Potential Tumour Inhibitors. Esters of 4-Di-(2-hydroxyethyl)aminopyridine and Quaternary Derivatives of 2 : 3-Dihydroglyoxalino[1 : 2-a]pyridine.

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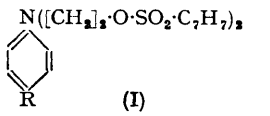
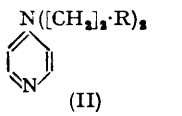
Reaction between 4-di-(2-hydroxyethyl)aminopyridine and a number of sulphonyl chlorides gave (with certain exceptions) the corresponding disulphonyloxy-amines but use of thionyl chloride gave 4-di-(2-chloroethyl)-aminopyridine. Unlike the corresponding benzene derivative, the sulphonic esters were basic and formed stable salts and methiodides. Similar attempts to esterify 2-di-(2-hydroxyethyl)aminopyridine and 2-di-(2-hydroxyethyl)-amino-5-nitropyridine gave 2 : 3-dihydroglyoxalino[1 : 2-*a*]pyridinium salts (or isomers). Methylation of 2 : 3-dihydro- and 2 : 3-dihydro-6-nitro-glyoxalino[1 : 2-*a*]pyridine takes place in the 1-position, but 2 : 3-dihydroglyoxalino[1 : 2-*a*]pyridine and ethylene dibromide gave a mixture.

Some members of a series of sulphonic esters, originally prepared in these laboratories and derived from *NN*-di-(2-hydroxyethyl)aniline; *e.g.*, *NN*-di-(2-toluene-*p*-sulphonyloxyethyl)-aniline and its *p*-chloro-analogue (I; R = H or Cl respectively) (B.P. 662,645) markedly inhibited the growth of the Walker tumour in rats (Ann. Reports, British Empire Cancer Campaign, 1949, p. 43; Haddow and Timmis, Acta Union Intern. contre le Cancre, 1951, Vol. VII, p. 469). The activity of these esters, which, as alkylating agents, are related to the active aryl nitrogen mustards (Haddow, Kon, and Ross, *Nature*, 1948, **162**, 82; Ross, *J.*, 1949, 183 *et seq.*), suggested the preparation of related heterocyclic compounds.

4-Di-(2-hydroxyethyl)aminopyridine (II; R = OH), prepared from 4-chloropyridine and excess of diethanolamine at 180°, reacted smoothly in pyridine with methanesulphonyl chloride and with aromatic sulphonyl chlorides except those carrying an electron-attracting group. The expected esters (II; R = $O{\cdot}SO_2{\cdot}C_7H_7$) separated initially as salts (see Table) which gave the parent bases on treatment with excess of ammonia. These bases were readily converted into methiodides to which the structure (III) has been tentatively assigned (cf. Tschitschibabin and Konowalowa, *Ber.*, 1926, **59**, 2055; Mann and Watson, *J. Org. Chem.*, 1948, **13**, 507). With thionyl chloride, the alcohol gave the hydrochloride of the dichloride (II; R = Cl) which also afforded a crystalline base and methiodide. These pyridine esters were evidently more powerful bases than the corresponding arylamine compounds; *e.g.*, the sulphonates (I; R = H or Cl) were found by one of us (G. M. T.) to be feebly basic, resembling the analogous chloroethyl compounds (Ross, *J.*, 1949, 183). An appreciable difference is also found between the basic strengths of the corresponding primary amines [cf. 4-aminopyridine, pK_a 9·2 (Albert, *J.*, 1951, 1376); aniline, pK_a



(I)



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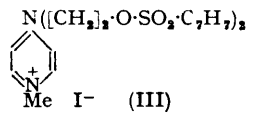
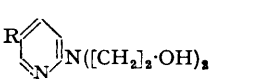
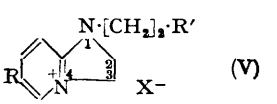


(III)

4·65 (Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3469)]. Some of the salts of the pyridine sulphonate esters were electrometrically titrated by Dr. T. S. G. Jones; in 50% aqueous acetone they had pK_a' between 7·2 and 7·4 (see Table).

As was expected from Bremer's work (*Annalen*, 1936, **521**, 286) similar attempts to prepare analogous esters from 2-di-(2-hydroxyethyl)aminopyridine (IV; R = H) and 2-di-(2-hydroxyethyl)amino-5-nitropyridine (IV; R = NO_2) led to 2 : 3-dihydroglyoxalino-[1 : 2-*a*]pyridinium salts (V) (Ring Index, No. 765) (an alternative formulation is discussed below). *E.g.*, equimolar proportions of (IV; R = NO_2) and 4-methyl-3-nitrobenzenesulphonyl chloride gave 2 : 3-dihydro-1-2′-hydroxyethyl-6-nitroglyoxalino[1 : 2-*a*]pyridinium chloride (V; R = NO_2, R′ = OH, X = Cl), whilst two mols. of the acid chloride afforded 2 : 3-dihydro-1-(2-4′-methyl-3′-nitrobenzenesulphonyloxyethyl)-6-nitroglyoxalino[1 : 2-*a*]pyridinium 4-methyl-3-nitrobenzenesulphonate (V; R = NO_2, R′ = X = 3 : 4 : 1-$NO_2{\cdot}C_6H_3Me{\cdot}SO_3$). The isolation of these salts was, of course, complicated by the different possible combinations of cations and anions in the crude reaction mixture. Three analogous salts (V; R = NO_2, R′ = *p*-$NHAc{\cdot}C_6H_4{\cdot}SO_3$, X = Cl; R = H, R′ = OH, X = 3 : 4 : 1-$NO_2{\cdot}C_6H_3Me{\cdot}SO_3$; and R = H, R′ = X = *p*-$NHAc{\cdot}C_6H_4{\cdot}SO_3$) were similarly

(IV)




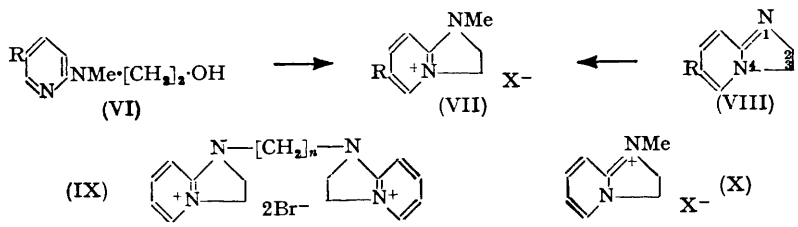
(V)

prepared. With thionyl chloride, the alcohol (IV; R = NO_2) gave the chloride (VII; R = NO_2, R′ = X = Cl). All the analyses of these compounds were complicated by hydration.

Since the salt (V; R = NO_2, R′ = OH, X = Cl) slightly (but temporarily) inhibited the growth of the Walker tumour in rats, some exploratory work was carried out on an alternative synthesis. Raison's work (*J.*, 1939, 3319) suggested that quaternisation of the parent 2 : 3-dihydroglyoxalino[1 : 2-*a*]pyridines (VIII) should take place on the doubly bound nitrogen of the amidine system which is present, *i.e.*, at position 1, and Osbond (*J.*, 1950, 1853) reached similar conclusions for the related 2 : 3-dihydroglyoxalino[1 : 2-*a*]-quinolines. This was confirmed in two simple instances. 2-(*N*-2-Hydroxyethyl-*N*-methylamino)pyridine (VI; R = H) was prepared from 2-bromopyridine and 2-*N*-methylaminoethanol; it was converted by thionyl chloride (cf. Bremer, *loc. cit.*) into the chloride (VII; R = H, X = Cl) and thence into (VII; R = H, X = I) which was identical with the product obtained from 2 : 3-dihydroglyoxalino[1 : 2-*a*]pyridine (VIII; R = H) (see below) and methyl iodide. Similarly the synthesis of the nitro-iodide (VII; R = NO_2, X = I) by these two procedures also gave indistinguishable products. The base (VIII; R = H)

has been previously synthesised (*idem, loc. cit.*) and its m. p. reported to be **64—65°**, whereas we found m. p. 37—39°. It seems likely that the former product was a monohydrate since on exposure to water vapour our product, m. p. 37—39°, was converted into a monohydrate, m. p. **60—61°**. It is noteworthy that Bremer dried his material before analysis which would account for his correct analytical figure; in agreement with this author, the picrate had m. p. 213°.

The base (VIII; R = H) and ethylene dibromide gave a mixture of two substances which, in accordance with the above conclusions, have been assigned structures (V; R = H, R′ = X = Br) (or its isomer, see below) and (IX; $n = 2$). The same mixture resulted



when ethylene dibromide was used in large excess; it seems likely that in the monosalt first formed (V) the powerful electron-attracting effect of the quaternary grouping—possibly relayed through the amidine group (see below)—makes the bromine atom in the side chain more susceptible than the bromine atoms in ethylene dibromide to nucleophilic attack by the base (VIII; R = H). The salt (IX; $n = 3$) was similarly prepared.

In the above quaternary compounds it seems likely that the preferred location of the quaternary centre is position 4, as in (VII), since such a formulation permits free resonance in the pyridine ring. However, as far as we are aware there is no direct evidence which completely excludes the alternative formulation (X), and this reservation applies to all structures which we have based above on (V), (VII), and (IX). The interchangeability of the two quaternary centres is implicit in the alternative syntheses described above.

The results of tests for tumour-inhibitory activity were disappointing. Of the compounds tested by Prof. A. Haddow on the Walker 256 carcino-sarcoma in the rat, according to the method described by Badger, Elson, Haddow, Hewett, and Robinson (*Proc. Roy. Soc.*, 1942, *B*, **130**, 255), only (II; R = O·SO_2·C_6H_4·NHAc-*p*) induced a definite (but slight) inhibition of growth of the tumour.

Experimental

4-Di-(2-hydroxyethyl)aminopyridine (II).—4-Chloropyridine (8·9 g.) (Wibaut and Brockman, *Rec. Trav. chim.*, 1939, **58**, 885) and diethanolamine (30 g.) were heated together at ~180° for 5 hr., then poured into a suspension of powdered anhydrous sodium carbonate (12 g.) in propan-2-ol (150 ml.) and refluxed therein for 30 min. After being kept overnight at 0° the insoluble inorganic solids were filtered off, the filtrate was evaporated, and the residue distilled *in vacuo*. *4-Di-(2-hydroxyethyl)aminopyridine* resulted as a viscous liquid, b. p. 220—225°/0·05 mm. (7·8 g.), which rapidly crystallised. It was insoluble in chloroform, ethyl acetate, and acetone and recrystallised from propan-2-ol and acetone as slender pointed prisms, m. p. 108·5—110° (Found: C, 59·5; H, 7·75. $C_9H_{14}O_2N_2$ requires C, 59·3; H, 7·7%).

Reaction of 4-Di-(2-hydroxyethyl)aminopyridine with Sulphonyl Chlorides.—A suspension of 4-di-(2-hydroxyethyl)aminopyridine (3·6 g.; 0·02 mol.) in dry pyridine (15 ml.) was stirred at *ca.* 5° during the gradual addition of the sulphonyl chloride (0·05 mol.). The mixture was kept at 5° for a further 15 min. and then allowed to warm spontaneously to a maximum temperature of 30°. After 1 hr. the mixture was poured into cold water, giving the products as solids, or as oils which subsequently solidified. These were filtered off, washed, and dried thoroughly *in vacuo* before recrystallisation (see Table). At this stage the products were obtained as the salts described in the Table. The solid parent bases were regenerated by grinding these salts with excess of 2N-ammonia and filtration. The methiodides were prepared in anhydrous methanol. The product from methanesulphonyl chloride was water-soluble and was therefore isolated by precipitation with propan-2-ol; the liquid base was isolated by extraction with ethyl acetate since it was immiscible with ether. *p*-Chlorobenzenesulphonyl chloride and

4-methyl-3-nitrobenzenesulphonyl chloride gave no identifiable products in the above reaction although different conditions and isolation procedures were investigated.

4-Di-(2-sulphanilyloxyethyl)pyridine.—4-Di-(2-*N*-acetylsulphanilyloxyethyl)pyridine (3·6 g.) dissolved in methanol (60 ml.) when a rapid stream of hydrogen chloride was passed in. The product crystallised; the mixture was then cooled and the solid 4-di-(2-sulphanilyloxyethyl)-pyridine trihydrochloride was filtered off. It recrystallised from a large volume of methanol containing a little hydrogen chloride. The free base, prepared by means of aqueous sodium carbonate, was dried *in vacuo* (2·2 g.). Its recrystallisation caused considerable loss.

Esters (II; R = O·SO_2R').

No.	R	Derivative	Solvent for crystn.	M. p.	Formula
1	Me	Base	—	Liquid	—
2	,, ...	*Hydrochloride*	EtOH	120—121°	$C_{11}H_{19}O_6N_2ClS_2$
3	,, ...	*Methiodide monohydrate*	EtOH–EtOAc	74	$C_{12}H_{21}O_6N_2IS_2,H_2O$
4	Ph	*Base* *	$COMe_2$–H_2O	115—116	$C_{21}H_{22}O_6N_2S_2$
5	,, ...	*Benzenesulphonate*	MeOH–Et_2O	133—134	$C_{27}H_{28}O_9N_2S_3$
6	,, ...	*Methiodide*	EtOH	117—118	$C_{22}H_{25}O_6N_2IS_2$
7	*p*-C_6H_4Me ...	*Base* *	MeOH	82—86	$C_{23}H_{26}O_6N_2S_2$
8	,, ...	*Toluene*-p-*sulphonate monohydrate* *	EtOH	152	$C_{30}H_{34}O_9N_2S_3,H_2O$
9	,, ...	*Methiodide* *	MeOH	95—96	$C_{24}H_{29}O_6N_2IS_2$
10	*p*-MeO·C_6H_4	*Base*	MeOH	95—96	$C_{23}H_{26}O_8N_2S_2$
11	,,	p-*Methoxybenzenesulphonate*	MeOH	96—98	$C_{30}H_{34}O_{12}N_2S_3$
12	*p*-NHAc·C_6H_4	*Base*	EtOH	200—201	$C_{25}H_{28}O_8N_4S_2$
13	,,	*Hydrochloride*	EtOH	150—152	$C_{25}H_{29}O_8N_4ClS_2$
14	,,	*Methiodide*	H_2O	168—169	$C_{26}H_{31}O_8N_4IS_2$
15	*p*-NH_2·C_6H_4	*Base*	EtOH	Collapse 170; decomp. >260	$C_{21}H_{24}O_6N_4S_2$
16	,,	*Trihydrochloride*	MeOH	Soft, 166; decomp. >220	$C_{21}H_{27}O_6N_4Cl_3S_2$
17	2-$C_{10}H_7$	*Base*	$COMe_2$–H_2O	155—158; soft, 130	$C_{29}H_{26}O_6N_2S_2$
18	,, ...	Naphthalene-2-sulphonate †	$MeNO_2$	203	$C_{39}H_{34}O_9N_2S_3$

No.	Found (%) C	H	N		Required (%) C	H	N		pK_a'
1	—	—	—	—	—	—	—	—	7·4
2	35·4	5·05	7·3	—	35·3	5·1	7·5	—	—
3	29·0	4·7	—	I, 25·7	28·9	4·7	—	I, 25·5	—
4	54·55	4·9	6·1	S, 13·8	54·5	4·8	6·1	S, 13·8	7·2
5	52·4	4·5	—	—	52·3	4·55	—	—	—
6	—	—	—	I, 21·1	—	—	—	I, 21·0	—
7	55·8	5·15	—	—	56·3	5·3	—	—	7·4
8	53·1	5·4	3·8	S, 14·1	52·9	5·3	4·1	S, 14·1	—
9	—	—	—	I, 20·1	—	—	—	I, 20·1	—
10	52·6	5·2	—	—	52·9	5·0	—	—	7·4
11	50·6	4·95	3·6	S, 13·2	50·7	4·8	3·9	S, 13·5	—
12	51·9	5·1	9·9	—	52·1	4·9	9·7	—	7·4
13	49·2	4·7	8·9	—	49·0	4·8	9·1	—	—
14	43·6	4·7	7·6	—	43·5	4·35	7·8	—	—
15	51·3	4·9	—	—	51·2	4·9	—	—	—
16	—	—	9·5	S, 10·1	—	—	9·3	S, 10·6	—
17	61·6	4·6	—	—	62·0	4·6	—	—	7·4
18	60·65	4·4	—	S, 12·3	60·8	4·4	—	S, 12·4	—

* Unstable on repeated crystallisation or prolonged storage.
† Required 48 hours' treatment with conc. ammonia to liberate the free base.

4-Di-(2-chloroethyl)aminopyridine.—Thionyl chloride (2 g.) was slowly added to a cooled suspension of 4-di-(2-hydroxyethyl)aminopyridine (1 g.) in chloroform (5 ml.), and the mixture heated under reflux for 2 hr. Addition of ether gave *4-di-(2-chloroethyl)aminopyridine hydrochloride* as a gum which crystallised from propan-2-ol in short flat prisms (1·3 g.), m. p. 172—173° (Found: C, 42·5; H, 5·1; Cl, 41·7. $C_9H_{13}N_2Cl_3$ requires C, 42·3; H, 5·1; Cl, 41·6%). With cold aqueous potassium carbonate this hydrochloride gave the *base* which, crystallised by dissolution in cold benzene and slow addition of light petroleum (b. p. 40—60°), had m. p. 131—132·5° (Found: C, 49·4; H, 5·5; Cl, 32·3. $C_9H_{12}N_2Cl_2$ requires C, 49·35; H, 5·5; Cl, 32·3%). The *methiodide*, prepared in acetone at room temperature and crystallised from ethanol, had

m. p. 204° (decomp.) (Found : C, 33·2; H, 4·2; N, 7·7. $C_{10}H_{15}N_2Cl_2I$ requires C, 33·3; H, 4·2; N, 7·8%).

2-*Di*-(2-*hydroxyethyl*)*aminopyridine* (IV; R = H).—This was prepared from 2-bromopyridine (15·8 g.) and diethanolamine (31 g.) according to Weiner and Kaye's method (*J. Org. Chem.*, 1949, **14**, 868) except that the free bases were liberated with sodium carbonate (20 g.) in propan-2-ol (200 ml.) as above. The inorganic salts were filtered off, the filtrate was evaporated, and the residue distilled *in vacuo*, giving 2-di-(2-hydroxyethyl)aminopyridine, b. p. 158—165°/0·01 mm. (10·5 g.) (Found : N, 15·7. Calc. for $C_9H_{14}O_2N_2$: N, 15·4%). Distillation gave a tarry residue, particularly from larger batches.

2-(N-2-*Hydroxyethyl*-N-*methylamino*)*pyridine* (VI; R = H), similarly prepared from 2-bromopyridine and 2-*N*-methylaminoethanol, had b. p. 106—108°/0·9 mm. (Found : C, 62·9; H, 7·7; N, 18·5. $C_8H_{12}ON_2$ requires C, 63·1; H, 7·95; N, 18·4%).

2-*Di*-(2-*hydroxyethyl*)*amino*-5-*nitropyridine* (IV; R = NO_2).—2-Chloro-5-nitropyridine (4 g.), diethanolamine (3·5 g.) and fused sodium acetate (2·1 g.) were heated in ethanol (20 ml.) for 3 hr. (cf. Mangini and Frengalli, *Gazzetta*, 1939, **69**, 86). The resulting suspension was filtered whilst hot and the cooled filtrate rapidly deposited golden prisms. These were collected, washed with a little fresh ethanol, dried, and then heated *in vacuo* to remove unchanged 2-chloro-5-nitropyridine. The residual *product*, recrystallised from water or ethanol, had m. p. 103·5—105° (Found : C, 47·6; H, 5·5; N, 18·7. $C_9H_{13}O_4N_3$ requires C, 47·6; H, 5·8; N, 18·5%).

2-(N-2-*Hydroxyethyl*-N-*methylamino*)-5-*nitropyridine* (VI; R = NO_2), similarly prepared, crystallised from methanol in bright yellow needles, m. p. 86·5—87·5° (Found : C, 48·5; H, 5·5; N, 21·2. $C_8H_{11}O_3N_3$ requires C, 48·7; H, 5·6; N, 21·3%).

Reaction of 2-*Di*-(2-*hydroxyethyl*)*amino*-5-*nitropyridine and* 4-*Methyl*-3-*nitrobenzenesulphonyl chloride.*—(*a*) A suspension of 2-di-(2-hydroxyethyl)amino-5-nitropyridine (2·3 g.; 0·01 mol.) in dry pyridine (4 ml.) was stirred at 5—10° whilst 4-methyl-3-nitrobenzenesulphonyl chloride (2·5 g.; 0·01 mol.) was added during 30 min. The mixture was kept at 5—10° for a further 30 min., then allowed to warm spontaneously. After 4 hr. the resulting suspension was stirred into dry acetone, a yellow precipitate separating. This was filtered off and crystallised twice from ethanol giving very pale yellow needles (1·5 g.) of 2 : 3-*dihydro*-1-2′-*hydroxyethyl*-6-*nitroglyoxalino*[1 : 2-*a*]*pyridinium chloride*, m. p. 204—205° (V; R = NO_2, R′ = OH, X = Cl) (Found : C, 44·3; H, 4·9; N, 17·7; Cl, 13·8. $C_9H_{12}O_3N_3Cl$ requires C, 44·0; H, 4·9; N, 17·1; Cl, 14·4%), which gradually decomposed.

(*b*) Use of twice as much 4-methyl-3-nitrobenzenesulphonyl chloride in dry pyridine (8 ml.) at 5—10° gave 2 : 3-*dihydro*-1-(2-4′-*methyl*-3′-*nitrobenzenesulphonyloxyethyl*)-6-*nitroglyoxalino*[1 : 2-*a*]*pyridinium* 4-*methyl*-3-*nitrobenzenesulphonate monohydrate* (2·1 g.), m. p. 152—154° (from methanol–ether) (Found : C, 43·1; H, 3·8; N, 10·8; loss on drying, 2·0. $C_{23}H_{23}O_{12}N_5S_2,H_2O$ requires C, 42·9; H, 3·9; N, 10·9; H_2O, 2·8%).

1-(2-N-*Acetylsulphanilyloxyethyl*)-2 : 3-*dihydro*-6-*nitroglyoxalino*[1 : 2-*a*]*pyridinium chloride dihydrate*, similarly prepared from equimolecular amounts of 2-di-(2-hydroxyethyl)-5-nitropyridine and *N*-acetylsulphanilyl chloride, crystallised from ethanol containing 5% of water, as prisms, m. p. 129—130° (Found : C, 43·0; H, 4·6; N, 11·4; Cl, 7·4; S, 6·5. $C_{17}H_{19}O_6N_4ClS,2H_2O$ requires C, 42·65; H, 4·8; N, 11·7; Cl, 7·4; S, 6·7%).

2-*Di*-(2-*hydroxyethyl*)*aminopyridine and Sulphonyl Chlorides.*—Under similar conditions 2-di-(2-hydroxyethyl)aminopyridine and one equivalent of 4-methyl-3-nitrobenzenesulphonyl chloride gave 2 : 3-*dihydro*-1-2′-*hydroxyethylglyoxalino*[1 : 2-*a*]*pyridinium* 4-*methyl*-3-*nitrobenzenesulphonate*, which crystallised from propan-2-ol as prisms, m. p. 126·5—127·5° (Found : C, 50·55; H, 5·0; N, 11·3; S, 8·3. $C_{16}H_{19}O_6N_3S$ requires C, 50·4; H, 5·0; N, 11·0; S, 8·4%). With two equivalents of *N*-acetylsulphanilyl chloride there resulted 1-(2-N-*acetylsuphanilyloxyethyl*)-2 : 3-*dihydroglyoxalino*[1 : 2-*a*]*pyridinium* N-*acetylsulphanilate monohydrate*, m. p. 178—180° (from propan-2-ol) (Found : C, 50·2; H, 5·0. $C_{25}H_{28}O_8N_4S_2,H_2O$ requires C, 50·5; H, 5·0%).

1-2′-*Chloroethyl*-2 : 3-*dihydro*-6-*nitroglyoxalino*[1 : 2-*a*]*pyridinium Chloride* (V; R = NO_2, R′ = X = Cl).—2-Di-(2-hydroxyethyl)amino-5-nitropyridine (12 g.) was suspended in chloroform (30 ml.) and cooled to 10—15° during the gradual addition of thionyl chloride (16 g.). After 1 hr. at room temperature the mixture was heated to reflux for 3 hr., then cooled and the insoluble solid was filtered off and dried immediately *in vacuo* to remove occluded acid. It was then dissolved in hot propan-2-ol, and pyridine was added until the solution was no longer strongly acid. Ether was then slowly added to turbidity and, on cooling, needles rapidly separated. [Without the neutralisation the product could not be obtained free from acid though analysis indicated that it was substantially (V; R = NO_2, R′ = X = Cl) and not

2-di-(2-chloroethyl)-5-nitropyridine hydrochloride.] This product (V; R = NO_2, R′ = X = Cl) crystallised from propan-2-ol in needles, apparently the *monohydrate*, m. p. 82—84° (Found : C, 38·5; H, 4·6; O, 16·3; N, 15·1; Cl, 26·0; Cl^-, 13·0; loss at 100°, 5·9. $C_9H_{11}O_2N_3Cl_2,H_2O$ requires C, 38·3; H, 4·6; O, 17·0; N, 14·9; Cl, 25·2; Cl^-, 12·6; H_2O, 6·4%). The dried *salt* was also analysed (Found : C, 41·0; H, 4·2. $C_9H_{11}O_2N_3Cl_2$ requires C, 40·9; H, 4·2%).

2 : 3-*Dihydroxyglyoxalino*[1 : 2-*a*]*pyridine*.—The hydrochloride of the base was prepared by Bremer's method (*loc. cit.*) by gently warming 2-2′-chloroethylaminopyridine or, alternatively, by boiling a benzene solution of this substance for 3 hr., the desired hydrochloride slowly separating. The free base was precipitated from cooled aqueous solution by excess of potassium hydroxide and, crystallised from benzene, had m. p. 60—61°. It rapidly sublimed at 60°/0·1 mm. to give deep yellow needles, m. p. 36—38° (not clear until 48°), of anhydrous 2 : 3-*dihydroglyoxalino*[1 : 2-*a*]*pyridine*. It was analysed immediately (Found : C, 69·2; H, 6·5. $C_7H_8N_2$ requires C, 69·7; H, 6·7%). After 24 hours' exposure, in a sealed vessel, to water vapour the colour had become lighter and, after drainage on a porous tile, the m. p. was 60—61° (Found : C, 60·85; H, 7·3; N, 20·0; O, 10·9. $C_7H_8N_2,H_2O$ requires C, 60·85; H, 7·3; N, 20·3; O, 11·6%). Its *picrate* formed golden needles, m. p. 213° (Found : C, 44·7; H, 3·0. $C_{13}H_{11}O_7N_5$ requires C, 44·7; H, 3·2%). Bremer (*loc. cit.*) also found m. p. 213° but gave no analysis.

2 : 3-Dihydro-6-nitroglyoxalino[1 : 2-*a*]pyridine was obtained by the method previously recorded (*idem, loc. cit.*); it decomposed at 258—259°.

2 : 3-*Dihydro*-1-*methylglyoxalino*[1 : 2-*a*]*pyridinium Iodide* (VII; R = H; X = I).—To 2-(*N*-2-hydroxyethyl-*N*-methylamino)pyridine (10 g.) in chloroform (30 ml.) thionyl chloride (10 ml.) was slowly added with cooling. The mixture was then refluxed for 1 hr. and the chloroform removed *in vacuo*. The residue was dissolved in cold water (20 ml.), the solution made alkaline with excess of potassium carbonate, and the precipitated oil extracted with ether. The ethereal solution was rapidly dried and evaporated and the residue warmed on the steam-bath until it crystallised. This solid was added to a suspension of powdered potassium iodide (10 g.) in boiling ethanol (30 ml.), a precipitate of potassium chloride being rapidly formed. This was filtered off and ethyl acetate added to the filtrate to precipitate 2 : 3-*dihydro*-1-*methylglyoxalino*[1 : 2-*a*]*pyridinium iodide* (5·1 g.). This was repeatedly crystallised from propan-2-ol–acetone and finally from ethanol, forming yellowish needles, m. p. 169—170° (Found : I, 48·8. $C_8H_{11}N_2I$ requires N, 10·7; I, 48·4%).

Alternatively, anhydrous 2 : 3-dihydroglyoxalino[1 : 2-*a*]pyridine (1 g.) and methyl iodide (2 ml.) in methanol (5 ml.) were heated under reflux. After 30 min., the product was precipitated with ethyl acetate and recrystallised from ethanol in cream-coloured needles (2·2 g.), m. p. and mixed m. p. 169—170° (Found : N, 10·7; I, 49·0%).

2 : 3-*Dihydro*-1-*methyl*-6-*nitroglyoxalino*[1 : 2-*a*]*pyridinium Iodide*.—2-(*N*-2-Hydroxyethyl-*N*-methylamino)-5-nitropyridine was similarly converted into this *iodide*, yellow prisms, m. p. 246—247° (from methanol) (Found : I, 41·4. $C_8H_{10}O_2N_3I$ requires N, 13·65; I, 41·3%).

The same compound resulted from the prolonged reaction between 2 : 3-dihydro-6-nitroglyoxalino[1 : 2-*a*]pyridine and methyl iodide in methanol and crystallised from methanol in short prisms, m. p. and mixed m. p. 246—247° (Found : N, 13·5; I, 41·4%).

Reaction of 2 : 3-*Dihydroglyoxalino*[1 : 2-*a*]*pyridine and Ethylene Dibromide*.—2 : 3-Dihydroglyoxalino[1 : 2-*a*]pyridine (1·4 g.) and ethylene dibromide (5 ml.) in ethyl methyl ketone (10 ml.) were heated under reflux for 1 hr., then cooled, and the solid which separated was collected and dissolved in the minimum amount of cold water. Acetone was slowly added to the solution until crystallisation ensued. After 12 hr. the solid was filtered off and recrystallised by the same procedure, giving *ethylene*-1 : 2-*bis*-1′-(2 : 3-*dihydroglyoxalino*[1 : 2-*a*]*pyridinium dibromide*) *dihydrate* (IX; $n = 2$) (900 mg.), m. p. 318—320° (slight sintering at 132°) (Found : C, 41·5; H, 5·0; N, 12·1; Br, 34·5; loss on drying at 100°, 7·0. $C_{16}H_{20}N_4Br_2,2H_2O$ requires C, 41·4; H, 5·2; N, 12·1; Br, 34·5; H_2O, 7·7%). The acetone–water mother-liquors were evaporated and the residue crystallised twice from propan-2-ol and finally from propan-2-ol–ethanol (2 : 1). 1-2′-*Bromoethyl*-2 : 3-*dihydroglyoxalino*[1 : 2-*a*]*pyridinium bromide* (V; R = H, R′ = X = Br) was obtained as needles, m. p. 186—189° (250 mg.) (Found : C, 35·5; H, 3·8; N, 9·1; Br, 51·7. $C_9H_{12}N_2Br_2$ requires C, 35·1; H, 3·9; N, 9·1; Br, 51·9%).

Under similar conditions, 2 mols. of 2 : 3-dihydroglyoxalino[1 : 2-*a*]pyridine and 1 mol. of 1 : 3-dibromopropane gave *propylene*-1 : 3-*bis*-1′-(2 : 3-*dihydroglyoxalino*[1 : 2-*a*]*pyridinium dibromide*) *dihydrate* (IX; $n = 3$) which, crystallised from ethanol, had m. p. 156—157° (effervescence) (Found, after drying at 100° : N, 12·5; Br, 36·4. $C_{17}H_{22}N_4Br_2$ requires N, 12·5; Br, 36·2. Loss on drying, 7·3. $C_{17}H_{22}N_4Br_2,2H_2O$ requires H_2O, 7·5%).

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