265. *Some Amidines and Amidoximes with Trypanocidal Activity.*

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A series of alkylenediamidoximes and diamidoximes of diphenyl, diphenylmethane, dibenzyl, stilbene, and dibenzyl sulphide have been prepared. Some new alkylene-amidines are also described. The trypanocidal activity of these compounds has been investigated.

It was shown by King, Lourie, and Yorke (*Lancet*, 1937, **233**, 1360; *Ann. Trop. Med. Parasit.*, 1938, **32**, No. 2, 177) that long-chain alkylene-di*iso*thioureas, -diguanidines, or -diamidines had a curative action against mouse trypanosomiasis. For the di*iso*thioureas the maximum activity was found in the substance with six methylene groups, for the

diguanidines it occurred with from 10 to 14 methylene groups, and for the diamidines with 11 methylene groups. They also found that activity was shown by the *pp'*-diguanidino- or -diamidino-derivatives of diphenylmethane.

An analogous series of alkylenediamidoximes (I) has been prepared in which n is 5, 7, 9, 10, 11, or 13, and also the diamidoximes derived from diphenyl, diphenylmethane, dibenzyl (II; $n = 2$), and stilbene.

$NH_2 \cdot C(:NOH) \cdot [CH_2]_n \cdot C(:NOH) \cdot NH_2$ (I.)

$NH_2 \cdot C(:NOH) \cdot C_6H_4 \cdot [CH_2]_n \cdot C_6H_4 \cdot C(:NOH) \cdot NH_2$ (II.)

The higher members of the long-chain series, where n is 10, 11, or 13, have considerable activity against experimental mouse trypanosomiasis (*T. equiperdum*).* Control injections of undecanediamidine dihydrochloride in doses of 0·05 and 0·1 mg. per 20 g. of mouse intravenously and 0·2 and 0·1 mg. per 20 g. of mouse *per os* were found to be very effective in curing our mice. One experiment where the *decane-*, *undecane-*, and *tridecane-dicarbonamidoximes* and undecanediamidine dihydrochloride were reinjected in the same doses whenever the infection reappeared after the preliminary dose of the drug showed that the diamidine compound was the most active on both oral and intravenous administration; this was closely followed by the undecanedicarbonamidoxime, and then successively by the decane- and the tridecane-dicarbonamidoxime. The comparison was only a rough one as we used small numbers of mice. The last compounds were of a similar order of toxicity to undecanediamidine dihydrochloride. Where $n = 9$ the compound showed only a slight activity, and where $n = 7$ or 5 the compounds were inactive in doses similar to the control undecanediamidine dosage.

These compounds were prepared by Tiemann's method by the action of hydroxylamine on the corresponding nitriles in aqueous alcohol (*Ber.*, 1884, **17**, 126). The alkylenediamidoximes derived from succinic and glutaric acids had been made by Sembritzki (*Ber.*, 1889, **22**, 2958) and by Biedermann (*ibid.*, p. 2967) by this method. The reaction goes readily with the higher homologues ($n = 10$—13) and also with the lowest one ($n = 5$). In the compounds where $n = 7$, 8, or 9 the yields were poor and the products difficult to purify. In some cases 1-amidoximes-ω-nitriles, 1-amidoximes-ω-amides and 1-amide-ω-nitriles were isolated as by-products. Of these, *1-cyanoundecane-11-carbonamidoxime hydrochloride* in doses of 0·2 mg. intravenously and 2·0 mg. orally, *1-cyano-13-carbonamidoximetridecane hydrochloride* 0·4 mg. intravenously, and *undecane-1-carbonamide-11-carbonamidoxime hydrochloride* 0·4 mg. intravenously, all per 20 g. of mouse, were inactive. The alkylenediamidoximes are not so strongly basic as the corresponding diamidines, but form stable dihydrochlorides which are usually readily soluble in water.

Diacetyldecane-1 : 10-dicarbonamidoxime has somewhat less activity than the parent substance. *Diphenylmethane-4 : 4'-dicarbonamidoxime dihydrochloride* shows a slight activity in doses of 0·1 mg. per 20 g. intravenously, whereas *diphenyl-4 : 4'-dicarbonamidoxime dihydrochloride* is inactive in doses of 0·1 mg. per 20 g. intravenously, but slightly active orally in doses of 0·2 g. per 20 g. *Dibenzyl-4 : 4'-dicarbonamidoxime dihydrochloride* is not quite so active as undecanediamidine dihydrochloride at similar dosage levels: it is slightly less toxic but is better than *dibenzyl sulphide-4 : 4'-dicarbonamidoxime dihydrochloride* which is but moderately active and is more toxic. *Stilbene-4 : 4'-dicarbonamidoxime dihydrochloride* is also less active than undecanediamidine dihydrochloride but more active than the dibenzyl sulphide compound, and approximately as toxic as dibenzyl-4 : 4'-dicarbonamidoxime dihydrochloride.

A few new diamidines have also been prepared. *Decane-1 : 4-dicarbonamidine dihydrochloride* was practically inactive in doses of 0·1 mg. per 20 g. intravenously and 0·2 mg. per 20 g. orally. This confirms the theory that with this type of substance a long chain of methylene groups is necessary for trypanocidal activity, since the isomeric decane-1 : 10-dicarbonamidine has been shown by King, Lourie, and Yorke (*loc. cit.*) and confirmed by us to have considerable activity. The chemical properties and analyses of undecane-, tridecane-, and tetradecane-dicarbonamidine are included since they are not given by King,

* A. C. White is responsible for the animal experiments.

Lourie, and Yorke, who, however, examined them for trypanocidal activity. Easson and Pyman (J., 1931, 2991) prepared the picrate of undecane-1 : 11-dicarbonamidine.* Diamides, amide-nitriles, and amidine-nitriles, isolated as by-products, are described. One of these, *tridecane*-1-*carbonamide*-13-*carbonamidine hydrochloride* was inactive in doses of 2·0 mg. per 20 g. orally. *Tetradecanemonocarbonamidine hydrochloride* was inactive in doses of 2 mg. per 20 g. of mouse by mouth.

Substitution of the nitrogen atoms in decanedicarbonamidine by phenyl or *cyclo*hexyl destroys its activity. *Decanebis*-(NN'-*diphenylcarbonamidine*) and *decanebis*-(N-cyclo*hexylcarbonamidine*) *dihydrochloride* were inactive in doses of 0·4 mg. intravenously or 2·0 mg. orally per 20 g. of mouse.

A cyclic diamidine, 1 : 10-*bis*-(4 : 5-*dihydro*-2-*glyoxalinyl*)*decane* was prepared and found to be inactive in doses of 0·4 mg. per 20 g. intravenously and 0·5 mg. per 20 g. by mouth. This agrees with the results of Sharp (J., 1938, 1191) who prepared a number of cyclic amidines derived from 2-aminopyridine, which were found to be inactive. On the other hand, King, Lourie, and Yorke (*loc. cit.*) found that 1 : 10-bis-(4-methyl-2-glyoxalinyl)-decane had considerable activity.

Experimental.

The amidoximes were prepared by mixing the appropriate dinitrile (0·025 mol.) in alcohol (20 c.c.) with hydroxylamine hydrochloride (7·0 g.). To the cold solution, sodium (2·3 g.) in alcohol (60 c.c.) was added gradually with shaking. The mixture was heated in a pressure bottle at 60° for 20—30 hours. After cooling, sodium chloride was filtered off and the solution concentrated. In some cases the diamidoxime crystallised out and was purified by recrystallisation from alcohol. In others, an oil separated. This was mixed with water and neutralised with hydrochloric acid. Unchanged dinitrile was removed by extraction with ether, and the neutral aqueous solution was concentrated until the cyano-amide crystallised out. From the mother-liquor the cyano-amidoxime and the diamidoxime were precipitated by sodium carbonate and separated by crystallisation from alcohol or ethyl acetate. Apart from pentanedicarbonamidoxime, the diamidoximes are sparingly soluble in water. The m. p.'s are not corrected. For analysis, the substances were in most cases dried at 100° in a vacuum.

Pentane-1 : 5-*dicarbonamidoxime* separates from methyl alcohol in plates, m. p. 142—144° (Found : C, 44·8; H, 8·4; N, 29·8. $C_7H_{16}O_2N_4$ requires C, 44·7; H, 8·6; N, 29·8%). The *dihydrochloride* crystallises from alcohol–ether in irregular plates, m. p. 150—155° (Found : C, 32·2; H, 7·1; N, 21·4; Cl, 27·2. $C_7H_{16}O_2N_4$,2HCl requires C, 32·2; H, 6·9; N, 21·5; Cl, 27·2%).

Heptane-1 : 7-*dicarbonamidoxime* separates from alcohol in small leaflets, m. p. 156° (Found : C, 50·3; H, 9·2; N, 25·7. $C_9H_{20}O_2N_4$ requires C, 50·0; H, 9·3; N, 25·9%). *Nonane*-1 : 9-*dicarbonamidoxime* crystallises from methyl alcohol in small plates, m. p. 167° (Found : C, 54·0; H, 9·7; N, 22·9. $C_{11}H_{24}O_2N_4$ requires C, 54·1; H, 9·9; N, 22·9%). *Decane*-1 : 10-*dicarbonamidoxime* forms plates from alcohol, m. p. 184—186° (decomp.) (Found : C, 56·0; H, 10·1; N, 21·6. $C_{12}H_{26}O_2N_4$ requires C, 55·8; H, 10·1; N, 21·7%). The *dihydrochloride* crystallises from acetone–alcohol, m. p. 149—158° (Found : C, 43·7; H, 8·5; N, 16·7; Cl, 21·5. $C_{12}H_{26}O_2N_4$,2HCl requires C, 43·5; H, 8·5; N, 16·9; Cl, 21·4%). The *diacetyl* derivative, m. p. 129°, prepared by the action of acetic anhydride, crystallises from alcohol. It is deacetylated by the action of cold dilute hydrochloric acid (Found : C, 56·0; H, 8·8; N, 16·2. $C_{16}H_{30}O_4N_4$ requires C, 56·1; H, 8·8; N, 16·4%).

Undecane-1 : 11-*dicarbonamidoxime* separates from methyl alcohol in small plates, m. p. 166° (Found : C, 57·2; H, 10·4; N, 20·0. $C_{13}H_{28}O_2N_4$ requires C, 57·3; H, 10·4; N, 20·6%). The *dihydrochloride* crystallises from acetone–methyl alcohol, m. p. 178° (Found : C, 45·0; H, 8·7; N, 16·1; Cl, 20·5. $C_{13}H_{28}O_2N_4$,2HCl requires C, 45·2; H, 8·8; N, 16·2; Cl, 20·5%).

Undecane-1-*carbonamide*-11-*carbonamidoxime* separates from ethyl acetate in rosettes of needles, m. p. 157—158° (Found : C, 60·6; H, 10·6; N, 16·1. $C_{13}H_{27}O_2N_3$ requires C, 60·7; H, 10·6; N, 16·3). The *hydrochloride* crystallises from water, m. p. 144° (Found : Cl, 12·5. $C_{13}H_{27}O_2N_3$,HCl requires Cl, 12·1%). *Undecane*-1-*carbonitrile*-11-*carbonamidoxime* crystallises from methyl alcohol, m. p. 87—88° (Found : C, 64·9; H, 10·2; N, 17·4. $C_{13}H_{25}ON_3$ requires

* Easson and Pyman (*loc. cit.*) and King, Lourie, and Yorke (*loc. cit.*) refer to this substance which contains a total of 13 carbon atoms as undecane-1 : 11-diamidine. According to the report on organic nomenclature (J., 1931, 1612), this name should refer to the substance containing a total of 11 carbon atoms.

C, 65·2; H, 10·5; N, 17·6%), and its *hydrochloride* from acetone, m. p. 84° (Found : C, 56·0; H, 9·4; N, 15·1; Cl, 13·2. $C_{13}H_{25}ON_3$,HCl requires C, 56·6; H, 9·5; N, 15·2; Cl, 12·9%). *Tridecane*-1 : 13-*dicarbonamidoxime* separates from alcohol in plates, m. p. 170° (Found : C, 59·5; H, 10·7; N, 17·9. $C_{15}H_{32}O_2N_4$ requires C, 60·0; H, 10·7; N, 18·6%); its *dihydrochloride* crystallises from acetone–alcohol, m. p. 158—160° (Found : C, 48·2; H, 9·2; N, 15·0; Cl, 19·3. $C_{15}H_{32}O_2N_4$,2HCl requires C, 48·2; H, 9·2; N, 15·0; Cl, 19·0%). *Tridecane*-1-*carbonitrile*-13-*carbonamidoxime* crystallises from alcohol in small needles, m. p. 98° (Found : C, 67·0; H, 10·7; N, 15·2. $C_{15}H_{29}ON_3$ requires C, 67·4; H, 10·9; N, 15·7%); the *hydrochloride* forms short, pointed prisms from acetone, m. p. 96° (Found : C, 59·2; H, 9·9; N, 13·8; Cl, 12·2. $C_{15}H_{29}ON_3$,HCl requires C, 59·3; H, 9·9; N, 13·8; Cl, 11·7%).

Diphenyl-4 : 4′-*dicarbonamidoxime* is precipitated by sodium carbonate from a solution of its hydrochloride as a white powder consisting of indefinite micro-crystals, m. p. 245° (decomp.). It is insoluble in the usual solvents (Found : C, 62·1; H, 5·2; N, 20·5. $C_{14}H_{14}O_2N_4$ requires C, 62·2; H, 5·2; N, 20·7%). The *dihydrochloride*, crystallised by addition of acetone to the hot aqueous solution, forms small needles soluble in water; m. p. 290° (decomp.) (Found : C, 49·2; H, 4·8; N, 16·6; Cl, 21·1. $C_{14}H_{14}O_2N_4$,2HCl requires C, 49·0; H, 4·7; N, 16·3; Cl, 20·7%). *Diphenylmethane*-4 : 4′-*dicarbonamidoxime* separates from alcohol in colourless plates, m. p. 215°, after preliminary sintering (Found : C, 63·0; H, 5·6; N, 19·5. $C_{15}H_{16}O_2N_4$ requires C, 63·4; H, 5·7; N, 19·7%). The *dihydrochloride* forms needles from dilute acetone, and decomposes at 220° (Found : Cl, 20·8. $C_{15}H_{16}O_2N_4$,2HCl requires Cl, 19·9%). *Dibenzyl*-4 : 4′-*dicarbonamidoxime* is insoluble in the usual solvents. It decomposes at about 243° (Found : C, 63·9; H, 5·6; N, 18·2. $C_{16}H_{18}O_2N_4$ requires C, 64·4; H, 6·1; N, 18·8%). The *dihydrochloride* forms pale yellow prisms from dilute hydrochloric acid (Found : C, 52·4; H, 5·3; N, 14·7; Cl, 18·9. $C_{16}H_{18}O_2N_4$,2HCl requires C, 51·8; H, 5·4; N, 15·1; Cl, 19·1%).

4 : 4′-*Dicyanostilbene*.—7·9 G. of 4 : 4′-diaminostilbene (prepared from the high-melting dinitrostilbene) were diazotised, and the diazo-solution was added slowly with stirring to a hot solution of 9·4 g. of copper sulphate and 10 g. of potassium cyanide in 55 c.c. of water. After cooling, the precipitate was boiled with benzene, which extracted 3·0 g. of crude dinitrile. Recrystallised from benzene, it forms small orange leaflets which melt indefinitely at 278° after preliminary sintering (Found : C, 83·0; H, 4·4; N, 12·0. $C_{16}H_{10}N_2$ requires C, 83·4; H, 4·4; N, 12·2%).

Stilbene-4 : 4′-*dicarbonamidoxime* forms plates from alcohol; m. p. >320° (decomp.) (Found : C, 64·2; H, 5·3; N, 18·2. $C_{16}H_{16}O_2N_4$ requires C, 64·8; H, 5·4; N, 18·9%). The *dihydrochloride* separates from dilute hydrochloric acid in needles. It chars at about 300° and is decomposed by water (Found : C, 51·9; H, 5·0; N, 14·9; Cl, 19·1. $C_{16}H_{16}O_2N_4$,2HCl requires C, 52·0; H, 4·9; N, 15·2; Cl, 19·2%).

The amidines were prepared from the nitriles by way of the imino-ethers (Easson and Pyman, *loc. cit.*).

Decane-1 : 4-*dicarbonamidine dihydrochloride* was prepared from crude α-*n*-hexyladiponitrile, obtained by way of the dibromo-compound from the crude cyclic ether resulting from the action of sulphuric acid on decamethylene glycol, which Franke and Kroupa have shown to be mainly the 1 : 4-derivative (*Monatsh.*, 1930, **56**, 347; 1933, **62**, 119; 1937, **69**, 167). The *dihydrochloride* crystallises from alcohol–acetone, m. p. 227—228° (decomp.) (Found : C, 48·2; H, 9·3; N, 18·4; Cl, 23·7. $C_{12}H_{26}N_4$,2HCl requires C, 48·2; H, 9·4; N, 18·7; Cl, 23·7%), and the picrate from acetic acid, m. p. 233°.

Decane-1-*carbonitrile*-10-*carbonamide* was obtained as a by-product of the action of potassium cyanide on dibromodecane. It crystallised from ether–methyl alcohol, m. p. 87° (Found : C, 68·7; H, 10·6; N, 13·0. $C_{12}H_{22}ON_2$ requires C, 68·5; H, 10·5; N, 13·3%). *Decanebis*-(NN′-*diphenylcarbonamidine*) crystallises from alcohol in pointed needles, m.p. 163—165° (Found: C, 81·2; H, 7·8; N, 10·3. $C_{36}H_{42}N_4$ requires C, 81·5; H, 8·0; N, 10·5%). *Decanebis*-(N-cyclo*hexylcarbonamidine*) crystallises from alcohol–acetone in needles, m. p. 122° (Found : C, 73·7; H, 11·6; N, 14·1. $C_{24}H_{46}N_4$ requires C, 73·8; H, 11·9; N, 14·3%); its *dihydrochloride* separates from alcohol–acetone in indefinite plates, m. p. 273° (Found : C, 62·1; H, 10·2; N, 12·0; Cl, 15·4. $C_{24}H_{46}N_4$,2HCl requires C, 62·2; H, 10·4; N, 12·1; Cl, 15·3%). *Undecane*-1-*carbonitrile*-11-*carbonamide*, obtained as a by-product of the action of potassium cyanide on dibromoundecane, crystallises from methyl alcohol, m. p. 101° (Found : C, 69·7; H, 10·8; N, 12·1. $C_{13}H_{24}ON_2$ requires C, 69·6; H, 10·8; N, 12·5%). Undecane-1 : 11-dicarbonamidine dihydrochloride separates from alcohol–acetone, m. p. 150—151° (Found : C, 50·1; H, 9·7; N, 17·5; Cl, 22·9. Calc. for $C_{13}H_{28}N_4$,2HCl : C, 49·8; H, 9·7; N, 17·9; Cl, 22·6%).

Tridecane-1-*carbonitrile*-13-*carbonamide*, obtained as a by-product during the preparation of the dinitrile, crystallises from alcohol, m. p. 103—104° (Found: C, 71·2; H, 11·0; N, 11·0. $C_{15}H_{28}ON_2$ requires C, 71·4; H, 11·2; N, 11·1%), and tridecane-1 : 13-dicarbonamidine dihydrochloride from acetone–alcohol, m. p. 165—167° (Found: C, 52·4; H, 9·8; N, 16·1; Cl, 21·0. Calc. for $C_{15}H_{32}N_4,2HCl$: C, 52·8; H, 10·0; N, 16·4; Cl, 20·8%). The picrate separates from acetic acid, m. p. 190—191°. *Tridecane*-1-*carbonamide*-13-*carbonamidine hydrochloride* is soluble in hot water, but sparingly so in cold, m. p. 164—165° (Found: C, 59·1; H, 10·2; N, 13·5; Cl, 11·4. $C_{15}H_{31}ON_3,HCl$ requires C, 59·1; H, 10·2; N, 13·8; Cl, 11·6%).

Tridecane-1 : 13-*dicarbonamide*, obtained as a by-product during the preparation of tridecane dicarbonamidine, crystallises from alcohol; m. p. 176° (Found: C, 66·6; H, 10·9; N, 9·9. $C_{15}H_{30}O_2N_2$ requires C, 66·6; H, 11·2; N, 10·4%).

Tetradecanemonocarbonamidine hydrochloride is sparingly soluble in cold, but readily so in hot water; m. p. 138°, after preliminary sintering (Found: C, 65·1; H, 11·7; N, 10·2; Cl, 12·8. $C_{15}H_{32}N_2,HCl$ requires C, 65·1; H, 12·0; N, 10·1; Cl, 12·8%). The picrate crystallises from acetic acid, m. p. 166°.

1 : 10-*Bis*-(4 : 5-*dihydro*-2-*glyxalinyl*)*decane* was prepared by heating the hydrochloride of decanedicarboniminoethyl ether with an alcoholic solution of ethylenediamine at 70° for 8 hours (cf. preparation of mono-4 : 5-dihydro-2-glyoxalinyl compounds from palmitic and stearic acids; Bockmühl and Knoll, B.P. 308,218). It crystallises from alcohol in plates, m. p. 181° (Found: C, 69·2; H, 10·7; N, 19·8. $C_{16}H_{30}N_4$ requires C, 69·0; H, 10·9; N, 20·1%). The picrate forms plates from acetic acid, m. p. 223—224°, and the *hydrochloride* forms plates from acetone–methyl alcohol, m. p. 183° (Found: C, 54·1; H, 9·1; N, 15·6; Cl, 20·3. $C_{16}H_{30}N_4,2HCl$ requires C, 54·7; H, 9·1; N, 15·9; Cl, 20·2%).

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