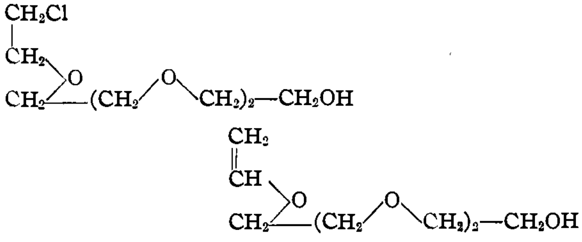
apart, indicating that the decomposition is a function of the length of the ethylene oxide chain.

Tetraethylene glycol monochlorohydrin and diethylene glycol dimethyl ether were the only two derivatives of the polyethylene glycols investigated in which decomposition on heating below the boiling point was noted.

The low decomposition temperature of tetraethylene glycol monochlorohydrin (140°) as compared with that of the corresponding tetraethylene glycol (238°) can only be ascribed to the substitution of the chlorine atom for the hydroxyl group. The decomposition may involve the removal of hydrochloric acid from a molecule with the formation of a vinyl derivative thus



although in this event it is difficult to understand why dichloroethyl ether does not show a similar ease of decomposition.

The decomposition temperature of 60° for diethylene glycol dimethyl ether is low compared with that of the corresponding diethylene glycol (165°). The instability of the former substance is remarkable when compared with the stability of β,β′-dichloroethyl ether.

Acknowledgment.—The writers wish to acknowledge the kind assistance of Dr. O. Maass in the designing of the apparatus used in the vapor pressure measurements and in the interpretation of the experimental results. They also desire to thank the National Research Council of Canada for the award of a Bursary to one of them (A. F. G.).

Summary

The vapor pressures of mono-, di-, tri-, tetraethylene glycols and certain derivatives have been measured.

Certain of these substances show negative deviations from the ratio T_1/T_2 expected according to the Ramsay and Young rule, indicating deviations from the law of corresponding states.

The molecular latent heat and the value for Trouton's constant increase on ascending the glycol series, abnormal values being found with diethylene glycol. Replacement of hydroxyl by methoxyl or chlorine results, as anticipated, in greater volatility. The normal values of Trouton's constant and the low molecular latent heats of ethylene oxide, ethylene dichloride and 1,4-dioxane indicate that these liquids are not associated.

The initial decomposition temperatures of the glycols are seen to be a function of the length of the polyethylene oxide chain. The relative ease of decomposition of diethylene glycol dimethyl ether is unexpected in view of the stability of β,β′-dichloroethyl ether.

MONTREAL, CANADA RECEIVED OCTOBER 11, 1937

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

The Aromatic Character of the Furan Nucleus. Preparation and Reactions of Simple 3-Aminofurans

BY H. B. STEVENSON[1] AND JOHN R. JOHNSON

A number of chemical reactions have been used as a basis for comparing the aromatic properties ("aromaticity") of the furan and benzene systems. From studies of the selective cleavage of organo-lead compounds[2] and the relative ease of nuclear substitution reactions (halogenation, nitration, metalation, and Friedel–Crafts reactions)[3] Gilman has drawn the conclusion that the furan nucleus possesses an enhanced aromatic character[4] ("super-aromaticity") with reference to benzene. However, furan and its simple derivatives take part in the Diels–Alder diene synthesis,[5] and certain other aspects of their

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[1] This paper is an abstract of a portion of the doctoral dissertation of H. B. Stevenson, submitted to the Graduate Faculty of Cornell University in June, 1937.

[2] Gilman and Towne, *Rec. trav. chim.*, **51**, 1054 (1932).

[3] (a) Gilman and Calloway, THIS JOURNAL, **55**, 4197 (1933); (b) Gilman and Young, *ibid.*, **56**, 464 (1934); (c) Gilman and Breuer, *ibid.*, **56**, 1123 (1934).

[4] Gilman and Wright, *Chem. Rev.*, **11**, 323 (1932).

[5] Diels and Alder, *Ber.*, **62**, 554 (1929); Van Campen and Johnson, THIS JOURNAL, **55**, 430 (1933).

chemical behavior[6] indicate that the degree of unsaturation of furan is less than that of 1,3-dienes but greater than that of benzene.[7]

Since there are well-defined differences between aromatic amines and unsaturated aliphatic amines it seemed of particular interest to investigate the chemical behavior of simple amines of the furan series. Up to the present no simple aminofuran has been isolated, although several unsuccessful attempts to obtain α-aminofuran have been reported.[8] The only α- and β-aminofurans which have been isolated are those in which a negative substituent (nitro, cyano or carbethoxyl) is present to enhance the stability of the system.[9]

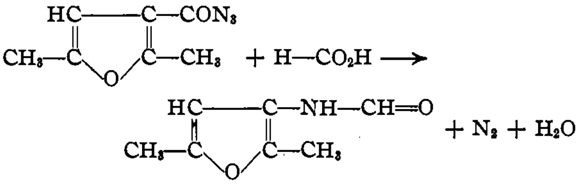
As a means of approach to the aminofurans several α-and β-furyl isocyanates were prepared in this Laboratory,[10] by means of the Curtius reaction, and from these other acylamino derivatives such as the urethans, *sym*-ureas, and benzoyl derivatives were obtained. The earlier work of Freundler, Marquis, and others[8] has shown that the hydrolysis of such compounds under the usual conditions leads to the formation of ammonia and other decomposition products. Likewise, Rinkes[11] has observed that the methylurethan of 2-aminocoumarone (2-amino-3,4-benzofuran) undergoes deamination on hydrolysis with aqueous hydrochloric acid and yields 2-coumaranone.

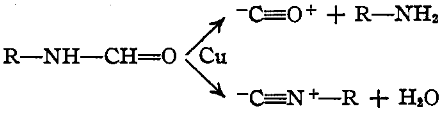
It seemed evident, therefore, that the isolation of a simple aminofuran would depend upon finding a special method of obtaining the amine from the isocyanate or other acylamino derivative, such that contact of the aminofuran with aqueous hydrolytic agents would be minimized. For this purpose a preliminary study of special methods was made with the readily accessible phenyl isocyanate, *sym*-diphenylurea, and other acyl derivatives of aniline. The results of these experiments were promising and indicated that several might be practicable for the aminofurans.

The primary β-aminofurans were selected for the present study rather than α-amino compounds, since the latter contain a system in which the amino group is directly attached to a carbon bearing an oxygen atom (aldehyde–ammonia type). In general the β-amino derivatives appear to be more stable than the α-compounds and consequently are better suited for comparison with the aromatic amines.

For the projected synthesis of 2-methyl-3-aminofuran and 2,5-dimethyl-3-aminofuran the starting materials were ethyl 2-methyl-3-furoate and ethyl 2,5-dimethyl-3-furoate. These esters were converted to the corresponding hydrazides and azides in excellent yields,[10] and thence to the isocyanates, methyl carbamates (urethans) and *sym*-ureas. After many unsuccessful experiments 2-methyl-3-aminofuran was obtained in low yields and in a somewhat impure state by the dry distillation of the methyl carbamate or the *sym*-urea with solid sodium hydroxide.

In an effort to find a better method for obtaining the β-aminofurans a study was made of the preparation of the formyl derivatives from the azides and isocyanates, and of their conversion to the free amines. It was found that cautious decomposition of the azides in the presence of glacial formic acid gave the desired 2-methyl- and 2,5-dimethyl-3-formaminofurans in a pure state. Only small amounts of the *sym*-ureas were formed in this reaction. Heating the formyl derivative of 2,5-dimethyl-3-aminofuran with copper powder to effect elimination of carbon monoxide gave an impure specimen of the amine contaminated with the corresponding isocyanide. Under similar conditions formanilide gave a mixture of aniline (60% yield) and phenyl isocyanide (15%). Evidently a reaction of dehydration proceeds concurrently with the elimination of carbon monoxide, but the latter predominates.





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(6) (a) Allylic rearrangement of the α-furfuryl group: Runde, Scott and Johnson, *ibid.*, **52**, 1284 (1930); Scott and Johnson, *ibid.*, **54**, 2551 (1932). (b) Formation of definite preliminary addition compounds in halogenation and nitration reactions: Moureu, Dufraisse and Johnson, *Ann. chim.*, [10] **7**, 8 (1927); Gilman and Wright, THIS JOURNAL, **52**, 3349 (1930); Freure and Johnson, *ibid.*, **53**, 1142 (1931).

(7) Gilman and Lichtenwalter, *Rec. trav. chim.*, **55**, 588 (1936), have pointed out that the unusually high rate of reaction of 2-furonitrile with phenylmagnesium bromide may lead to the conclusion that furan has decidedly aliphatic properties. They propose a concept in which "the decidedly aromatic radicals would flow into or merge with the decidedly aliphatic radicals."

(8) Freundler, *Bull. soc. chim.*, [3] **17**, 424 (1897); Leimbach, *J. prakt. Chem.*, [2] **65**, 35 (1902); Marquis, *Ann. chim.*, [8] **4**, 196, 272 (1905).

(9) Marquis, ref. 8; Traube and Lazar, *Ber.*, **46**, 3438 (1913); Rinkes, *Rec. trav. chim.*, **51**, 353 (1932); Gilman and Wright, *ibid.*, **53**, 13 (1934).

(10) Blomquist and Stevenson, THIS JOURNAL, **56**, 146 (1934).

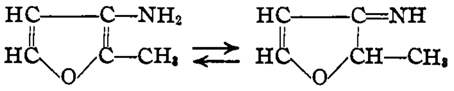
(11) Rinkes, *Rec. trav. chim.*, **51**, 353 (1932).

When the formyl derivative was mixed with dry sodium hydroxide and distilled rapidly in an inert atmosphere, the free amine was obtained in a fairly pure state in 50% yield.

Since the formyl derivatives of arylamines are hydrolyzed much more readily than other acyl derivatives,[12] it seemed possible that the free aminofurans might be obtained by a very rapid hydrolysis of the formyl derivatives with aqueous alkalies. A small steam distillation apparatus was arranged so that the reactants could be introduced in an inert atmosphere and the distillation of the amine completed in less than two minutes (for 5–6 g. of the formyl derivative). This method proved to be very successful and gave the amines in 80% yields. After redistillation under a reduced pressure of nitrogen or methane, pure 2-methyl-3-aminofuran (b. p. 51–52° at 4 mm.) and 2,5-dimethyl-3-aminofuran (b. p. 55–56° at 4 mm.) were obtained as water-white liquids, having an odor resembling dibutylamine and piperidine.

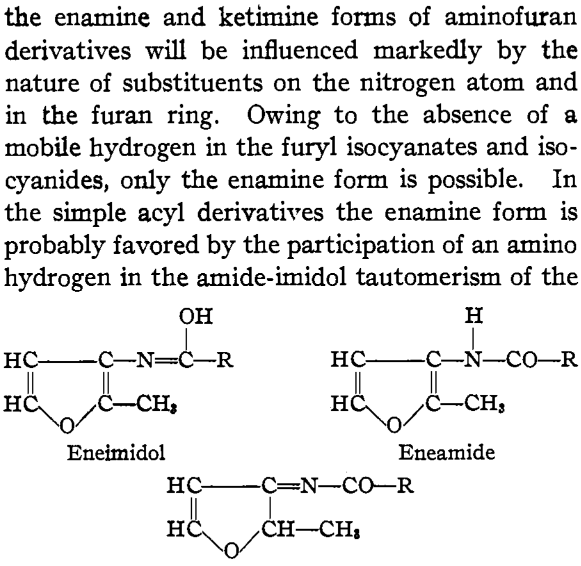
Upon exposure to air the amines discolored rapidly and the odor changed. After an hour in the air 2-methyl-3-aminofuran had been converted to a soft resinous material; the 2,5-dimethyl compound altered somewhat less rapidly. With chloroform and alkali both amines gave a strong, positive carbylamine reaction. The odor of the isocyanides persisted for several days, indicating that the isocyanides are much more stable than the amines toward aqueous reagents and toward air.

Benzoylation of the amines gave crystalline derivatives: 2-methyl-3-benzoylaminofuran and 2,5-dimethyl-3-benzoylaminofuran. The former was shown to be identical with the benzoyl derivative previously synthesized by treating 2-methyl-3-furyl isocyanate with phenylmagnesium bromide.[10] With benzaldehyde 2,5-dimethyl-3-aminofuran gave a crystalline compound which had the composition of an addition product ($C_{13}H_{15}O_2N$), and efforts to effect dehydration to the benzylidine derivative were unsuccessful.



Eneamine form Ketimine form

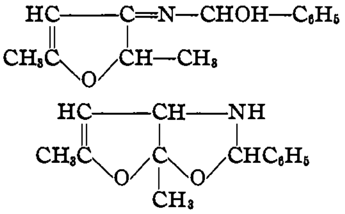
The 3-aminofurans are tautomeric systems of the ketimine $\rightleftarrows$ enamine type, and it seems probable that the ketimine form predominates in the equilibrium mixture. The relative amounts of the enamine and ketimine forms of aminofuran derivatives will be influenced markedly by the nature of substituents on the nitrogen atom and in the furan ring. Owing to the absence of a mobile hydrogen in the furyl isocyanates and isocyanides, only the enamine form is possible. In the simple acyl derivatives the enamine form is probably favored by the participation of an amino hydrogen in the amide-imidol tautomerism of the



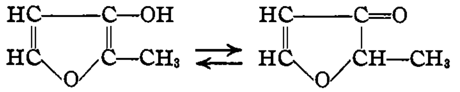
Eneimidol Eneamide

Acyl-ketimine

amide group. The benzaldehyde adduct may be formulated as a derivative of the ketimine form (I), or as a bicyclic structure (II) derived from the eneamine form. Either structure would account for its failure to undergo dehydration to the benzylidene derivative.



It is of interest to compare 2-methyl-3-aminofuran and the corresponding hydroxyl compound, which can exhibit keto–enol tautomerism. Since 2-methyl-3-hydroxyfuran gives only about one-third of a mole of methane[13] when treated with methylmagnesium iodide, it is evident that the



keto form is present to an extent of 65% or more. From analogy with other enolizing systems such as malonic and acetoacetic esters, which contain only small amounts of the enol forms and yet give almost 100% of methane in the Zerewitinoff reaction, it is probable that the hydroxyfuran exists almost entirely in the keto form. Auwers

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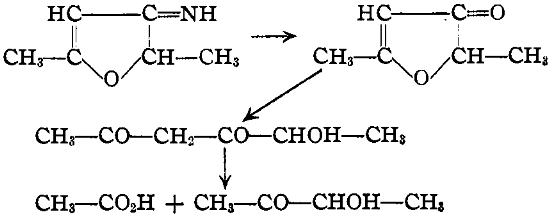
[12] Davis, *J. Chem. Soc.*, **95**, 1400 (1909).

[13] Votoček and Malachta, *Coll. Czechoslov. Chem. Comm.*, **4** 87 (1932); *Chem. Zentr.*, **103**, **I**, 3061 (1932). For studies of other hydroxyfurans see Hoehn, *Iowa State College J. Sci.*, **11**, 66 (1936).

and his co-workers[14] have shown that in every case of ketimine–enamine tautomerism that was studied there was less of ketimine form than of the keto form in the corresponding keto-enol system. This observation, taken with the facts relating to 2-methyl-3-hydroxyfuran, merely indicates that an appreciable quantity of the amino form may be expected in the 3-aminofurans.

The 3-aminofurans are sensitive to the action of hot aqueous acids or alkalies. Hot dilute sulfuric acid rapidly hydrolyzed 2-methyl-3-aminofuran with nearly quantitative elimination of ammonia. Neither of the 3-aminofurans could be isolated by acid hydrolysis of the benzoyl derivatives, followed by addition of alkali and steam distillation. Acid hydrolysis of 2,5-dimethyl-3-formaminofuran followed by steam distillation with alkali, gave a very low yield of the impure amine.[15]

On heating 2,5-dimethyl-3-aminofuran with aqueous potassium hydroxide or barium hydroxide ammonia was evolved; acetic acid and acetoin were identified as the other products of hydrolysis. In this reaction the first step is probably the hydrolysis of the imino form to give ammonia and the ketodihydrofuran. The latter then undergoes ring opening with the formation of an hydroxy-1,3-diketone, which is cleaved by the alkali to give acetoin and acetic acid. This view is supported by Votoček and Malachta's observation that 5-methyl-4-hydroxy-2-furoic acid gives acetoin and oxalic acid upon alkaline hydrolysis.[13] An attempt to arrest the reaction before ring-opening occurred, at the stage of the hydroxyfuran, was unsuccessful.



The β-aminofurans were treated with aqueous sodium nitrite in the presence of an excess of dilute sulfuric acid, but the reaction appeared to resemble the nitrosation of an amine rather than a typical diazotization. With alkaline β-naphthol the diazo solutions gave crystalline, vermilion azo compounds but experiments designed to effect replacement of the diazo group by hydrogen or by the cyano group were unsuccessful. A similar result was reported by Gilman and Wright[9] who observed that the diazo solution obtained from ethyl 5-acetamino-4-amino-2-furoate underwent coupling with β-naphthol but did not react normally in replacement reactions.

It is now evident that the 3-aminofurans do not lend themselves to the manifold transformations that are possible with typical aromatic amines. The ease of hydrolysis of the amines by aqueous acids and alkalies, their sensitivity to atmospheric oxygen, and abnormal behavior in the diazotization reaction, indicate that the furan nucleus does not confer upon a primary amino group (in the 3-position) those qualities which are regarded as most typical of the aromatic primary amines. It is also true that the simple 3-hydroxyfurans do not exhibit the characteristic behavior of phenols. Consequently, if the aromaticity of the benzene ring is responsible for the most typical effects produced upon a primary amino or hydroxyl group directly attached to the ring, then the furan ring must be regarded as having only weakly aromatic properties rather than superaromaticity.

Previous attempts to prepare a simple 2-aminofuran have been unsuccessful. Our experiments in this direction have now proceeded as far as the preparation of 2-furyl and 5-methyl-2-furyl isocyanates in a pure state.[16] A preliminary attempt to obtain 2-aminofuran by one of the methods used for the 3-amino compounds confirms the view that 2-aminofuran is less stable than the 3-aminofurans.

Experimental Part

Preparation of the Aminofurans

2-Methyl-3-furoyl Azide.—Ethyl 2-methyl-3-furoate on heating at 115–125° with 1.9 moles of absolute hydrazine hydrate for fifty-four hours gave the hydrazide, m. p. 152–153°, in 90–93% yields. The hydrazide was treated with sodium nitrite and acetic acid in dilute aqueous solution and the azide was isolated by extraction with benzene. The solvent and admixed water were distilled off under reduced pressure with a bath temperature *not exceeding* 40°. The yield of azide, m. p. about 25°, was 95% of the theoretical.

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[14] Auwers and others, *Ber.*, **63**, 1072 (1930); **64**, 2748 (1931).

[15] Burtner, This Journal, **56**, 667 (1934), has reported the hydrolysis of 2-methyl-3-acylaminofurans by means of aqueous acids and alkalies but the resulting amine was not isolated in a pure state nor identified by means of derivatives.

[16] Singleton and Edwards, in a paper presented at the Chapel Hill meeting of the American Chemical Society, April 12, 1937, have reported the preparation of 2-furyl isocyanate and related α-acylaminofurans. In view of their work our experiments with α-aminofurans have been discontinued.

sym-Bis-(2-methyl-3-furyl) Urea.—This compound was prepared in nearly quantitative yield by refluxing the azide with distilled water for eight hours in an atmosphere of nitrogen. After washing with water and ether the product melted at 220–222°.

The urea was also obtained, together with 2-methyl-3-furyl isocyanate, when the azide was added slowly in small portions to hot glacial acetic acid and the product subjected to vacuum distillation.

Treatment of 2-methyl-3-furyl isocyanate with dry sodium hydroxide, followed by acidification with glacial acetic acid also gave the urea. A sample of 4.8 g. of the freshly distilled isocyanate (b. p. 40° at 13 mm.) which had been prepared by cautious decomposition of the azide in the absence of a solvent, was dissolved in 5 cc. of anhydrous ether and the solution was dropped slowly with shaking into an ice-cold suspension of 2.0 g. of powdered sodium hydroxide (dried over phosphorus pentoxide) in 15 cc. of anhydrous ether. The operations were carried out in an atmosphere of dry nitrogen. After standing for ten minutes the mixture was treated with 2.9 g. of glacial acetic acid and refluxed gently for fifteen minutes. The solid material was collected on a filter, washed with water, and crystallized from alcohol. There was obtained 3.7 g. (87%) of pure white crystals of *sym*-bis-(2-methyl-3-furyl) urea, m. p. 220–222°. Evaporation of the ethereal filtrate left only a trace of solid material.

2-Methyl-3-formaminofuran.—For the decomposition of the azides in the presence of formic (or acetic) acid a special flask was made by sealing a 2-cm. length of 16-mm. tubing to the side of a 26-cc. Pyrex distilling flask at an angle of 45–50° with the neck of the flask. This side arm was bent close to the flask so that any liquid that splashed up would drain back into the flask. The original neck of the flask was fitted tightly with a cork and the new neck was provided with a reflux condenser. Dry nitrogen or methane was admitted through the side arm, and a few pieces of No. 20 carborundum were placed in the flask. A small amount (1 g.) of glacial formic acid (Kahlbaum) was introduced quickly into the flask and heated to boiling with a very small flame. A 0.5-g. portion of the melted azide was added, and vigorous decomposition occurred with evolution of nitrogen. Successive portions of 0.3 g. of formic acid and 0.5 g. of azide were added alternately, and decomposed in the same way. It is important to ensure decomposition of each portion of the azide before a fresh one is added. In this manner 10 g. of 2-methyl-3-furoyl azide was decomposed with 6 g. of formic acid. Distillation of the reaction product gave 6 g. (73% yield) of 2-methyl-3-formaminofuran, b. p. 149–150° at 15 mm. or 138–140° at 8 mm. A small residue remaining in the distilling flask was recrystallized from alcohol and found to be the urea. For analysis a sample of the formamino compound was purified by distillation in a modified Hickman still and then melted at 65.5–67°.

Anal. Calcd. for $C_6H_7O_2N$: N, 11.18. Found: (micro-Dumas) N, 11.22, 11.18.

2,5-Dimethyl-3-furoyl Azide.—Ethyl 2,5-dimethyl-3-furoate for this preparation was obtained by ring closure of ethyl acetonylacetoacetate, which was prepared in 65% yields from bromoacetone and ethyl sodioacetoacetate in benzene.

In a 2-liter three-necked flask fitted with a dropping funnel, reflux condenser, and an efficient mechanical stirrer of the Hershberg type, were placed 23 g. of powdered sodium and 500 cc. of dry benzene. Through the dropping funnel 130 g. (1 mole) of ethyl acetoacetate was added as rapidly as possible (ten to fifteen minutes). It is important to complete the addition before the mixture gelatinizes. The reaction is vigorous and must be controlled. After standing for twenty-four hours, the reaction mixture was cooled in ice and 135 g. (0.98 mole) of freshly distilled bromoacetone was added. This addition was carried out slowly at first, and then more rapidly as the operation of the stirrer became more effective. After one hour, 200 cc. of water was added and the benzene layer was washed with four 100-cc. portions of cold brine. Distillation gave 118 g. (63% yield) of acetonylacetoacetic ester, b. p. 131–133° at 17–18 mm.

A mixture of 450 cc. of 10% sulfuric acid, 50 cc. of ethanol, and 222 g. (1.2 moles) of pure acetonylacetoacetic ester was refluxed gently for eight hours. The upper layer was separated and the lower (aqueous) layer was extracted with two portions of ether. The upper layer and ether extracts were united and washed twice with dilute sodium bicarbonate solution. Distillation gave 133 g. of ethyl 2,5-dimethyl-3-furoate, b. p. 96–100° at 16 mm. The low- and high-boiling fractions were refluxed again with dilute sulfuric acid and alcohol, and gave an additional 20 g. of the product. The total yield in the ring-closure reaction was 74% of the theoretical.

A mixture of 125 g. of ethyl 2,5-dimethyl-3-furoate, 20 cc. of ethanol, and 70 g. of absolute hydrazine hydrate was refluxed for seventy hours. While still hot and fluid the reaction mixture was poured into a large evaporating dish to cool. The waxy mass was cut into thin slices and washed once with ether and twice with ice water. Several concentrations of the mother liquor were necessary to avoid loss of material. The total yield of hydrazide, m. p. 136–137°, was 110 g. (95% of the theoretical). The method given above for 2-methyl-3-furoyl azide was used for converting the 2,5-dimethyl derivative to the azide, m. p. 24–25°, in 94–96% yields.

2,5-Dimethyl-3-formaminofuran.—This compound was prepared from the azide by the procedure described under 2-methyl-3-formaminofuran. From 14 g. of the azide and 11 g. of formic acid there was obtained 9.3 g. (80% yield) of 2,5-dimethyl-3-formaminofuran, b. p. 163–166° at 23 mm. or 152–154° at 11 mm. On further purification the compound melted at 80.5–81.5°.

Anal. Calcd. for $C_7H_9O_2N$: N, 10.07. Found: (micro-Dumas) N, 10.07, 10.24.

2-Furyl Isocyanate.—In the earlier work we had been unable to separate the isocyanate from the ligroin (b. p. 90–100°) which was used as a solvent medium for decomposing 2-furoyl azide, or to avoid explosions in attempting to decompose the azide in the absence of a solvent. This difficulty has been overcome by decomposing 2-furoyl azide in successive small portions in the modified flask described under 2-methyl-3-formaminofuran. This procedure is essentially a decomposition of the azide using the resulting isocyanate as the solvent medium. From 15 g. of the azide there was obtained 8.2 g. (75% yield) of 2-furyl isocyanate, b. p. 110.5–111° at 740 mm. The substance is a colorless liquid having powerful lachrymatory properties. This compound has been reported recently by Singleton and Edwards,[16] who also have prepared several α-acylaminofuran derivatives from it.

Following the usual procedure for obtaining the formamino derivatives, 10 g. of 2-furoyl azide and 6 g. of glacial formic acid were decomposed in small portions. The resulting brown, viscous material was distilled and gave about 1 g. of a colorless liquid, b. p. 95–100° at 9 mm. The liquid was odorless, neutral to litmus, and did not fume when exposed to hydrochloric acid. It was probably a mixture of 2-formaminofuran and *bis*-(2-furyl) urea. On heating with 1 g. of powdered copper, at atmospheric pressure, in an attempt to obtain 2-aminofuran, there was obtained about 0.3 g. of a liquid which had an ammoniacal odor, turned litmus blue, fumed with hydrochloric acid, and appeared to decompose on contact with water. The product may have been an impure specimen of 2-aminofuran, but the small amount available did not permit a definite characterization.

2-Methyl-3-aminofuran. (a) From Methyl 2-Methyl-3-furylcarbamate.—The carbamate was prepared by refluxing 16 g. of 2-methyl-3-furoyl azide with 50 cc. of anhydrous methyl alcohol for twenty-four hours and removing the excess methyl alcohol by distillation from a steam-bath. An attempt was made to distil the urethan, but some decomposition occurred, so the urethan was used without purification.

In a 15-cc. distilling flask were placed 7.5 g. of the urethan and 4 g. of dry, powdered sodium hydroxide. The apparatus was flushed with dry nitrogen and heated until no more distillate was obtained. The distillate was collected in a small Claisen flask over 0.5 g. of dry sodium hydroxide, since it was thought that sodium hydroxide would tend to dry, as well as to stabilize, the amine. Only a few drops of impure amine was obtained when the crude product was redistilled at 15 mm. under nitrogen. A brown tarry residue remained in the Claisen flask.

(b) From sym-bis-(2-Methyl-3-furyl)-urea.—When a mixture of 4 g. of this urea and 2 g. of dry, powdered sodium hydroxide was heated in a 10-cc. distilling flask under nitrogen, about 2 cc. of liquid distilled. Redistillation under nitrogen gave about 0.3 g. of impure amine, b. p. 40–50° at 3 mm. There was a considerable amount of nonvolatile, viscous residue.

(c) From 2-Methyl-3-formaminofuran.—A mixture of 5 g. of 2-methyl-3-formaminofuran and 3 g. of dry, powdered sodium hydroxide was heated with a low flame in a small distilling flask under nitrogen. A yellow liquid distilled over at 130–140°. Redistillation was difficult because of foaming and decomposition, and only about 0.5 g. of impure amine was obtained.

The most satisfactory method of preparing the amine was found to be by alkaline hydrolysis of the formyl derivative. In a small, modified Pozzi-Escot[17] steam-distillation apparatus which had been flushed thoroughly with methane, and through which a slow stream of methane was being passed, was placed 6 g. of 2-methyl-3-formaminofuran. A hot solution of 10 g. of potassium hydroxide in 15 cc. of water was added and steam distillation completed as soon as possible. Usually the large drops of amine stopped coming over in about two minutes. The water-white distillate amounting to 12–15 cc. was collected in a gas-filled 25-cc. separatory funnel. Some amine was insoluble and sank to the bottom, but most of it remained as an emulsion. Freezing and remelting caused the amine to precipitate in colorless droplets. The amine was transferred to a small Claisen flask and distilled under methane. The first fraction contained the water which had dissolved in the amine. The main fraction boiled at 51–52° (4 mm.) and was preserved by sealing in small ampoules. The water-white amine was highly refractive and had an odor resembling dibutylamine and piperidine. Exposure of the amine to air caused an immediate yellow coloration and a thin layer after about one hour had resinified completely. The total yield of amine was above 80%.

Anal. Calcd. for C_5H_7ON: N, 14.42. Found: (micro-Dumas) N, 14.11, 14.27.

2,5-Dimethyl-3-aminofuran.—A mixture of 4 g. of 2,5-dimethyl-3-formaminofuran and 2 g. of powdered copper was distilled from a small flask in an atmosphere of nitrogen. About 2 cc. of an oily liquid (containing some unchanged formamino compound) distilled in the range 190–240°. This was treated with 1 g. of copper powder and redistilled. There was obtained about 1 g. of amine, which had a strong odor of isocyanide.

Hydrolysis of the formamino derivative with aqueous alkali, as described under 2-methyl-3-aminofuran, proved to be the best method of obtaining the amine and gave yields above 80% of the theoretical. 2,5-Dimethyl-3-aminofuran was obtained as a colorless liquid, b. p. 55–56° at 4 mm. This amine is much less soluble in water than the 2-methyl compound, has a milder odor, and on exposure to air undergoes discoloration and resinification less rapidly.

Anal. Calcd. for C_6H_9ON: N, 12.6. Found: (micro-Dumas) N, 12.09, 12.15.

The analytical values for nitrogen were somewhat low for both of the amines. This was probably due in part to the presence of traces of moisture, and to the difficulty of filling tubes for the micro-Dumas determinations without some exposure of the specimens to the air.

Reactions of the 3-Aminofurans

2-Methyl-3-benzoylaminofuran.—To a solution of 1 cc. of 2-methyl-3-aminofuran in 5 cc. of pyridine was added 1 cc. of benzoyl chloride. After shaking for ten minutes the mixture was poured into water and the benzoyl derivative collected with suction. After washing thoroughly and recrystallizing from dilute alcohol (with addition of charcoal) the compound formed white crystals, m. p. 137–137.5°, and showed no depression when mixed with an authentic sample.[10] The amine was also benzoylated in ether solution in the presence of anhydrous potassium carbonate.

3,5-Dimethyl-3-benzoylaminofuran.—The benzoyl derivative of 2,5-dimethyl-3-aminofuran was prepared in the presence of pyridine. After recrystallization from dilute alcohol (with addition of charcoal) and sublimation at 140° (3 mm.), white crystals were obtained melting at 152–152.4°.

Anal. Calcd. for $C_{13}H_{13}O_2N$: N, 6.51. Found: (micro-Dumas) N, 6.53, 6.54.

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(17) Pozzi-Escot, *Bull. soc. chim.*, [3] **31**, 932 (1904).

Isocyanide (Carbylamine) Reaction.—Both amines gave strong, positive carbylamine tests when warmed with chloroform, potassium hydroxide solution, and alcohol. The isocyanides were judged to be relatively stable but no attempt was made to isolate them.

Reaction of 2,5-Dimethyl-3-aminofuran with Benzaldehyde.—A solution of 6 g. of benzaldehyde in 10 cc. of alcohol was added to 7 g. of 2,5-dimethyl-3-aminofuran in 10 cc. of water. The reactants dissolved completely and a heavy oil began to separate at once. After standing for twenty-four hours at −10°, crystals had formed in the oily layer. The upper, aqueous layer was poured off, a little alcohol was added to dissolve the oil, and the resulting suspension was filtered quickly. The solid material was washed with three small portions of cold alcohol and dried in a desiccator. The pale yellow, crystalline product weighed 3.7 g. and melted at 113–115°. Since all attempts to purify the compound led to decomposition, the crystals were analyzed directly. The analytical data show that the substance corresponds to the addition of a molecule of benzaldehyde *without* elimination of water.

Anal. Calcd. for $C_{13}H_{15}O_2N$: N, 6.45. Calcd. for $C_{13}H_{13}ON$: N, 7.0. Found: (micro-Dumas) N, 6.47, 6.44.

Alkaline Ring Cleavage of 2,5-Dimethyl-3-aminofuran.—The amine was prepared from 5 g. of the formyl derivative and steam distilled directly onto 10 g. of solid barium hydroxide in a 200-cc. round-bottomed flask until about 75 cc. of distillate had been collected. The mixture was refluxed under methane until a slow stream of gas passing through the apparatus no longer had an odor of ammonia. The solution was then treated with carbon dioxide and the barium carbonate filtered off. A test portion of the hydrolysate caused a rapid reduction of Fehling's solution in the cold—indicating the presence of acetoin.

In one portion of the filtrate acetoin was identified by the formation of diacetyl phenylosazone, m. p. 242–244°, and in another portion acetic acid was identified by means of *p*-nitrobenzyl acetate, m. p. 75–76°. Both derivatives were compared with authentic specimens.

Hydrolysis with potassium hydroxide gave a similar result but the reaction was much slower. An attempt to arrest the reaction at an intermediate stage, by methylation with dimethyl sulfate, was unsuccessful.

Acid Hydrolysis of 2-Methyl-3-aminofuran.—An ampoule containing 0.44 g. of pure 2-methyl-3-aminofuran was placed in a 50-cc. extraction flask carrying a condenser, separatory funnel, and an inlet tube for flushing with methane. A tube from the condenser led to a bubbler containing standard sulfuric acid. After completely flushing the apparatus with methane, the ampoule was broken by shaking, 20 cc. of 15% sulfuric acid was added, and the mixture was boiled for ten minutes. The flask was immediately cooled with ice, and 25% potassium hydroxide solution was added. The ammonia was determined and amounted to 89% of the theoretical.

Diazotization of 2-Methyl-3-aminofuran.—To 20 cc. of ice-cold 10% sulfuric acid was added 2 g. of 2-methyl-3-aminofuran. A light yellow precipitate appeared, but dissolved very rapidly. A small portion of sodium nitrite solution was added, which caused the momentary formation of a blue-green color. A positive starch–potassium iodide test was obtained, so the remainder of the theoretical amount of sodium nitrite was added in portions. The transient blue-green color appeared after each addition.

A part of the diazotized solution was poured into an excess of very cold 10% sodium hydroxide solution, giving a light red-brown solution which evolved a gas on standing.

Addition of a portion of the diazotized solution to dimethylaniline in 5% sodium hydroxide solution gave a light scarlet, slightly turbid solution.

The remainder of the diazotized solution was added to β-naphthol in sodium hydroxide to give an orange precipitate. This was filtered and sublimed to give vermilion crystals of the azo compound melting at 122–122.5°.

Anal. Calcd. for $C_{15}H_{12}O_2N_2$: N, 11.10. Found: (micro-Dumas) N, 11.15, 11.14.

The azo compound was slightly soluble in concentrated hydrochloric acid or 50% sulfuric acid, giving a brilliant magenta color which was destroyed by the addition of stannous chloride.

An unsuccessful attempt was made to replace the diazo group by cyanide. The diazo solution from 1 g. of 2-methyl-3-aminofuran was poured into 25 cc. of hot cuprous cyanide solution and held at 60–70° for thirty minutes. To this was added 100 cc. of water and the mixture was steam distilled. No 2-methyl-3-furoic acid could be obtained by the action of sodium hydroxide on the distillate. Benzoic acid had been prepared from aniline in a similar manner in a control experiment.

Diazotization of 2,5-Dimethyl-3-aminofuran.—This amine was treated with sulfuric acid and sodium nitrite under the same conditions used for 2-methyl-3-aminofuran. The reaction was similar except that the blue-green coloration, which developed on adding the nitrite, often persisted for ten or fifteen minutes.

A portion of diazotized solution was poured into hot cuprous cyanide solution, but no definite product was obtained.

Another portion was added to dimethylaniline in 5% sodium hydroxide solution, and a scarlet, turbid solution resulted. After removing excess dimethylaniline there was obtained about 50 mg. of deep red crystals, which had no melting point. The material was red in alkaline, and yellow in acid solution. From alcohol containing a small drop of 10% sodium hydroxide, purple-red crystals without a melting point were obtained. The rest was recrystallized from ligroin–benzene mixture and gave bright yellow crystals, m. p. 237–240°. Analysis showed that the substance contained only 8.5% nitrogen, and it is evidently not the expected azo-compound (N, 17.3%). The structure of the compound was not determined. It is clear that the diazotized 3-aminofurans do not react with dimethylaniline in a normal fashion.

Addition of the diazonium solution to β-naphthol in sodium hydroxide solution caused the formation of a brown-red solid. This was collected on a filter and extracted with alcohol. Reprecipitation and sublimation gave vermilion crystals of the azo compound, m. p. 108–110°. Its reactions were identical with those of the corresponding compound obtained from 2-methyl-3-aminofuran.

Anal. Calcd. for $C_{16}H_{14}O_2N_2$: N, 10.52. Found: (micro-Dumas) N, 9.96.

In an attempt to replace the amino group by hydrogen, 2.5 g. of 2,5-dimethyl-3-aminofuran was diazotized in 50 cc. of alcohol containing 7 cc. of sulfuric acid and 10 cc. of water. Addition of copper powder caused vigorous evolution of a gas, which must have contained some nitric oxide since it turned brown on contact with air. After fifteen minutes in the ice-bath, the mixture was warmed cautiously on a steam-bath. Neither 2,5-dimethylfuran nor the product of ring opening, acetonylacetone, could be detected in the reaction mixture. Control experiments indicated that a quantity of dimethylfuran corresponding to a 5% yield in the replacement reaction could have been detected.

Summary

Methods have been developed for the synthesis of aminofurans. Two simple β-aminofurans, 2-methyl-3-aminofuran and 2,5-dimethyl-3-aminofuran, have been prepared in a pure state and their chemical behavior has been investigated.

The amines were found to resinify upon exposure to air, and to undergo hydrolytic cleavage on warming with aqueous acids or alkalies. The amines have been diazotized and coupled with β-naphthol, but other reactions of the diazotized amines appear to be abnormal.

The behavior of the 3-aminofurans indicates that they possess only to a limited extent the properties that are most typical of aromatic amines. The furan nucleus appears to have weakly aromatic properties rather than superaromaticity.

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The Synthesis of Conjugated Bile Acids. IV. The Bondi and Mueller Procedure

BY FRANK CORTESE

We are now able to furnish practical details for a successful accomplishment of the old Bondi and Mueller[1] procedure in the synthesis of conjugated bile acids. The present revised methods offered are more convenient to carry out than the synthesis we have already published.[2]

Experimental Part

Ethyl Cholate.—Ten cc. of colorless c. p. fuming sulfuric acid (20–30% SO_3) is added to 250 cc. of commercial absolute alcohol previously cooled to 0°. The mixture is shaken with 25 g. of c. p. cholic acid for two hours or until solution occurs. After standing for twenty-four hours at room temperature, or in the ice-box on very warm days, the mixture is cooled to 0° and poured slowly, in portions and with stirring, into an ice-cold solution of 20 g. of sodium hydroxide in 2000 cc. of water, previously sprinkled with ethyl cholate. It is well to wait a few minutes until each added portion crystallizes in order to avoid large lumps. Fifty cc. of ethyl acetate is now stirred in well to neutralize the excess alkali. After standing in the refrigerator for ten or more hours, the product is filtered by *gentle* suction, washed well with water, thoroughly dried over calcium chloride in a vacuum desiccator, and dissolved in 200 cc. of boiling ethyl acetate. Enough petroleum ether (30–60°) is added to the hot solution to make a final volume of one liter. After twenty-four to forty-eight hours, but not longer, at room temperature, the product is washed on the filter with the same solvent mixture and air dried; yield, 22–24 g. (82–90%); m. p. 162–163°.[3]

Methyl Cholate.—The preparation is the same as the preceding except for the substitution of methyl alcohol as the solvent. The crude product, 25.8 g., is dissolved in 150 cc. of hot 95% alcohol. After cooling, 225 cc. of water is added. When crystals appear, the mixture is stored at 0° for twenty-four hours; yield 25 g.; m. p. 155–156°. (It is heated slowly between 90–105°.)

Ethyl Deoxycholate.—To a filtered solution of the crude product, prepared in the same way as ethyl cholate, in 85 cc. of ether (a cover glass is put on the gravity filter to prevent clogging) is added 265 cc. of light petroleum ether or enough to cause incipient cloudiness. The crystals are filtered, after forty-eight hours at room temperature, washed with a mixture of petroleum ether and ether (10:1) and air dried. The filtrate is spontaneously evaporated and only the dry material under the ring of gum is recrystallized. The total product is crystallized once more; yield, 23–25 g. (90%); m. p. 98–99°.

Cholyl Hydrazide.—Ten grams of pure ethyl cholate is refluxed for twenty-four hours with 8 cc. of commercial absolute alcohol and 4 cc. of hydrazine hydrate, excluding moisture with a calcium chloride tube. After diluting with 100 cc. of hot 95% alcohol, enough boiling water is added to make a total volume of 750 cc. The mixture is seeded, stirred well and stored at 0° for twenty-four hours. The product, filtered by gentle suction, washed with water and air dried for two days, should be completely soluble in very dilute hydrochloric acid: yield, 8.5 g. (88%); m. p. 188–189°.

Increasing the amount of hydrazine or the time of refluxing or the temperature results in the formation of a by-product insoluble in acid, presumably the symmetrically disubstituted hydrazide. Reducing the amount of hydrazine produces a lower yield and may give an inferior product.

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[1] Bondi and Mueller, *Z. physiol. Chem.*, **47**, 499 (1906).

[2] Cortese and Bashour, *J. Biol. Chem.*, **119**, 177 (1937).

[3] All melting points given in this article are corrected.