ture. Two molar equivalents excess of the sodium salt were used to neutralize the acidic by-products present from the chlorination reaction. After hydrolysis of the reaction mixture, the desired products were obtained by distillation of the toluene layer *in vacuo* as light yellow, unstable oils which decompose rapidly at room temperature and slowly even at −80°. In the presence of mineral acids, the compounds are destroyed within a few seconds to yield blue–violet solutions or tars. They are stable, however, to alkali and to organic acids and were isolated crystalline as their colorless, non-hygroscopic dihydrogen citrate salts.

When tested in guinea pigs by the histamine aerosol technique or by intravenous injection of histamine,[4] the furfuryl derivative (I, X = H) was found to be equally as effective as N,N-dimethyl - N′ - (2 - pyridyl) - N′ - benzylethylenediamine (Pyribenzamine)[5] in protecting against death while the bromofurfuryl derivative (I, X = Br) was only slightly less effective. The results on the furfuryl derivative are in agreement with those reported by Viaud.[2] When tested for acute, twenty-four-hour toxicity by intraperitoneal injection in white mice, the furfuryl derivative had the same toxicity as Pyribenzamine, whereas the bromofurfuryl derivative was approximately 50% less toxic.

We are indebted to Dr. J. T. Litchfield, Jr., and to the Misses Maxine R. Adams and Marion S. Jaeger of these Laboratories for the pharmacological data reported here.

Experimental[6]

N,N-Dimethyl-N′-(2-pyridyl)-N′-furfurylethylenediamine.—To a suspension of 36 g. (1.5 moles) of sodium hydride in 1500 cc. of dry toluene was added 248 g. (1.5 moles) of N,N-dimethyl-N′-(2-pyridyl)-ethylenediamine[5,7] and the mixture heated at reflux for one and one-half hours, or until the evolution of hydrogen ceased, and then cooled to 15° in an ice-bath. In a separate flask, 49 g. (0.5 mole) of redistilled furfuryl alcohol was placed in 300 cc. of dry toluene and the solution cooled with stirring to −30° in a Dry Ice–acetone-bath. A solution of 59.5 g. (0.5 mole) of thionyl chloride in 50 cc. of toluene was then added dropwise at this temperature over a twenty to thirty minute period while passing a steady stream of nitrogen through the apparatus. A large amount of tar and resin was formed toward the end of the addition. The clear, dark green toluene solution was decanted from the resin and added over a five- to ten-minute period to the previously prepared suspension of the sodium salt of N,N-dimethyl-N′-(2-pyridyl)-ethylenediamine also in toluene. The resulting exothermic reaction was maintained at 15° for forty-five minutes. The reaction mixture was then allowed to warm to room temperature and hydrolyzed cautiously with 750 cc. of water. The toluene layer was separated, concentrated, and the residue distilled *in vacuo* to yield 30.2 g. (25%) of impure product as a light yellow oil, b. p. 100–140° (0.4 mm.). Also obtained was 137.5 g. (83% of theoretical recovery) of the excess starting ethylenediamine, b. p. 70–85° (0.5 mm.). The crude material was refractionated to yield 18.6 g. (15%) of pure product, b. p. 136–137° (0.7 mm.); $n^{30}\mathrm{D}$ 1.5486. This is obtained in 95% yield as a stable, non-hygroscopic dihydrogen citrate by precipitation of the salt from alcohol solution with ether and recrystallization from methyl ethyl ketone, m. p. 95–97°.

Anal. Calcd. for $C_{14}H_{19}N_3O \cdot C_6H_8O_7$: C, 54.91; H, 6.22; N, 9.61. Found: C, 54.96, 55.22; H, 5.98, 6.06; N, 9.34, 9.49.

N,N-Dimethyl-N′-(2-pyridyl)-N′-(5-bromofurfuryl)-ethylenediamine.—The sodium salt of N,N-dimethyl-N′-(2-pyridyl)-ethylenediamine was prepared as in the previous example from 13 g. (0.54 mole) of sodium hydride and 89 g. (0.54 mole) of the diamine in 200 cc. of toluene. In a separate flask 32 g. (0.18 mole) of 5-bromofurfuryl alcohol[8] dissolved in 150 cc. of toluene was treated with 21.5 g. (0.18 mole) of thionyl chloride in 50 cc. of toluene at −30°, as described above, and the reaction mixture was added to the previously prepared suspension of the sodium salt of N,N-dimethyl-N′-(2-pyridyl)-ethylenediamine. After reaction and hydrolysis were complete, the product was isolated as before and distilled *in vacuo* to yield 26.5 g. (44% of the theoretical recovery) of the excess ethylenediamine used, and 16 g. (28%) of impure product, b. p. 140–175° (1 mm.). This material was refractionated to yield 10 g. (17%) of pure product as a greenish yellow oil, b. p. 156–158° (0.5 mm.); $n^{30}\mathrm{D}$ 1.5603. Treatment of this with one equivalent of alcoholic citric acid and precipitation with ether gave the stable dihydrogen citrate salt in 97% yield. After recrystallization from methyl ethyl ketone, the colorless crystals melt at 105–107°.

Anal. Calcd. for $C_{14}H_{18}BrN_3O \cdot C_6H_8O_7$: C, 46.52; H, 5.08; Br, 15.48; N, 8.14. Found:[9] C, 46.88, 46.91; H, 5.12, 5.28; Br, 15.41, 15.31; N, 8.14, 8.24.

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[4] Litchfield, Adams, Goddard, Jaeger and Alonso, *Bull. Johns Hopkins Hosp.*, **81**, 55 (1947).

[5] Huttrer, Djerassi, Beears, Mayer and Scholz, THIS JOURNAL, **68**, 1999 (1946).

[6] All melting points are corrected. The microanalyses were carried out in these Laboratories under the direction of Dr. J. A. Kuck, to whom we are indebted for these data.

[7] Whitmore, Mosher, Goldsmith and Rytina, THIS JOURNAL, **67**, 393 (1945).

[8] Prepared from 5-bromofurfural [Gilman and Wright, THIS JOURNAL, **52**, 1170 (1930)] by the crossed Cannizzaro reaction method of Davidson and Bogert, *ibid.*, **57**, 905 (1935); *cf.* Chute, Orchard and Wright, *J. Org. Chem.*, **6**, 157 (1941).

[9] Carbon values were obtained using silver pumice mixed with copper oxide as a substitute for the copper oxide–lead chromate layer in the Pregl microcombustion tube. Unsatisfactory high values were consistently obtained when the conventional tube filling was used.

Concerning the Acylation of Kojic Acid at Elevated Temperatures

BY L. L. WOODS

The acylation of kojic acid at elevated temperatures with acetic anhydride in a modified Nencki[1] reaction is anomalous. The reaction described produces a ketone, I, having an empirical formula $C_{10}H_{18}O_7$. Under hydrolytic conditions the latter compound loses an acetyl group (compound II). Data are lacking for assignment of structures to these two compounds, although some pertinent observations should be noted. The compounds do not have the phenolic character of the parent compound and do contain one aceto group as evidenced by their reactivity toward carbonyl reagents.

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[1] Blatt, "Organic Syntheses," Coll. Vol. 2, John Wiley and Sons, New York, N. Y., p. 304.

Experimental

Acylation of Kojic Acid (I).—Twenty grams (0.142 mole) of kojic acid was mixed with 125 g. (1.22 moles) of acetic anhydride and 10 g. of zinc chloride. The mixture was heated over a water-bath under reflux and protected from moisture with a calcium chloride tube until the first vigorous reaction had subsided. The water-bath was then removed and replaced with an oil-bath. The heating was continued by gradually increasing the temperature to 145°, and then maintaining the temperature between 135–145° for one and one-half hours. Upon completion of the heating of the mixture, the excess acetic anhydride and acetic acid were removed under reduced pressure.

The residue was then treated with 200 ml. of boiling water and set aside to cool. After cooling, the crystals were filtered off. The filtrate was extracted with three successive 100-ml. portions of benzene. The combined benzene fractions were added to the crystals, which immediately dissolved. The mixture was washed once with cold water, dried with anhydrous magnesium sulfate, and decolorized with Norite.

The benzene was allowed to evaporate and 24.8 g. of a pale yellow compound were obtained. The substance was recrystallized by dissolving it in the smallest quantity of boiling water necessary to obtain complete solution (500–600 ml.). The white compound thus obtained was air dried. The analytical sample was dried in the vacuum desiccator over sulfuric acid for three weeks, m. p. 106°. The compound was quite soluble in ether, alcohol, benzene and ethyl acetate as well as hot water.

Anal. Calcd. for $C_{10}H_{13}O_7$: C, 48.98; H, 5.30; mol. wt., 245. Found: C, 49.06, 49.28, 49.10; H, 5.39, 5.72, 5.62; mol. wt. 248. (Each of the three carbon–hydrogen analyses was on a sample from a different run.[2])

Impure samples of the compound always gave a faint red color with dilute ferric chloride solutions; however, the pure samples failed to give the test. The compound did not react with dilute sodium bicarbonate solution. When 1.6137 g. of the ketone was heated ten hours in the electric drying oven at a temperature of 100–102° it lost 0.0376 g. (2.31%) of its weight, one molecule of water would require a loss of 7.34%. This loss of weight, perhaps, cannot be entirely attributed to the loss of moisture because the material developed a faint odor at this temperature.

The 2,4-dinitrophenylhydrazine derivative of compound (I) had a melting point of 114°.

Anal. Calcd. for $C_{10}H_{13}O_3$ $(C_6H_4N_4O_4)_4$: N, 23.21. Found: N, 23.18, 23.40.

Hydrolysis of Compound (I) to Form Compound (II).—A small portion (1 g.) of purified compound (I) dissolved in 50 ml. of hot water was refluxed for fifteen hours. The solution was cooled, decolorized with a little Norite, and filtered. After the water was evaporated and the solid dissolved in absolute ethanol, the solvent was removed under reduced pressure; and the compound was completely dried in the vacuum desiccator. The compound was a colorless glassy material which had a m. p. of 55–57°. Its semicarbazide had a m. p. of 247°. The compound was very soluble in water and in alcohol, but insoluble in acetone and ether. The material was not acidic and did not give any color with dilute ferric chloride solution.

Anal. Calcd. for $C_8H_{11}O_6$: C, 47.29; H, 5.41. Found: C, 47.50; H, 5.84.

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[2] Analyses by Dr. Carl Tiedcke.

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NEW COMPOUNDS

Esters of Mucic Acid

The new compounds[1] listed in Table I were prepared by refluxing and stirring mechanically a mixture of 50 g. of mucic acid and 500 g. of the corresponding alcohol in the presence of 2 g. of *p*-toluenesulfonic acid. The esters all crystallized directly from the cooled reaction mixtures, after removal of unreacted mucic acid by filtration, and were recrystallized from 95% ethanol.

TABLE I

ESTERS OF MUCIC ACID

Di-esters	M. p., °C.	Yield, %	Formula	Analyses Carbon, % Calcd.	 Found	 Hydrogen, % Calcd.	 Found	 Sapon. equiv. Calcd.	 Found
n-Propyl	149–150	48	$C_{12}H_{22}O_8$	48.98	48.9	7.54	7.64	147.1	146.8
n-Butyl	142.5–143.5	93	$C_{14}H_{26}O_8$	52.16	52.2	8.13	8.17	161.2	160
n-Amyl	147–147.5	74	$C_{16}H_{30}O_8$	54.84	54.9	8.63	8.68	175.2	174.2
n-Hexyl	143–144	55	$C_{18}H_{34}O_8$	57.12	57.0	9.06	8.94	189.2	189.1
Allyl	156.5–158	78	$C_{12}H_{18}O_8$	49.65	49.6	6.25	6.35	145.1	145.6

The *n*-propyl and *n*-butyl mucates were prepared by refluxing the reaction mixtures for thirty and ten hours, respectively. The *n*-amyl and *n*-hexyl esters were prepared in essentially the same manner except that 200 g. of xylene was added to the mixture, which was refluxed under a Bidwell–Sterling water trap for twenty and forty hours, respectively. In the preparation of allyl mucate, 250 g. of benzene was added, and refluxing and stirring continued for thirty hours, after which benzene, allyl alcohol and water were slowly distilled through a fractionating column until the final reaction solution was approximately 150 ml.

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(1) Dimethyl and diethyl mucates were prepared by Fischer and Speir (*Ber.*, **28**, 3252 (1895)), the former by reaction of mucic acid and methanol–hydrochloric acid in a sealed tube at 100° and the diethyl ester by refluxing mucic acid with ethanol and hydrochloric acid.

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N-(Acetylsalicyloyl)-piperidine

Fifty grams of acetylsalicylic acid and 250 ml. of thionyl chloride were refluxed for two hours. Excess thionyl chloride was removed on a steam-bath and with vacuum. The residue was taken up in dry benzene and a solution of 55 ml. (100% excess) of piperidine in dry benzene was added cautiously and with cooling. After filtering off the piperidine hydrochloride, the combined liquors and