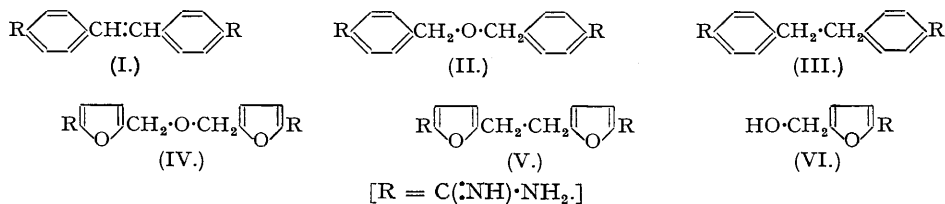


80. The Conversion of Sucrose into Furan Compounds. Part III. Some Amidino-furans.

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Several new amidino-derivatives of furan have been obtained. Two of them, namely 5 : 5'-diamidino- $\alpha\beta$ -2 : 2'-difurylethane and 5 : 5'-diamidinodifurfuryl ether, are analogues of diamidines of the benzene series found to be active against trypanosomes. The new furan compounds, however, possess high toxicity and show only little activity against *T. equiperdum* *in vivo*.

SINCE it was demonstrated (Warrington Yorke *et al.*, *Trans. Roy. Soc. Trop. Med. Hyg.*, 1940, **33**, 463) that certain amidine derivatives possessed trypanocidal activity, the value of this type of drug in combating trypanosomiasis and leishmaniasis has been well established. Subsequently a great deal of effort has been directed towards the preparation and chemotherapeutic evaluation of a large number of amidino-compounds. Ewins *et al.* (*J.*, 1942, 103), have found that the most active compounds in the benzene series are "stilbamidine" [4 : 4'-diamidinostilbene (I)], 4 : 4'-diamidino- $\alpha\gamma$ -diphenoxypropane, 4 : 4'-diamidino- $\alpha\varepsilon$ -diphenoxypentane, 4 : 4'-diamidino-dibenzyl ether (II), and 4 : 4'-diamidino- $\alpha\beta$ -diphenylethane (III).



It occurred to us that it would be of interest to prepare the furan analogues of some of these compounds in order to discover the effect on trypanocidal activity of replacement of the benzene by the furan nucleus. Furan analogues of compounds (II) and (III), namely 5 : 5'-diamidinodifurfuryl ether (IV) and 5 : 5'-diamidino- $\alpha\beta$ -2 : 2'-difurylethane (V) (isolated at its *dihydrochloride*), have now been obtained. Only the latter, however, showed any trypanocidal activity. A mono-amidino-compound, 5-amidinofurfuryl alcohol (VI) (isolated as its *hydrochloride*) was also prepared, but this possessed no activity against trypanosomes.

Compound.	Minimum effective dose (mg./g.).	Maximum tolerated dose (mg./g.).
4 : 4'-Diamidinodibenzyl ether	0.0005	0.015
4 : 4'-Diamidino- $\alpha\beta$ -diphenylethane	0.001	0.015
5 : 5'-Diamidino- $\alpha\beta$ -2 : 2'-difurylethane	0.025	0.25
5 : 5'-Diamidinodifurfuryl ether	No action	0.25
5-Amidinofurfuryl alcohol	No action	2.5

The new amidinofurans were obtained in the following way. A convenient starting material for the synthesis of 5 : 5'-diamidinodifurfuryl ether was 5 : 5'-diformyldifurfuryl ether, a by-product in the preparation of 5-hydroxymethylfurfuraldehyde by the action of oxalic acid on sucrose (Kiermayer, *Chem. Ztg.*, 1895, **19**, 1003; Haworth and Jones, *J.*, 1944, **667**). The dialdehyde was converted into its dioxime and this, by dehydration with acetic anhydride, gave 5 : 5'-*dicyanodifurfuryl ether* which was then converted into its *di-iminoether dihydrochloride*. The conversion of this substance into the diamidine proved somewhat difficult. The iminoether possessed considerable stability towards ammonia at 0°, the usual procedure for conversion of an iminoether into an amidine, and by this treatment the dihydrochloride gave only the free iminoether, identified as its dihydrochloride, and ammonium chloride. To form the amidino-compound it was necessary to employ alcoholic ammonia at 100° under pressure, and under these conditions 5 : 5'-diamidinodifurfuryl ether was obtained, and was further characterised as its *dipicrate*.

5 : 5'-Diamidino- $\alpha\beta$ -2 : 2'-difurylethane was synthesised from the main product of the action of dilute oxalic acid on sucrose, namely 5-hydroxymethylfurfuraldehyde. This was converted by a modified procedure of Middendorp (*Rec. Trav. chim.*, 1919, **38**, 1) into 5-bromomethylfurfuraldehyde which, on treatment with freshly precipitated silver according to the method of Fenton and Gostling (*J.*, 1901, **79**, 807), gave $\alpha\beta$ -2 : 2'-difurylethane-5 : 5'-dialdehyde. The dioxime of this compound gave 5 : 5'-*dicyano- $\alpha\beta$ -2 : 2'-difurylethane* on dehydration. The *di-iminoether dihydrochloride* obtained therefrom proved to be just as stable to ammonia as the corresponding derivative of 5 : 5'-diformyldifurfuryl ether, and its treatment with ammonia in the cold led mainly to the formation of the free *di-iminoether*, together with ammonium chloride and a very small amount of 5 : 5'-diamidino- $\alpha\beta$ -2 : 2'-difurylethane. The purification of the free di-iminoether was achieved with some difficulty, although its dihydrochloride was a well-defined compound. When the difurylethaned-di-iminoether dihydrochloride was treated with alcoholic ammonia at 110°, the diamidine was the main product.

5-Amidinofurfuryl alcohol was obtained from 5-hydroxymethylfurfuraldehyde by the usual procedure.

EXPERIMENTAL.

Dioxime of 5 : 5'-Diformyldifurfuryl Ether.—5 : 5'-Diformyldifurfuryl ether (7.2 g.), obtained as a by-product in the preparation of 5-hydroxymethylfurfuraldehyde from sucrose, was dissolved in 50% alcohol (130 c.c.), and a solution containing hydroxylamine hydrochloride (8.6 g.) and sodium carbonate (6.5 g.) in water (50 c.c.) added. The solution was boiled under reflux for 3 hours and, on cooling, crystalline material separated. This recrystallised from alcohol in the form of fine needles, m. p. 167—168° (Kiermayer, *loc. cit.*, gives m. p. 167°). Yield, 1.25 g. (Found : C, 54.8; H, 4.6. Calc. for $C_{12}H_{12}O_5N_2$: C, 54.8; H, 4.6%).

5 : 5'-*Dicyanodifurfuryl Ether*.—The dioxime (1.25 g.) was boiled under reflux with acetic anhydride (50 c.c.) for 1 hour. Thereafter it was poured into water and neutralised with sodium bicarbonate, and the solution extracted thrice with chloroform. The combined extracts were dried ($MgSO_4$) and filtered with charcoal. Evaporation of the solvent under diminished pressure gave a syrup which crystallised on trituration with alcohol; on recrystallisation from alcohol-water the *dicyanide* formed pale yellow plates, m. p. 57—58°. Yield, 0.78 g. (Found : C, 63.5; H, 3.3; N, 12.8. $C_{12}H_8O_3N_2$ requires C, 63.2; H, 3.5; N, 12.3%).

Difurfuryl Ether 5 : 5'-Di-iminoether Dihydrochloride.—The dicyanide (3.4 g.) was dissolved in absolute alcohol (40 c.c.) saturated with dry hydrogen chloride at 0°, and the solution kept thereat for 48 hours. The crystalline material which separated was filtered off and washed with dry ether until free from hydrogen chloride. Yield, 5.5 g. (96%). Recrystallised from absolute alcohol, the *dihydrochloride* had m. p. 134—135° (decomp.) (Found : C, 48.7; H, 5.2; N, 7.3. $C_{16}H_{20}O_5N_2 \cdot 2HCl$ requires C, 48.8; H, 5.6; N, 7.1%).

The iminoether (5 g.) was treated with absolute alcoholic ammonia (saturated at 0°) and the solution kept at 0° for 48 hours. Thereafter, evaporation to a quarter volume led to the separation of ammonium chloride (0.3 g.). Further evaporation of the solvent gave a syrup (3.9 g.), which was alkaline to litmus. On passing dry hydrogen chloride into an ethereal solution of the syrup the dihydrochloride of the iminoether was recovered, m. p. 133—135°.

5 : 5'-*Diamidinodifurfuryl Ether*.—The iminoether hydrochloride (2.4 g.) was heated at 110° for 8 hours with absolute alcoholic ammonia (100 c.c. saturated at 0°). On cooling, crystals separated which, when recrystallised from absolute alcohol, formed plates, m. p. 198—198.5° (1.07 g.) (Found : C, 54.7; H, 5.3. $C_{12}H_{14}O_3N_4$ requires C, 54.7; H, 5.3%). The *amidine* was only sparingly soluble in water

(0.2 g./100 g. H₂O). The *dipicrate* recrystallised from water in the form of plates and had an indefinite decomposition point above 300° (Found: C, 40.3; H, 3.1. C₂₄H₂₀O₁₇N₁₀ requires C, 40.0; H, 2.8%).

5-Bromomethylfurfuraldehyde.—5-Hydroxymethylfurfuraldehyde (50 g.) dissolved in dry ether (200 c.c.) was added slowly to a solution of dry hydrogen bromide in dry ether (50%) at 0°. The mixture was allowed to reach room temperature and kept thereat for 2 hours. By this time signs of humin formation had become apparent and the solution was dark purple. It was neutralised with anhydrous sodium carbonate, the ethereal solution filtered, and the solid residue washed thoroughly with ether. Evaporation of the combined filtrate and washings gave a syrup (47 g.) which crystallised completely on nucleation. Recrystallisation from ether gave 5-bromomethylfurfuraldehyde, m. p. 59–60°, in yellow prisms (40% yield). The procedure is a modification of that of Middendorp (*loc. cit.*).

αβ-2:2'-Difurylethane-5:5'-dialdehyde.—5-Bromomethylfurfuraldehyde (13.8 g.) was dissolved in dry benzene (25 c.c.) and finely divided silver (30 g.) added. After boiling under reflux for 6 hours, the silver residues were extracted with boiling benzene several times and the combined extracts evaporated. The semi-solid mass was washed with a little benzene so that a yellow crystalline material (7.7 g.) remained. This recrystallised from benzene in yellow needles, m. p. 118–120° (Fenton and Gostling, *loc. cit.*, give m. p. 119.5–121°). Evaporation of the benzene washings gave a little more material. Total yield, 4.5 g. (54.5%).

αβ-2:2'-Difurylethane-5:5'-dialdoxime.—This was prepared according to the procedure of Fenton and Gostling (*loc. cit.*) but it had m. p. 200.5–201.5° whereas the earlier workers record m. p. 182° (Found: C, 58.4; H, 4.8; N, 11.8. Calc. for C₁₂H₁₀O₄N₂: C, 58.1; H, 4.8; N, 11.3%).

5:5'-Dicyano-αβ-2:2'-difurylethane.—Difurylethanedialdoxime (1.77 g.) was boiled under reflux with acetic anhydride (25 c.c.) for ½ hour. The solution was poured into water, neutralised with sodium bicarbonate, and extracted with chloroform. The chloroform extract was dried (MgSO₄), filtered, and evaporated to dryness. The *dicyanide* recrystallised from alcohol in pale yellow needles, m. p. 115–116° (Found: C, 68.4; H, 3.6; N, 13.0. C₁₂H₈O₂N₂ requires C, 67.9; H, 3.7; N, 13.2%).

αβ-2:2'-Difurylethane-5:5'-di-iminoether Dihydrochloride.—The above dicyanide (2.4 g.) was treated with absolute alcohol saturated with dry hydrogen chloride at 0° (150 c.c.) for 4 days. The crystals which had separated were filtered off and washed with dry ether until free from hydrogen chloride. Yield, 2.5 g.; m. p. 245–252°. After recrystallisation from absolute alcohol, the *dihydrochloride* had m. p. 253–255° (Found: N, 7.2. C₁₆H₂₀O₄N₂·2HCl requires N, 7.4%).

The iminoether dihydrochloride (4.0 g.) was treated with a solution of alcoholic ammonia (100 c.c. saturated at 0°) for 2 days. On evaporation of the solution to half volume crystals of ammonium chloride (0.9 g.) separated. Further evaporation gave a solid residue. This was extracted with ether, and from the ethereal extract upon cooling there were deposited feathery crystals of *αβ-2:2'-difurylethane 5:5'-di-iminoether*, m. p. 79–80.5° (Found: N, 8.8. C₁₆H₂₀O₄N₂ requires N, 9.2%). The ether-insoluble residue was dissolved in alcohol, and a little ether added, when unchanged dihydrochloride was isolated. Further addition of ether gave more of the free base contaminated with ammonium chloride.

5:5'-Diamidino-αβ-2:2'-difurylethane Dihydrochloride Dihydrate.—The iminoether dihydrochloride (2.6 g.) was heated with ethyl alcoholic ammonia (100 c.c.) at 110° for 6 hours. On evaporation to 20 c.c., fine needles (1.04 g.) separated which, on being recrystallised from ethyl alcohol, had m. p. 251° (Found: C, 40.3; H, 5.6; N, 15.5; H₂O, 10.6. C₁₂H₁₄O₂N₄·2HCl·2H₂O requires C, 40.5; H, 5.6; N, 15.8; H₂O, 10.2%). This *dihydrate* of 5:5'-diamidinodifurylethane dihydrochloride was soluble in water to the extent of 2.7 g. per 100 c.c. of solution. On being heated at 110° for 3 hours, it yielded the anhydrous salt, m. p. 282–283° (Found: C, 45.8; H, 5.2. C₁₂H₁₄O₂N₄·2HCl requires C, 45.1; H, 5.0%).

2-Cyano-5-acetoxymethylfuran.—5-Hydroxymethylfurfuraldoxime (Kiermayer, *loc. cit.*) (21 g.) was boiled under reflux with acetic anhydride (60 c.c.) and fused sodium acetate (3 g.) for ½ hour. After being poured into water, the solution was neutralised with sodium bicarbonate and then extracted with ether. The extract was dried (MgSO₄), the solution filtered, and the ether removed. The liquid remaining distilled at 140° (bath temp.)/0.01 mm. as a colourless oil having n_D^{20} 1.4970. Yield, 16.4 g. (Found: N, 8.9. C₈H₇O₂N requires N, 8.5%).

5-Acetoxymethylfuran-2-iminoether Hydrochloride.—The above *cyanide* (7.5 g.) was dissolved in absolute alcohol (20 c.c.) saturated with dry hydrogen chloride, and kept at 0° for 4 days. The iminoether *hydrochloride* which separated was filtered off and washed with dry ether until free from hydrogen chloride. It recrystallised from absolute alcohol-ether in clusters of needles, m. p. 121–121.5° (6.6 g.) (Found: C, 48.2; H, 5.9. C₁₀H₁₃O₄N·HCl requires C, 48.4; H, 6.1%).

5-Amidinofurfuryl Alcohol Hydrochloride.—The iminoether hydrochloride (5 g.) was dissolved in absolute alcohol saturated with ammonia at 0° and kept at 0° for 24 hours. On evaporation of the solvent at room temperature under diminished pressure a solid residue was obtained which recrystallised from dry alcohol-ether in needles, m. p. 147–148°. It was very soluble in water (Found: C, 40.7; H, 5.1; N, 15.5. C₈H₉O₂N₂·HCl requires C, 40.9; H, 5.1; N, 15.9%). The same *product* was obtained if the reaction was conducted at 110° in a sealed tube. The amidine formed a well-defined *picrate* which recrystallised from water in needles, m. p. 223–225° (Found: C, 39.0; H, 3.1. C₁₂H₁₁O₆N₅ requires C, 39.1; H, 3.0%).

The authors are grateful to Professor C. R. Harington, F.R.S., Director of Research, Medical Research Council, who arranged for the testing of the compounds for trypanocidal activity. Their thanks are also due to the Colonial Products Research Council for financial support.