53. *Some Guanyl- and Guanido-naphthalenes. Group Migration in Cyanonaphthalenes.*

By Harold King and E. V. Wright.

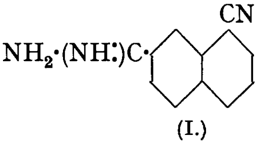
A new class of trypanocidal agents was described by King, Lourie, and Yorke (*Lancet*, 1937, ii, 1360). The most active representatives were aliphatic long straight-chain diguanidines or diamidines. The present paper records some incidental observations which have been made during the preparation of diamidines and diguanidines in which the aliphatic chain has been replaced by a naphthalene nucleus. On the biological side it has been found that such alteration of the carrier of the polar groups does not greatly modify the trypanocidal activity. Furthermore, the aliphatic straight chains can also be replaced by cyclic hydroaromatic structures. On the chemical side, migration of cyano-groups from the β- to the α-position has been observed in the mild pyrogenic preparation of dicyanonaphthalenes.

It was shown by King, Lourie, and Yorke (*loc. cit.*; *Ann. Trop. Med. Parasit.*, 1938, **32**, 177) that a marked trypanocidal action is exhibited by aliphatic diguanidines, di*iso*thioureas and diamidines of a certain molecular size, maximum activity being shown by undecanediamidine, $NH_2\cdot C(:NH)\cdot[CH_2]_{11}\cdot C(:NH)\cdot NH_2$. The most favourable requirements for trypanocidal activity seemed to be a central carbon chain of about 10 to 12 carbon atoms with terminal strongly basic, polar groups. The present communication records the synthesis of allied compounds in which the aliphatic chain is replaced by a naphthalene nucleus.

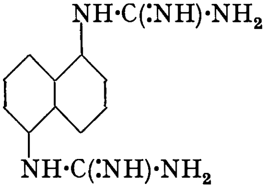
In the preparation of naphthylenediamidines (diguanylnaphthalenes) the necessary intermediates are dicyanonaphthalenes, and during the preparation of 2 : 7-dicyanonaphthalene by distillation of potassium 2-cyanonaphthalene-7-sulphonate with potassium cyanide the formation of a by-product, 1 : 7-dicyanonaphthalene, was observed. The same two cyanonaphthalenes were formed when sodium naphthalene-2 : 7-disulphonate was used, so in both cases a partial migration of the cyano-group from the 2- to the 1-position takes place.

An exactly analogous reaction takes place when sodium 2-cyanonaphthalene-6-sulphonate is distilled with potassium cyanide. The distillate is mainly 2 : 6-dicyanonaphthalene mixed with a small proportion of 2 : 5-dicyanonaphthalene. Migration thus takes the same course as was found previously, the cyano-group tending to move to the 1-position, which, at the temperatures involved, is presumably the more stable position.

2 : 6- and 2 : 7-Dicyanonaphthalenes gave 2 : 6- and 2 : 7-naphthylenediamidines in the usual way *via* the imino-ethers; the sparing solubility of the dicyanonaphthalenes raised experimental difficulties which were overcome by use of dioxan as the solvent for the preparation of the imino-ethers. It is known that 1-cyanonaphthalenes cannot be converted into amidines and in agreement 1 : 7-dicyanonaphthalene gave the *hydrochloride* of 1-*naphthonitrile*-7-*amidine* (I). Although 1-amidines were unobtainable, the corresponding guanidines could be made. Thus 1 : 5-naphthylenediamine dihydrochloride, treated repeatedly with cyanamide, gave 1 : 5-diguanidonaphthalene (II), isolated as the *dinitrate*. Under similar conditions 2 : 7-naphthylenediamine dihydrochloride gave 2 : 7-*diguanidonaphthalene dinitrate* and 7-*guanido*-2-*naphthylamine nitrate*. On the other hand 1 : 8-naphthylenediamine dihydrochloride with cyanamide gave aminoperimidine hydrochloride (III), previously obtained by Sachs (*Annalen*, 1909, **365**, 143) by heating 1 : 8-naphthylenediamine with ammonium thiocyanate to 160°.



(I.)



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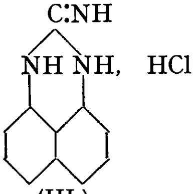
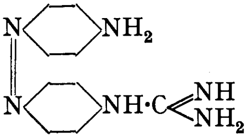


(III.)

In our experience complete conversion of the second amino-group in aromatic diamines into the guanidine group is often difficult, repeated treatment with a large excess of cyanamide being necessary. 4 : 4′-Diaminoazobenzene dihydrochloride, for instance, treated with 30 molecular proportions of cyanamide, gave only the *nitrate* of 4-*guanido*-4′-*aminoazobenzene* (IV). Wheeler's excellent method (*Amer. Chem. J.*, 1903, **29**, 478) for the preparation of guanidines by the action of methyl*iso*thiourea hydriodide on an amine applies only to aliphatic amines, with a few exceptions. It was successfully used for the conversion of 4 : 4′-dipiperidyl into 1 : 1′-*diguanyl*-4 : 4′-*dipiperidyl dihydrochloride* (V), but in the case of 2 : 4′-dipiperidyl, only a monoguanyl derivative, presumably 1′-*guanyl*-2 : 4′-*dipiperidyl dihydriodide* (VI), was obtained.



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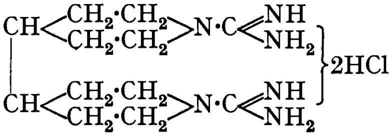

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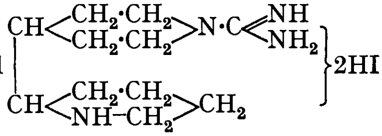

(VI.)

We are indebted to Professor Warrington Yorke and Dr. E. M. Lourie of the Liverpool School of Tropical Medicine for testing these amidines and guanidines for trypanocidal action. As the table shows, the methylene chain of the aliphatic compounds can be replaced by the aromatic naphthalene nucleus with retention of activity.

Substance.	Trypanocidal titre *in vitro*.	Toxicity.*	Therapeutic effect in infected mice.
1 : 5-Diguanidonaphthalene dinitrate	64/256,000	0·5	Nil
2 : 7- ,, ,,	1,000,000	1·0	Curative
Aminoperimidine hydrochloride	1,000,000	1·0	Nil
2 : 6-Naphthylenediamidine dihydrochloride	4,000,000	2·0	Considerable
2 : 7- ,, ,,	4/16,000,000	1·0—2·0	Curative
1-Naphthonitrile-7-amidine hydrochloride	64,000	4·0	Nil
1 : 1′-Diguanyl-4 : 4′-dipiperidyl dihydrochloride	4,000,000	2·0	Slight
1′-Guanyl-2 : 4′-dipiperidyl dihydriodide	$<$64,000	16·0	Nil

* M.L.D. in mg. per 20 g. mouse.

EXPERIMENTAL.

Potassium 2-*Cyanonaphthalene*-7-*sulphonate*.—A solution of sodium 2-naphthylamine-7-sulphonate (12·3 g.) and sodium nitrite (3·8 g.) in water (320 c.c.) was run into a stirred solution of ice-cold sulphuric acid (90 c.c.; 20%). The solid crystalline diazo-sulphonate was collected and, whilst still damp, added in small portions during 30 minutes to a solution kept at 50—60°, prepared from copper sulphate (25 g.), potassium cyanide (32 g.), and water (150 c.c.). When cold, the solution was acidified, and the cuprous cyanide removed and extracted with hot water, which was added to the main filtrate. On concentration *potassium* 2-*cyanonaphthalene*-7-*sulphonate* crystallised. It was soluble in 1·4 parts of boiling water and crystallised in golden-brown plates or rhombs (Found: Loss at 120°, 13·6, 13·2. $C_{11}H_6O_3NSK,2\frac{1}{2}H_2O$ requires H_2O, 14·2%. Found for the dried solid: K, 14·2. $C_{11}H_6O_3NSK$ requires K, 14·4%).

Preparation of 1 : 7- *and* 2 : 7-*Dicyanonaphthalenes.*—(a) *From potassium* 2-*cyanonaphthalene*-7-*sulphonate.* A mixture of the potassium salt (8·3 g.) and potassium cyanide (12 g.) was heated in a stream of carbon dioxide until no more solid sublimed. The crude dinitrile (1·6 g.), crystallised from glacial acetic acid (23 c.c.), gave pure 2 : 7-dicyanonaphthalene (0·7 g.), m. p. 268°. The mother-liquors contained a much more soluble solid, which on crystallisation from alcohol gave 1 : 7-dicyanonaphthalene, m. p. 158—159°, identical with an authentic specimen (see below).

(b) *From sodium naphthalene*-2 : 7-*disulphonate.* This salt in 2·5 g. batches was mixed with potassium cyanide (3·75 g.) and heated as described under (a). The sublimate (1·6 g. from 12·5 g. of sodium salt) was crystallised from glacial acetic acid (20 c.c.) and gave 2 : 7-dicyanonaphthalene, m. p. 268° (yield, 22%). The mother-liquors deposited a more soluble solid (0·4 g.), m. p. 144—147°, which on sublimation and crystallisation from alcohol gave 1 : 7-dicyanonaphthalene, m. p. 158—159° (Found: C, 81·0; H, 3·4; N, 15·8. Calc.: C, 80·9; H, 3·4; N, 15·7%). This dinitrile was identical with an authentic specimen prepared from sodium 2-cyanonaphthalene-8-sulphonate (see below).

1 : 7-*Dicyanonaphthalene from sodium* 2-*cyanonaphthalene*-8-*sulphonate.* The salt was prepared in 82% yield from sodium 2-naphthylamine-8-sulphonate (Bradbrook and Linstead, J., 1936, 1739). By distillation with potassium cyanide in a current of carbon dioxide, it (10 g.) gave 1 : 7-dicyanonaphthalene (1·9 g.), m. p. 158°. On sublimation in a high vacuum and subsequent crystallisation from alcohol the m. p. was raised to 161—162° and was unchanged on repeated crystallisation. Kruber and Shade (*Ber.*, 1936, **69**, 1727) give m. p. 152—154°; Bradbrook and Linstead give 167°.*

2 : 7-*Naphthylenediamidine Dihydrochloride.*—2 : 7-Dicyanonaphthalene (3·6 g.) was dissolved in boiling dioxan (80 c.c.). To the cooled solution, which had partly crystallised, absolute ethyl alcohol (3·7 g.; 4 mols.) was added, and the mixture then saturated at 0—5° with hydrogen chloride. The mixture was kept for 14 days at 0° and, after removal of the excess of hydrogen chloride by pumping, the fine needles of the imino-ether hydrochloride were collected, quickly transferred to a pressure bottle, treated with saturated ethyl-alcoholic ammonia (150 c.c.), and heated at 40—50° for 8 hours. When cold, some diamidine dihydrochloride and ammonium chloride had separated. [It is preferable not to collect the solid at this stage, but to pump off the ammonia and transfer the contents of the bottle to a flask, remove all solvent, and crystallise the residue from boiling water (60 c.c.).] The yield of 2 : 7-*naphthylenediamidine dihydrochloride*, which crystallised in needles and was unmelted at 290°, was 97% (Found: Loss at 100°, 6·0. $C_{12}H_{12}N_4,2HCl,H_2O$ requires H_2O, 6·0%. Found for dried material: Cl, 24·4. $C_{12}H_{12}N_4,2HCl$ requires Cl, 24·9%).

2 : 7-*Diguanidonaphthalene Dinitrate.*—2 : 7-Naphthylenediamine dihydrochloride (2·3 g.) in absolute ethyl alcohol (30 c.c.) was refluxed for 7 hours with cyanamide (10 mols.). As the diazo-reaction of a sample was still strongly positive, boiling was continued for a further 14 hours with addition of cyanamide (20 mols. in all) at intervals of 3½ hours. The solvent was removed, and the residue dissolved in water and precipitated with ammonium nitrate. The crystalline precipitate was recrystallised from water and separated in two forms, plates and needles. These were separated by fractional crystallisation, the plates being the less soluble. The plates (0·26 g.), m. p. 251—252°, proved to be 7-*guanido*-2-*naphthylamine nitrate* (Found: C, 50·0; H, 4·9. $C_{11}H_{12}N_4,HNO_3$ requires C, 50·2; H, 5·0%). This salt is soluble in 35 parts of boiling water and crystallises in rhomb-shaped plates. Its diazo-solution has a yellow colour and couples with alkaline β-naphthol, forming a purple precipitate. The needles (1·12 g.), m. p. 209°, proved to be 2 : 7-*diguanidonaphthalene dinitrate* (Found: C, 37·0, 36·9; H, 4·9, 4·9; N, 29·0. $C_{12}H_{14}N_6,2HNO_3,H_2O$ requires C, 37·3; H, 4·7; N, 29·0%).

Preparation of 1 : 6- *and* 2 : 6-*Dicyanonaphthalenes from Sodium* 2-*Cyanonaphthalene*-6-*sulphonate.*—A mixture of the sulphonate (Bradbrook and Linstead, *loc. cit.*) (10 g.) and potas-

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* Professor Linstead kindly supplied a specimen of this dinitrile and we confirm the m. p. given by him.

sium cyanide (15 g.) was heated so long as a sublimate was formed; yield, 2·3 g. This crystallised from glacial acetic acid (160 c.c.) in long needles of 2 : 6-dicyanonaphthalene, m. p. 294—297°. The mother-liquor on concentration gave a much more soluble substance (0·3 g.), m. p. 205—207°, which was proved to be 1 : 6-dicyanonaphthalene by direct comparison with a specimen, m. p. 205—207°, prepared from pure sodium naphthalene-1 : 6-disulphonate. Weissgerber and Kruber (*Ber.*, 1919, **52**, 345) give m. p. 208—210°; Bradbrook and Linstead give m. p. 211°.

2 : 6-*Naphthylenediamidine Dihydrochloride*.—2 : 6-Dicyanonaphthalene (1·7 g.) was boiled with dioxan (50 c.c.), absolute ethyl alcohol added (1·84 g.; 4 mols.), and the solution, containing a suspension of crystals, saturated with hydrogen chloride at 0° and kept in a sealed vessel for 14 days. The hydrogen chloride was then pumped off, and the crystals of the imino-ether hydrochloride were collected and heated at 40—50° with saturated alcoholic ammonia for 8 hours in a pressure bottle. The ammonia and solvent were removed, and the residue boiled with water and filtered from unchanged dicyanonaphthalene (0·6 g.). The filtrate deposited long needles of 2 : 6-*naphthylenediamidine dihydrochloride* (1·0 g.), unmelted at 300° (Found : Cl, 24·4. $C_{12}H_{12}N_4,2HCl$ requires Cl, 24·9%).

1 : 5-*Diguanidonaphthalene Dinitrate* (II).—1 : 5-Naphthylenediamine dihydrochloride (3·5 g.) was digested for 6 hours with cyanamide (6·7 g.; 10 mols.) in boiling ethyl alcohol (50 c.c.), and again for 12 hours after addition of a further quantity (7·0 g.) of cyanamide. The solvent was removed, the residue dissolved in water, and ammonium nitrate added in excess. The crude mixture of nitrates was extracted by grinding with cold water to remove material giving a diazo-reaction. The residue, crystallised from water, gave 1 : 5-*diguanidonaphthalene dinitrate* (0·5 g.) in clusters of microscopic rods or prisms, unmelted at 300° (Found : C, 39·2; H, 4·5; N, 30·5. $C_{12}H_{16}O_6N_8$ requires C, 39·1; H, 4·4; N, 30·4%).

Aminoperimidine Hydrochloride (III).—1 : 8-Naphthylenediamine dihydrochloride (3·1 g.) was refluxed with cyanamide (6 g.) in absolute ethyl alcohol (50 c.c.) for 10 hours. The alcohol was distilled from the dark solution, and the residue crystallised from water. Aminoperimidine hydrochloride separated in long rods (Found : Loss at 100° in a high vacuum, 6·8. Calc. for $C_{11}H_9N_3,HCl,H_2O$: H_2O, 7·6%. Found for dried material : C, 59·6; H, 4·7; N, 19·2; Cl, 16·0. Calc. for $C_{11}H_9N_3,HCl$: C, 60·1; H, 4·6; N, 19·1; Cl, 16·1%).

1 : 5-*Dicyanonaphthalene*.—Sodium naphthalene-1 : 5-disulphonate (10 g.), dry-distilled with potassium cyanide (15 g.), gave 1 : 5-dicyanonaphthalene (2·7 g.), m. p. 265° after crystallisation from alcohol. Attempts to convert this substance into the iminoethyl ether were unsuccessful in dioxan or benzene, the dinitrile being recovered unchanged.

1-*Naphthonitrile-7-amidine Hydrochloride*.—1 : 7-Dicyanonaphthalene (1·2 g.) was dissolved in boiling dioxan (10 c.c.), and the solution cooled, mixed with absolute ethyl alcohol (1·25 g.; 4 mols.), and saturated with hydrogen chloride at 0°. After 10 days, the excess of hydrogen chloride was pumped off, and the crystalline mass collected and treated with saturated alcoholic ammonia (80 c.c.) in a pressure bottle at 40—50° for 8 hours. The ammonia was pumped off, the solvent removed by distillation, and the residue crystallised from water. 1-*Naphthonitrile-7-amidine hydrochloride* separated in long silky needles (0·65 g.), m. p. 296—297° (Found : Cl, 15·1. $C_{12}H_9N_3,HCl$ requires Cl, 15·3%).

4-*Guanido-4′-aminoazobenzene Nitrate*.—4 : 4′-Diaminoazobenzene dihydrochloride (2·85 g.) was boiled in alcoholic solution (30 c.c.) with cyanamide (4·2 g.) for 8 hours, and a further 8·4 g. of cyanamide added in 2·1 g. portions every four hours. The solvent was removed, and the residue taken up in a little water and precipitated with solid ammonium nitrate. The crude nitrate, crystallised four times from water, gave 4-*guanido-4′-aminoazobenzene nitrate* in yellow needles (0·8 g.), m. p. 257° (decomp.). Further quantities were obtained from the mother-liquors (Found : C, 49·7, 49·8; H, 4·6, 4·6; N, 31·9, 32·0. $C_{13}H_{14}N_6,HNO_3$ requires C, 49·2; H, 4·8; N, 30·9%). This salt dissolves in excess of dilute mineral acids with an intense cherry-red colour. Careful examination of the mother-liquor failed to reveal the presence of any homogeneous material which gave no diazo-reaction.

1 : 1′-*Diguanyl-4 : 4′-dipiperidyl Dihydrochloride* (V).—Dipiperidyl (1·68 g.) containing some carbonate was dissolved in water (25 c.c.), methyl*iso*thiourea hydriodide (4·4 g.) added, and the mixture warmed to 50°. As there was no reaction, N-sodium hydroxide (20 c.c.) was added, and the temperature gradually raised until methylthiol was evolved at about 80°. After 30 minutes at this temperature the solution was concentrated to one-half its volume; on keeping, 1 : 1′-diguanyl-4 : 4′-dipiperidyl dihydriodide separated in large crystals (2·05 g.). Without further characterisation, it was converted by moist silver chloride into the *dihydrochloride*, which crystallised from water in elongated glassy tablets (0·9 g.), m. p. 361° (efferv.) (Found : C, 39·6, 39·4; H, 8·4, 8·4; N, 23·8, 23·9; Cl, 19·7, 19·6. $C_{12}H_{24}N_6,2HCl,2H_2O$ requires C,

39·9; H, 8·4; N, 23·3; Cl, 19·6%). The original mother-liquors on further concentration gave an oily layer which slowly crystallised. On crystallisation from 2·7 parts of hot water, *monoguanyl*-4 : 4'-*dipiperidyl hydriodide* separated in bold prisms, m. p. 136—137°, raised by drying at 100° to 166° (Found : C, 37·1, 37·2; H, 6·9, 7·0; N, 15·5, 15·3. $C_{11}H_{22}N_4,HI,H_2O$ requires C, 37·1; H, 7·1; N, 15·7%).

1'-*Guanyl*-2 : 4'-*dipiperidyl Dihydriodide* (VI).—2 : 4'-Dipiperidyl (Evans and Parkes, *J. Soc. Chem. Ind.*, 1938, **57**, 303) (1·68 g.) in water (25 c.c.) was treated with methyl*iso*thiourea hydriodide (4·36 g.; 2 mols.). Reaction took place when the temperature reached 80° and was complete after 30 minutes. When the solution was concentrated to a very small volume, 1'-*guanyl*-2 : 4'-*dipiperidyl dihydriodide* crystallised in plates (1·73 g.). For analysis the salt was recrystallised from a small volume of water (Found : C, 27·1, 27·0; H, 5·0, 5·1; N, 11·8, 11·8. $C_{11}H_{22}N_4,2HI,H_2O$ requires C, 27·3; H, 5·4; N, 11·6%). It melted indefinitely at about 123°. There was no evidence for the formation of a disubstituted derivative.

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NATIONAL INSTITUTE FOR MEDICAL RESEARCH,
HAMPSTEAD, LONDON, N.W. 3.

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