance was prepared by treating furfuryl chloride with sodium thiocyanate in acetone solution, a method suggested by the work of Steinkopf, Herold and Stöhr.[12] Sodium chloride precipitated immediately and the mixture was refluxed for two and one-half hours and allowed to stand overnight. The product was isolated by filtering, adding water, extracting with ether and then drying the ethereal solution over anhydrous sodium sulfate. Distillation in a vacuum yielded a colorless oil boiling at 111.5–112.5° at 27 mm.; yield, 70%; b. p. (2 mm.) 66–67°; d^{20}_{20} 1.18919; d^{20}_{4} 1.18709; n^{20}_{D} 1.5614; M_D (calcd. as RSCN) 36.083; M_D (obs.) 37.971.

Anal. Subs., 0.1998: $BaSO_4$, 0.3350. Calcd. for C_6H_5OSN: S, 23.04. Found: S, 23.03.

α-Furfuryl Mercaptan.—The only previous preparation of this compound which could be found in the literature was given in a patent issued to Staudinger and Reichstein.[13] Since only the abstract was available no details of the preparation could be learned except that furfural was converted into *bis*-furfuryl disulfide by treatment of furfural with ammonium hydrosulfide which was then reduced to the mercaptan. No physical properties of the compound were given.

The first synthesis attempted was the treatment of furfuryl chloride with sodium hydrosulfide; this was unsuccessful. The mercaptan was finally obtained by first condensing furfuryl chloride with thiourea and then hydrolyzing this product, without isolating it, to the mercaptan. After hydrolysis the mercaptan was extracted with carbon tetrachloride and dried. After removal of the solvent the product distilled very uniformly at 84° at 65 mm. It was a colorless oil with the usual penetrating mercaptan odor; yield, 33%; d^{20}_{20} 1.13386; d^{20}_{4} 1.13186; n^{20}_{D} 1.5329; M_D (calcd.) 31.489; M_D (obs.) 31.302.

Anal. Subs., 0.2045: $BaSO_4$, 0.4203. Calcd. for C_5H_6OS: S, 28.09. Found: S, 28.23.

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[12] Steinkopf, Herold and Stöhr, *Ber.*, **53**, 1007 (1920).

[13] Staudinger and Reichstein, Canadian Patent 283,765; *C. A.*, **22**, 4537 (1928).

α-Furfuryl Ethyl Sulfide.—The furfuryl mercaptan was converted into the previously unknown sulfide by treatment of its sodium derivative with ethyl bromide in alcoholic solution. Sodium bromide precipitated immediately and the reaction mixture was heated on a steam-bath for one hour. On cooling the solution was decanted from the sodium bromide and after extraction of the sodium bromide with ether the solution and extract were distilled and the residue was fractionated in vacuum. The product, a colorless liquid of pungent odor, boiled at 90.5–91° at 28 mm.; yield, 80%; d_{20}^{20} 1.05144; d_{4}^{20} 1.04958; n_{D}^{20} 1.5140; M_{D} (calcd.) 41.005; M_{D} (obs.) 40.773.

Anal. Subs., 0.1983: $BaSO_4$, 0.3379. Calcd. for $C_7H_{10}OS$: S, 22.55. Found: S, 23.40.

Summary

1. By using α-furfuryl chloride as the starting material, the following new substances have been prepared: ethyl-α-furfurylmalonic ester, ethyl-α-furfurylbarbituric acid, α-furfurylacetoacetic ester, α-furfuryl nitrile, α-furylacetic acid, α-furfuryl thiocyanate and α-furfuryl ethyl sulfide.

2. The following substances, which had previously been prepared by indirect methods starting with furfural, have now been directly synthesized from α-furfuryl chloride: α-furfurylmalonic ester, α-furfurylbarbituric acid, 2-α-furfurylacetic acid, α-furfurylacetone and its semicarbazone and α-furfuryl mercaptan.

3. Ethyl-α-furfurylbarbituric acid has possibilities as an hypnotic. Its physiological activity is being studied and will be published later. It is expected that this study will yield some information concerning the effect of the α-furfuryl group upon physiological action.

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PARA-CYMENE STUDIES. XIII. PARA-CYMYLHYDRAZINE-2 AND DERIVATIVES[1]

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Phenylhydrazine is widely used in the identification of aldehydes and ketones. A limited number of its homologs have been prepared but phenylhydrazine remains the most available from the cost standpoint. The tolylhydrazines should follow and then cymylhydrazine. The latter compound seems to have been made so far in only one investigation.[2] It was not analyzed and a wide fraction, boiling at 110–120° at 1.5 mm., was taken as cymylhydrazine. The authors prepared the hydrochloride, the acetate and the hydrazones of glucose, mannose and galactose. The cymylhydra-

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[1] This paper is an abstract of a thesis submitted by Charles L. Thomas in partial fulfilment of the requirements for the degree of Master of Science at the University of North Carolina in June, 1929.

[2] Kremers and Demonbreun, *J. Am. Pharm. Assocn.*, **12,** 589 (1923).