220. *Alkylene Derivatives of Cyclic Bases. Part I. Derivatives of 2-Aminopyridine.*

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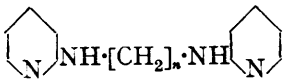
A homologous series of bis-2-pyridylaminoalkanes has been prepared by the condensation of 2-aminopyridine with dibromoalkanes in the presence of sodamide. Three members of the series, namely, those containing one, three, and four carbon atoms in the chain, failed to react in the expected manner; the remainder, containing up to 10 carbon atoms, reacted normally. The compounds have been tested as trypanocides.

BEFORE the discovery of Jancsó and Jancsó (*Z. Immun. Forsch.*, 1936, **81**, 1) that synthalin [decamethylenediguanidine (I)] had trypanocidal activity, the only drugs available for the treatment of sleeping sickness were arsenicals such as tryparsamide (sodium phenylglycineamide-*p*-arsonate) and complex ureas of the type of Bayer 205 (symmetrical urea of *m*-aminobenzoyl-*m*-amino-*p*-toluoylnaphthylamine-4 : 6 : 8-trisulphonic acid). The recent work of King, Lourie, and Yorke (*Lancet*, 1937, **233**, 1360) has made it possible to envisage new types of compounds which might be expected to show a similar chemotherapeutic activity.

$NH_2 \cdot C(:NH) \cdot NH \cdot [CH_2]_{10} \cdot NH \cdot C(:NH) \cdot NH_2$ (I.)

$NH_2 \cdot C(:NH) \cdot [CH_2]_{11} \cdot C(:NH) \cdot NH_2$ (II.)



(III.)

They examined a number of homologues of synthalin and a homologous series of alkylene-diamidines and -dithioureas and found that, as the series were ascended, an increase in activity was obtained, reaching a maximum in the synthalin series with 10 to 14 carbon atoms in the chain, and in the amidine series with 11 carbon atoms in the chain; a further increase in the length of chain caused a diminution in activity. There was also a parallel but slower increase in the toxicity. The most active substance tested was *n*-undecane-1 : 11-diamidine (II), previously prepared for another purpose by Easson and Pyman (J., 1931, 2991). Other series of compounds were tested with similar results, but the activity was much lower than in the synthalin and amidine series. The common factor in all these compounds is the fairly long chain of methylene groups connecting two basic groups. The basic groups hitherto tried have been of the open-chain type, and the object of the present investigation was to ascertain whether such a structure is necessary for trypanocidal activity. For this purpose 2-aminopyridine has been chosen as a simple cyclic compound containing the group –N : Ċ·NH– also present in the amidines and has been condensed with alkylene dihalides to yield a homologous series of the general formula (III).

Tschitschibabin, Konovalova, and Konovalova (*Ber.*, 1921, **54**, 814) found that the direct action of methyl iodide on 2-aminopyridine gave a quaternary iodide, from which *N*-methylpyridoneimine was obtained with silver oxide, whereas when methyl iodide was allowed to react with the sodium derivative of 2-aminopyridine the main product was 2-methylaminopyridine. By the latter method, ethylene dibromide and αε-dibromopentane gave poor yields, but the αω-dibromo-derivatives of hexane, heptane, octane, nonane, and decane gave good yields, of compounds of the formula (III) where $n = 2$, **5**, 6, 7, 8, 9 and 10. That the compounds have the structure (III) has been proved in the case of the decamethylene derivative by reduction with sodium and alcohol to piperidine and 1 : 10-decamethylenediamine. A similar decomposition has been observed by Kirsanov and Ivaschtschenko (*J. Gen. Chem. Russ.*, 1937, **7**, 2092), who reduced 2-aminopyridine to piperidine and ammonia but also obtained cadaverine. The reaction between 2-aminopyridine and αγ-dibromopropane and αδ-dibromobutane took a different course, giving in poor yield substances which have not been completely separated from 2-aminopyridine. They are very volatile and distil together with aminopyridine. It is

possible that they are dicyclic compounds similar to that obtained by Scherlin and Velitschkin (*J. Gen. Chem. Russ.*, 1935, **5**, 1586) from 2-aminopyridine and trimethylene chlorobromide. The matter is under investigation. Methylene iodide gave only tarry products.

The trypanocidal action of the compounds has been tested by Dr. White of the Wellcome Physiological Research Laboratories. They all have a low toxicity, but are inactive in mouse trypanosomiasis.

Experimental.

2-Aminopyridine (9·4 g.; 0·1 mol.)(Feist, *Arch. Pharm.*, 1934, **272**, 106) was mixed with powdered sodamide (3·12 g.; 0·08 mol.) and dry toluene (80 c.c.), and the mixture boiled under reflux (calcium chloride guard-tube) for 3 hours. The appropriate alkylene dibromide (0·02 mol.), diluted with dry toluene (5 c.c.), was then run in during 30 minutes, and the mixture boiled for 4—5 hours. After cooling overnight, the contents of the flask were diluted with water (50 c.c.), and the products isolated by means appropriate to the individual compound. (*a*) In the cases of the di-, penta-, and hepta-methylene derivatives, the toluene was separated and evaporated, the aqueous layer extracted with ether (chloroform in the case of the heptamethylene derivative), and the solvent removed by distillation. The combined extracts were distilled from an oil-bath at 120° under reduced pressure until no more aminopyridine passed over. The solid residue was then crystallised to yield the desired compound. (*b*) In the cases of the hexa-, octa-, nona-, and deca-methylene derivatives, the product was present as a solid in the toluene–water mixture and was filtered off and crystallised directly. A small amount more was obtained by extraction with chloroform as described under (*a*). The yields recorded are calculated on the amount of dibromide used.

αβ-*Bis*-2-*pyridylaminoethane* forms colourless glistening platelets from benzene, m. p. 134—135° (corr.) (Found: C, 67·2, 67·4; H, 6·3, 6·1; N, 25·9. $C_{12}H_{14}N_4$ requires C, 67·2; H, 6·6; N, 26·15%). Yield, 14%. The *dihydrochloride* crystallises from dry alcohol in soft needles, m. p. 239—241° (corr.) (Found: Cl, 24·8, 25·0. $C_{12}H_{14}N_4$,2HCl requires Cl, 24·7%).

αε-*Bis*-2-*pyridylamino*-n-*pentane* separates from methyl alcohol in clusters of prisms, m. p. 150° (corr.) (Found: C, 70·6, 70·4; H, 8·0, 8·0; N, 21·2, 21·2, 22·8, 22·9. $C_{15}H_{20}N_4$ requires C, 70·3; H, 7·9; N, 21·9%). Yield, 13%. The *dihydrochloride* forms aggregates of small crystals, m. p. 164° (corr.), from acetone–methyl alcohol (Found: Cl, 21·3, 21·4. $C_{15}H_{20}N_4$,2HCl requires Cl, 21·5%).

αζ-*Bis*-2-*pyridylamino*-n-*hexane* crystallises from methyl alcohol in rods, m. p. 152—154° (corr.) (Found: C, 70·9, 70·75; H, 8·0, 7·9; N, 21·25. $C_{16}H_{22}N_4$ requires C, 71·05; H, 8·2; N, 20·7). Yield, 80%. The *dihydrochloride* crystallises from methyl alcohol–acetone in small prisms, m. p. 216—218° (corr.) (Found: Cl, 20·65, 20·5. $C_{16}H_{22}N_4$,2HCl requires Cl, 20·65%).

αη-*Bis*-2-*pyridylamino*-n-*heptane* forms clusters of torpedo-shaped crystals from benzene, m. p. 104—105° (corr.) (Found: C, 71·7, 71·7; H, 8·5, 8·4; N, 19·6, 19·8. $C_{17}H_{24}N_4$ requires C, 71·8; H, 8·5; N, 19·7%). Yield, 85%. The *dihydrochloride* crystallises from methyl alcohol–acetone in clusters of small prisms, m. p. 203—205° (corr.) (Found: Cl, 19·95, 19·95. $C_{17}H_{24}N_4$,2HCl requires Cl, 19·8%).

αθ-*Bis*-2-*pyridylamino*-n-*octane* crystallises from dry alcohol in fine needles, m. p. 110—112° (corr.) (Found: C, 72·5, 72·35; H, 8·4, 8·45; N, 18·5. $C_{18}H_{26}N_4$ requires C, 72·5; H, 8·8; N, 18·8%). Yield, 62%. The *dihydrochloride* separates from methyl alcohol–acetone in rosettes of prisms, m. p. 197—198° (corr.) (Found: Cl, 19·35, 19·25. $C_{18}H_{26}N_4$,2HCl requires Cl, 19·1%).

αι-*Bis*-2-*pyridylamino*-n-*nonane* forms thin rods from methyl alcohol, m. p. 140—141° (corr.) (Found: C, 72·7; H, 8·8; N, 17·9. $C_{19}H_{28}N_4$ requires C, 73·0; H, 9·0; N, 17·9%). Yield, 76%. The *dihydrochloride* separates in balls of fine hygroscopic needles, m. p. 136—139° (dry, corr.), from methyl alcohol–acetone (Found: Cl, 18·05. $C_{19}H_{28}N_4$,2HCl requires Cl, 18·4%).

ακ-*Bis*-2-*pyridylamino*-n-*decane* crystallises from methyl alcohol in thin rods, m. p. 122—124° (corr.) (Found: C, 73·6, 73·7; H, 9·1, 9·2; N, 17·6. $C_{20}H_{30}N_4$ requires C, 73·55; H, 9·3; N, 17·2%). Yield, 74%. The *dihydrochloride* forms wart-like aggregates, m. p. 149—152° (corr.), from methyl alcohol-acetone (Found: Cl, 17·4, 17·3. $C_{20}H_{30}N_4$,2HCl requires Cl, 17·7%).

Reduction of ακ-*Bis*-2-*pyridylamino*-n-*decane*.—The base (1·0 g.), dissolved in dry alcohol (20 c.c.), was treated with sodium (2 g.) and boiled under reflux until the sodium dissolved.

Water (5 c.c.) was added, and the alcohol distilled off. Piperidine passed over with the alcohol and was identified as hydrochloride by mixed m. p. (243°) with an authentic specimen. The strongly alkaline residue contained decamethylenediamine as an oil floating on the surface. It was converted into the dibenzoyl derivative and identified as dibenzoyldecamethylenediamine by mixed m. p. with a specimen obtained by von Braun's method (*Ber.*, 1909, **42**, 4551). Yield, 0·75 g.; m. p. 152—153°.

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