ACTA CHEMICA SCANDINAVICA 20 (1966) 2637–2648

Quaternisation Reactions

I. Self-quaternisation of 3-Chloro-6-methylpyridazine

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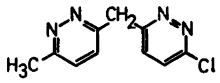
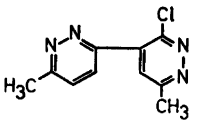
3-Chloro-6-methylpyridazine forms under acid catalysis a self-condensation product, $C_{10}H_9ClN_2$, which from degradation and spectroscopic data has been shown to be 8-chloro-6,7-dihydro-3-methyldipyridazino[2,3-a:4,3-d]pyrrole. Among the degradation products are derivatives of 6,7-diazaindole.

From the reaction between 6-methylpyridazone-3 and phosphoryl chloride Kumagai [1] isolated a condensation product, $C_{10}H_9ClN_4$, in addition to 3-chloro-6-methylpyridazine. For the condensation product was proposed the structures I or II. Later the same product was isolated by Basu and Rose [2] who suggested the structure III.



I



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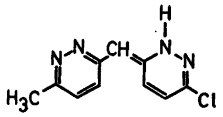


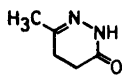
III

STRUCTURE OF THE CONDENSATION PRODUCT

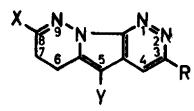
The empirical formula of the condensation product corresponded to $C_{10}H_9ClN_4$ and this formula was conclusively established by an absolute mass determination of the parent peak in the mass spectrum.

The NMR-spectrum of the condensation product (in trifluoroacetic acid) exhibited a singlet ($\sum H = 3$, $\delta = 3.02$), a multiplet resembling two deformed triplets ($\sum H = 4$, $\delta = 3.2-3.7$), and two singlets ($\sum H = 1$, $\delta = 6.85$; $\sum H = 1$, $\delta = 8.25$). The spectrum points to the presence of only one methyl group and one "aromatic" proton in the condensation product. These facts alone exclude the structures I, II, and III. The part of the spectrum from $\delta = 3$

to $\delta = 3.7$ was analogous to that of 6-methylpyridazinone-3 (IV) and this together with the above mentioned facts indicated a structure containing three rings. The structure of the condensation product was tentatively formulated as Va, which was subsequently proved by the spectroscopic, polarographic, and chemical data presented below. Va is in accordance with the suggestion of G. R. Bedford in the paper of Basu and Rose [2] and the preliminary results from an X-ray structure determination.[3]



IV



Va X = Cl Y = H R = CH_3
b X = H Y = H R = CH_3
c X = Cl Y = Br R = CH_3
d X = Cl Y = CH_3 R = C_2H_5
e X = H Y = Br R = CH_3

On catalytic hydrogenation, Va took up one mole of hydrogen and two products, Vb and IXa, were formed, both with the empirical formula $C_{10}H_{10}N_4$. The most conspicuous difference between the NMR-spectra of Va and Vb (Table 1) was a triplet centered at $\delta = 8.11$ ($\sum H = 1$, $J = 3$ cps) with the intensities 1:2:1. This signal is assigned to the proton in Vb replacing the chlorine in Va and it shows that the chlorine in Va is a neighbour to a methylene group and that X thus in Va is chlorine.

This assignment is substantiated by further details in the NMR-spectrum. The signal from the methylene group neighbour to the chlorine is shifted upfield on replacement of chlorine with hydrogen and coalesces with the signal from the methyl group. The coupling between this methylene group and the triplet of $\delta = 8.11$ was proved by decoupling which transformed the triplet into a singlet. The coupling constant between the two methylene groups was found to 7 cps.

Table 1. NMR-spectra of some 6,7-dihydrodipyridazino[2,3-a:4,3-d]pyrroles. Chemical shifts in ppm (δ-units) from TMS, coupling constants J in cps, solvent trifluoroacetic acid.

Proton Compound	3-CH_3	3-C_2H_5	4-H	5-H	5-CH_3	6-H_2	7-H_2	8-H
Va	3.02(s)		8.25(s)	6.85(s)		3.2–3.7(m)		
Vb	3.02(s)		8.24(s)	6.84(s)		3.52(t) $J_{6,7} = 7$	2.8–3.2(m)	8.11(t) $J_{7,8} = 3$
Vc	3.03(s)		8.18(s)			3.2–3.7(m)		
Vd		1.61(t) 3.37(q) $J_{Et} = 7$	8.26(s)		2.45(s)	3.2–3.7(m)		
Ve	3.08(s)		8.19(s)			3.43(t) $J_{6,7} = 7$	2.8–3.1(m)	8.01(t) $J_{7,8} = 3$

s = singlet, t = triplet, q = quartet, m = multiplet.

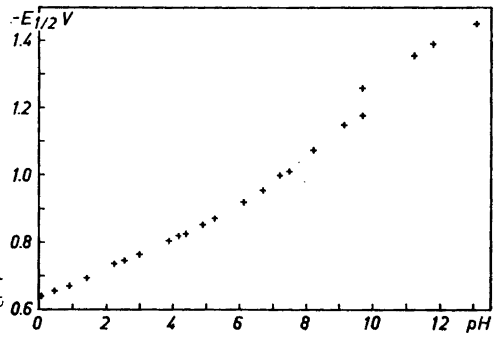
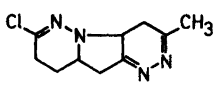


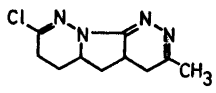
Fig. 1. Dependence on pH of the half-wave potentials (*vs.* S.C.E.) of the first wave of Va.

The relative position of the pyridazine rings could not be proved from the spectra of Va or Vb. Two possibilities could seriously be considered: a) The position shown in Va, which would be formed by an initial self-quaternisation reaction and b) a ring structure as in VI, which would result from an initial attack on the methyl group as suggested in the formulas I and III.

Va is polarographically reducible (Fig. 1), and on controlled potential reduction at pH 2.5 a compound, $C_{10}H_{13}ClN_4$, was obtained in a reaction which consumed 4 electrons per molecule. The IR-spectrum indicated the absence of nitrogen-hydrogen bonds, and the NMR-spectrum showed that no hydrogens were bonded to double bonded or aromatically bonded carbon atoms. This indicates that the reduction product can be formulated as either VI or VII.



VI



VII

The tertiary hydrogen atoms would be expected to give signals at the highest δ-values. The tertiary hydrogen atoms of VI would most probably have nearly the same chemical shift as they both are neighbours to a nitrogen atom, and the one in the dihydropyridazine ring is part of an ABX-system. Only one of the tertiary hydrogen atoms of VII is a neighbour to a nitrogen atom and both of them would be expected to give rather broad signals owing to a coupling to several differently situated hydrogen atoms. The NMR-spectrum of the reduction product contains two rather broad signals at $\delta = 4.1-4.6$ and $\delta = 3.3-3.8$ each corresponding to one proton. The other 11 protons give signals at higher field. The NMR-spectrum of the reduction product is thus in accordance with VII and the condensation product can, therefore, with confidence be formulated as Va = 8-chloro-6,7-dihydro-3-methyl-dipyridazino[2,3-a:4,3-d]pyrrole = 8-chloro-6,7-dihydro-3-methyl-pyrrolo[1,5-b:2,3-c']dipyridazine. This structure is further confirmed by the data presented below and the preliminary results from an X-ray structure determination.[3]

PHYSICAL AND CHEMICAL PROPERTIES OF THE CONDENSATION PRODUCT

The dipyridazinopyrrole Va is slightly more basic than pyridazine and resembles more 3-aminopyridazine, the pK is 5.3. The basic center is at N-1 or N-2; MO-calculations [4] point to the possibility of addition of a proton to N-1, N-2, or C-5. The salt formation of Va does not take place at C-5, as the proton at C-5 is not exchanged with deuterium when kept in deuterated trifluoroacetic acid for 24 h; however, when the solution was heated at 65° for two days a complete exchange of the hydrogen was induced at C-5 but not of hydrogen atoms in other positions.

Quaternisation with methyl iodide of Va gave a mixture containing 15 % quaternised at N-1 and 85 % quaternised at N-2. The analysis of the mixture was performed by means of NMR-spectroscopy. The position of the signal from the methyl group at C-3 of the quaternised compound is dependent on the location of the positive charge; in trifluoroacetic acid the signals from the methyl groups of the two isomers are found at $\delta = 3.00$ (85 %) and $\delta = 2.87$ (15 %). The signal at $\delta = 3.00$ is attributed to the isomer with the positive charge at N-2. The assignment is substantiated by the fact that in the mixtures of products obtained by quaternisation of methyldiazines [5] the methyl group which gives rise to the low field signal exchanges its hydrogens quickly with deuterium in deuterium oxide containing potassium carbonate; the rapid exchange is caused by the activation of the methyl group by the positive charge on the nitrogen atom in the adjacent position.

Treatment of Va with *m*-chloroperbenzoic acid produces an *N*-oxide. The position of the oxygen has not been established, but in view of the results from the quaternisation reaction N-2 seems the most probable site. The *N*-oxide can be reduced polarographically to the parent compound.

Va reacts readily with electrophilic reagents in the 5-position. The exchange with deuterium in deuterated trifluoroacetic acid has been mentioned above. The reaction between Va and bromine in chloroform produces the hydrobromide of Vc.

The assignment of the position of the bromine in Vc is made from a comparison of the NMR-spectra of Va and Vc. The singlet at $\delta = 6.85$ in the spectrum of Va assigned to the proton at C-5 has no counterpart in the spectrum of Vc, whereas all other signals are analogous in the two spectra.

Heating of Va to about 200°C or refluxing in *o*-dichlorobenzene with a palladium catalyst produces the aromatic system VIIIa. This compound was also found as a minor product (5—10 %) during the preparation of Va. VIIIa can easily be brominated in the 5-position to VIIIc. This assignment rests on similar considerations as those presented above for Vc (Table 2).

Besides the signals from the methyl group and the hydrogens at C-4 and C-5 the NMR-spectrum of VIIIa (Table 2) was found to exhibit two doublets centered at $\delta = 8.23$ and $\delta = 7.56$ with $J = 9$ cps; the former signal is attributed to the hydrogen at C-6 and the latter to the one at C-7. The methyl group of VIIIa couples with the proton at C-4 with $J = 0.6$ cps. A similar coupling is also found in VIIIc.

On being heated Vc loses hydrogen bromide and VIIIa is formed. This substitution-elimination is unusual and the mechanism of the reaction is

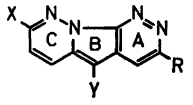
Table 2. NMR-spectra of some dipyridazino [2,3-a:4,3-d]pyrroles. Chemical shifts in ppm (δ-units) from TMS, coupling constants J in cps, solvent trifluoroacetic acid.

Proton Compound	3-CH_3	3-C_6H_5	4-H	5-H	6-H	7-H	8-H	8-CH_3
VIIIa	3.12(d) $J_{Me,4}=0.6$		8.46(q)	7.16(s)	8.23(d) $J_{6,7}=9$	7.56(d)		
VIIIb	3.16(s)		8.50(s)	7.20(s)	8.41(q) $J_{6,7}=9.6$	7.65(q) $J_{7,8}=4.3$	8.84(q) $J_{6,8}=1.6$	
VIIIc	3.14(d) $J_{Me4}=0.6$		8.40(q)		8.30(d) $J_{6,7}=9$	7.65(d)		
VIIId		7.7–8.1(m)	8.71(s)	7.20(s)	8.30(d) $J_{6,7}=9.5$	7.56(d)		2.80(s)

s = singlet, d = doublet, q = quartet, m = multiplet.

unknown at present. VIIIc is more stable than Vc and sublimes unchanged on being heated.

The reduction product Vb can be brominated in the 5-position to Ve and dehydrogenated on heating in trichlorobenzene with a palladium catalyst to the aromatic compound VIIIb. VIIIb is produced in better yield by boiling Ve in *o*-dichlorobenzene with loss of hydrogen bromide. In VIIIb, as in most other dipyridazinopyrroles, the hydrogen atoms in the methyl group ($\delta = 3.16$) and at C-4 ($\delta = 8.50$) and C-5 ($\delta = 7.20$) only couple slightly or not detectably with other hydrogen atoms. The signal from the proton at C-6 is a quartet centered at $\delta = 8.41$ with $J_{6,7} = 9.6$ cps and $J_{6,8} = 1.6$ cps. The quartet from the hydrogen at C-7 is centered at $\delta = 7.65$ with $J_{7,8} = 4.3$. The greater coupling between the protons at C-6 and C-7 than between those at C-7 and C-8 may indicate a certain fixation of the double bonds in ring C.



VIII

a R = CH_3; Y = H; X = Cl
b R = CH_3; Y = H; X = H
c R = CH_3; Y = Br; X = Cl
d R = C_6H_5; Y = H; X = CH_3

All the compounds containing a pyridazine ring are polarographically reducible. Va yielded a well defined wave from pH 0 to pH 13 (Fig. 1). The results plotted in Fig. 1 are consistent with the assumption that the protonated compound is the reduced species in the pH-region up to pH 10 and the free base above pH 10. The change in the slope of the E-$pH_{½}$ curve about pH 6 occurs at the pK_A of the compound. Up to about pH 8 the first wave is followed by two or three less to ill-defined waves, which are not shown in Fig. 1.

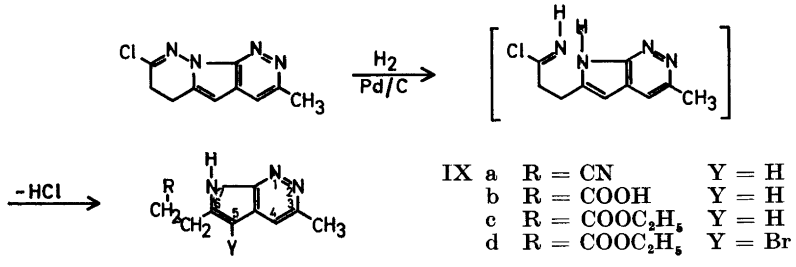
The height of the first wave corresponds to the uptake of two electrons. This is judged from the polarographic behaviour of the *N*-oxide of Va which in acid solution shows two waves of equal height followed by two less defined waves. The second, third and fourth wave occur at the potentials of the

first, second and third wave of Va, respectively. The *N*-oxide is thus assumed to be reduced to Va in a two electron reduction and the first wave of Va would, therefore, be a two-electron wave.

A preparative reduction of Va, however, yielded VII isolated in 50 % yield. This product requires four electron per molecule for its formation and can not be the primarily formed product under polarographic conditions. This is confirmed by the polarographic behaviour of VII which is reduced at a potential about 0.1 V more negative than that of the second wave of Va. Possibly the primarily formed species is transformed under preparative conditions into another tautomeric form which then is reduced to VII.

VIIIa is reducible at a potential about 0.2 V less negative than that of Va and the reduction proceeds simultaneously along different routes. Only a part of VIIIa is reduced to Va and the rest by another path. The polarograms in acid solution thus exhibit at least five reduction waves of which three are caused by the reduction of the Va formed. Whereas polarography is well suited to determine a small amount of VIIIa in Va, it is difficult to estimate the amount of Va in VIIIa by this method. Bromination of Va and VIIIa in the 5-position makes the compounds easier reducible; the halfwave potentials are shifted about 0.1 V to more positive values, but the reduction pattern seems not to be altered.

The other product from the catalytic reduction, IXa, $C_{10}H_{10}N_4$, gave an IR-spectrum with a sharp band at 2240 cm^{-1} which suggested the presence of a nitrile group and a band at 3110 cm^{-1} interpreted as a nitrogen-hydrogen bond. The reduction consists probably in a cleavage of the nitrogen-nitrogen bond followed by the loss of hydrogen chloride to form IXa. The presence of a nitrile group in IXa was corroborated by its hydrolysis to a compound containing a carboxyl group (IXb) which could be esterified to IXc.



IX a R = CN Y = H
b R = COOH Y = H
c R = $COOC_2H_5$ Y = H
d R = $COOC_2H_5$ Y = Br

The ring system common to IXa—IXd is 7H-pyrrolo[2,3-c] pyridazine. It resembles both the dipyridazinopyrroles and — as a diazaindole — indole. The chemical shifts of the corresponding protons in the NMR-spectra of the dipyridazinopyrroles and the pyrrolopyridazines (Table 1—3) are very similar, and the coupling constant (2—3 cps) between the hydrogen at N-7 and that at C-5 is similar to that between the nitrogen bonded hydrogen and the hydrogen at C-3 in indole.[6]

The reactivity towards electrophilic reagents in the 5-position of the pyrrolopyridazines is similar to that of the dipyridazinopyrroles. Reaction

Table 3. NMR-spectra of some pyrrolopyridazines. Chemical shifts in ppm (δ-units) from TMS, coupling constants J in cps, solvent trifluoroacetic acid.

Proton Compound	3-CH_3	4-H	5-H	7-H	$(CH_2)_2$	$COOC_2H_5$
IXa	3.00(s)	8.24(s)	6.89(d) $J_{5,7} = 2$	10.97(d)	3.0—3.7(m)	
IXc	2.93(s)	8.05(s)	6.75(d) $J_{5,7} = 2$	10.90(d)	3.0—3.7(m)	1.30(t) 4.31(q) $J_{Et} = 7$
IXd	3.00(s)	8.03(s)			3.0—3.6(m)	1.30(t), 4.31(q) $J_{Et} = 7$

s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

Table 4. UV-spectra of some dipyridazinopyrroles and pyrrolopyridazines in abs. ethanol.

Compound	λ_{max} mμ	log ε	λ_{max} mμ	log ε	λ_{max} mμ	log ε
VII	302	4.17				
Va	222	4.28	264	4.35	340	3.96
Vb	223	4.29	259	4.28	339	3.83
Vc	230	4.48	266	3.70	352	3.63
Vd	229	4.29	267	4.37	338	3.83
Ve	228	4.14	261	4.24	349	3.68
VIIIa	259	4.47	289	4.21	300	4.02
VIIIb	253	4.45	285	4.13	296	3.97
VIIIc	265	4.40	293	4.21	304	4.00
IXa	225	4.30	277	3.95	327	3.72
IXb	226	4.47	278	3.91	326	3.73
IXd	232	4.70	282	4.12	331	3.77
XII	255	4.60	324	3.87		

with bromine proceeds smoothly to the expected 5-bromo derivative. It is well-known that electrophilic reagents preferentially attack the corresponding 3-position of indole. The assignment of the position of the bromine in IXd rests on a comparison of the NMR-spectra of IXc and IXd. A signal corresponding to the proton at C-5 (Table 3) is found in the spectrum of IXc but not in that of IXd.

The polarographic behaviour of the pyrrolopyridazines and the dipyridazinopyrroles is similar; they owe their polarographic reducibility to the presence of the pyridazine ring. The UV-spectrum of the pyrrolopyridazines bears strong resemblance to that of indole (Table 4).

REACTIONS ROUTE

The dipyridazinopyrrole Va can be synthesised by heating 6-methylpyridazone-3 or 3-chloro-6-methylpyridazine in phosphoryl chloride; it is further formed when 3-chloro-6-methylpyridazine is heated to about 120°

Table 5. RF-values of some dipyridazinopyrroles and pyrrolopyridazines in thin layer chromatography on alumina with a 1:1 mixture of chloroform and light petrol as eluent.

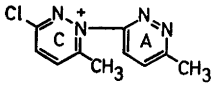
Compound	R_F-value	Compound	R_F-value
Va	0.38	VIIIa	0.46
Vb	0.16	VIIIb	0.17
Vc	0.71	VIIIc	0.62
Vd	0.35	VIIId	0.49
Ve	0.27	XII	0.39

without solvent or in a polar solvent as nitrobenzene or acetonitrile. In the latter case, traces of acid are necessary to initiate the reaction. The dipyridazinopyrroles (Va and VIIIa) have not been isolated in yields exceeding 65 %; as by-products are formed water-soluble compounds, none of which have been identified; the polarographic behaviour indicates that at least some of them contain an intact pyridazine ring.

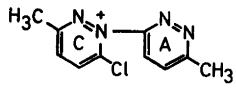
These facts point to a self-quaternisation as the initial step of the condensation reaction. Protonation of one molecule of 3-chloro-6-methylpyridazine makes its chlorine more active and an attack on one of the nitrogen atoms of an unprotonated molecule 3-chloro-6-methylpyridazine takes place with the formation of a quaternised product.

Quaternisation of 3-chloro-6-methylpyridazine with methyl iodide yields a mixture containing 22 % quaternised at N-2 and 78 % quaternised at N-1.[5] Although there is a certain dependence of the composition of a quaternisation mixture on the size of the attacking reagent, this dependence is not pronounced in the case of 3-chloro-6-methylpyridazine, and a mixture containing about 75 % of X and about 25 % of XI would be expected to result from a self-quaternisation of 3-chloro-6-methylpyridazine. Neither X nor XI have been isolated.

The methyl group of ring C in X is much more activated than the corresponding group in XI. It has, *e.g.*, been found [5] that only the methyl group at C-6 in 1,3,6-trimethylpyridazinium iodide exchanges its hydrogens with deuterium when dissolved in deuterium oxide containing potassium carbonate. Also the nucleophilic attack on the carbonyl group during the condensation reaction with benzaldehyde requires a positive charge next to the methyl group.



X



XI

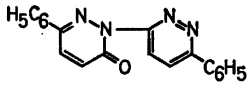
The activated methyl group of X is believed to attack ring A which then becomes a dihydropyridazine ring. The nucleophilic addition of the methyl group may be catalysed by the basic group of ring A and a 1,4-addition across

the pyridazine ring may take place. The mechanism of the subsequent oxidation-reduction reaction, which is necessary to transform this intermediate into Va, has not yet been established, but as the amount of VIIIa accompanying Va varies only slightly whether the reaction takes place without solvent or in nitrobenzene, phosphoryl chloride, or acetonitrile an intramolecular oxidation-reduction reaction seems probable.

XI has no activated methyl groups and a ring closure would not be expected to take place in this case. XI would on contact with water lose the chlorine by hydrolysis, as it is activated by the positive charge in the adjacent position. This compound or further quaternisation products would thus constitute the water-soluble by-products found in the reaction.

3-Chloro-6-phenylpyridazine quaternises with methyl iodide mainly at N-2.[5] When 3-chloro-6-phenylpyridazine is heated in nitrobenzene a hygroscopic, ether-insoluble product is formed, which on contact with water forms the pyridazinopyridazine XII.

The hygroscopic compound is thus the direct self-quaternisation product.



XII

When 3-chloro-6-ethylpyridazine is heated in nitrobenzene containing traces of hydrogen chloride the expected condensation product $C_{12}H_{13}ClN_4$ is formed and the IR-, UV-, and NMR-spectra are in accordance with the formulation of the product as 8-chloro-6,7-dihydro-3-ethyl-5-methyldipyridazino[2,3-a:4,3-d]pyrrole (Vd).

If the outlined reaction route consisting of an acid catalysed quaternisation followed by a base catalysed nucleophilic addition reaction and an oxidation-reduction is operative there seems to be no reason why the two reacting molecules need be identical. The requirements for the reaction would be that the attacking molecule contains a reactive quaternising group and be susceptible to a nucleophilic attack whereas the attacked molecule should be quaternised next to a group capable of performing the ring closure by a nucleophilic attack on the other ring.

From the reaction between 3-chloro-6-phenylpyridazine and a mixture of 3,6-dimethylpyridazine and its hydrochloride in nitrobenzene a condensation product was isolated. Its NMR-spectrum was in accordance with the formulation VIIId. Further studies are required to determine the scope of the reaction.

EXPERIMENTAL

The NMR-spectra were recorded at 60 Mc/s on a Varian Associates A-60 spectrometer. The temperature of the 15–20 % solutions was 33° ± 2°. Tetramethylsilane (TMS) was used as internal standard and the chemical shifts are expressed in ppm (δ units) from TMS taken as 0.00. The IR-spectra were recorded on a Beckman IR-10 spectrophotometer or on a Perkin-Elmer Infracord. The polarograph was a Radiometer

PO 4d; the potentiostat was a Wadsworth Controlled Potential Electro-Depositor. The UV-spectra were recorded on a Perkin-Elmer 137 UV-spectrophotometer. Analyses were made by Dr. Weiler and Dr. Strauss, Oxford, and our Analytical Department.

Materials. 3-Methylpyridazon-6 and 3-methyl-6-chloropyridazine were prepared according to Overend and Wiggins.[7] 3-Ethyl-6-chloropyridazine [8] was made from 4-ketohexanoic acid.[9]

6,7-Dihydro-3-methyl-8-chloro-dipyridazino[2,3-a:4,3-d]pyrrole (Va). 3-Chloro-6-methylpyridazine (6.9 g) was dissolved in phosphoryl chloride (30 ml) and water (1 ml) added slowly. The mixture was refluxed for 4 h and the excess of phosphoryl chloride removed *in vacuo*. The residue was poured on ice and the solution made slightly alkaline with concentrated sodium hydroxide. The solution was extracted several times with chloroform which was then dried and partly removed by distillation. On addition of dry ether a precipitate, 3.81 g, was formed and filtered. From the filtrate was isolated 1.27 g of the starting material.

The crude product contained 5—10 % of the aromatic dipyridazinopyrrole VIIIa. A separation of VIIIa from Va can be made in different ways with some loss of material.

a) Several recrystallisations from benzene or chlorobenzene followed by chromatography on a short column of alumina with chloroform as eluent gave pure Va in 40 % over-all yield.

b) Selective electrolytic reduction in acid solution at a cathode potential of −0.60 V *vs.* S.C.E. removed VIIIa. After the reduction the material was extracted from alkaline solution with chloroform, and the product isolated as described above for the crude material. The product was further purified by recrystallisation and chromatography as described above. Yield 40 %.

c) Small amounts could be separated on a long column of alumina using a 1:1 mixture of chloroform and light petrol as eluent.

M.p. 208° (decomp.). (Found: C 54.38; H 4.24; N 25.56; Cl 15.98. Calc. for $C_{10}H_9N_4Cl$: C 54.42; H 4.11; N 25.39; Cl 16.07). Principal bands in IR-spectrum (cm^{-1}): 3054(m), 1561(m), 1442(s), 1382(s), 1333(m), 1207(s), 1188(s), 1063(s), 776(m), 718(m).

Reaction with methyl iodide in acetonitrile produced a mixture containing 15 % quaternised at N-1 and 85 % quaternised at N-2. Recrystallisation from absolute alcohol yielded the major product in pure form, m.p. 225° (decomp.). (Found: C 36.73; H 3.32; N 15.46. Calc. for $C_{11}H_{12}N_4ClI$: C 36.41; H 3.34; N 15.47).

3-Methyl-8-chloro-dipyridazino[2,3-a:4,3-d]pyrrole (VIIIa). Va (1.0 g) was refluxed in 50 ml of *o*-dichlorobenzene with 0.02 g of a palladium catalyst (10 % Pd on carbon) for 7 h under nitrogen. After cooling, the catalyst was filtered and the product extracted with dilute hydrochloric acid. This was neutralised with sodium carbonate and extracted exhaustively with chloroform which was dried (potassium carbonate) and evaporated. The residue was recrystallised from benzene, 0.51 g, m.p. 208°. (Found: C 54.54; H 3.20; N 25.40; Cl 15.90. Calc. for $C_{10}H_7N_4Cl$: C 54.94; H 3.23; N 25.63; Cl 16.22). The above mentioned final residue could also be purified by chromatography on a column of alumina using chloroform-light petrol (1:1) as eluent. The yellow product was followed by a second fraction containing starting material. Principal bands in IR-spectrum (cm^{-1}): 3098(m), 1512(m), 1448(m), 1398(s), 1320(s), 1262(s), 1089(s), 867(s), 815(m), 692(m).

6,7-Dihydro-3-methyl-5-bromo-8-chloro-dipyridazino[2,3-a:4,3-d]pyrrole (Vc). Va (1.0 g) was dissolved in chloroform (50 ml) and bromine (0.30 ml) dissolved in chloroform (10 ml) was added dropwise to the stirred solution during 2 h. The precipitate formed was filtered, treated with sodium hydrogen carbonate solution, and extracted with chloroform. After being dried, the chloroform was evaporated and the residue purified on a column of alumina with a 1:1 mixture of chloroform and light petrol as eluent. The first fraction (orange) contained the brominated product Vc, 1.09 g, m.p. 160° (decomp.) and the second one some starting material. (Found: C 40.15; H 2.70; N 18.48; Cl 11.40; Br 26.85. Calc. for $C_{10}H_8N_4BrCl$: C 40.10; H 2.69; N 18.70; Cl 11.84; Br 26.68). Principal bands in IR-spectrum (cm^{-1}): 2955(m), 2921(m), 1438(s), 1398(m), 1370(m), 1180(m), 1078(s), 883(m), 872(m), 739(m).

3-Methyl-5-bromo-8-chloro-dipyridazino[2,3-a:4,3-d]pyrrole (VIIIc). VIIIa was brominated quantitatively and purified as described above for Vc. M.p. 233°. (Found: C 40.72; H 2.13. Calc. for $C_{10}H_6N_4BrCl$: C 40.37; H 2.03). Principal bands in IR-spectrum (cm^{-1}): 3080(m), 1576(m), 1521(m), 1479(s), 1260(m), 1175(m), 1141(m), 1110(s), 914(s), 751(m).

6,7-Dihydro-3-methyl-dipyridazino[2,3-a:4,3-d]pyrrole (Vb) and 3-methyl-6-(β-cyanoethyl)-7H-pyrrolo[2,3-c]pyridazine (IXa). A solution of Va (2.0 g) in alcohol (100 ml) containing concentrated aqueous ammonia (2 ml) was reduced catalytically using a palladium catalyst (Pd (10 %) on carbon, 1.5 g). After the uptake of an equimolar amount of hydrogen the catalyst was filtered off and the solvent removed *in vacuo*. The residue was chromatographed on a column of alumina with chloroform as eluent. The first fraction contained a small amount of starting material, the second one Vb, which was recrystallised from benzene, m.p. 158°, yield 1.03 g. (Found: C 63.62; H 5.37; N 29.75. Calc. for $C_{10}H_{10}N_4$: C 64.50; H 5.41; N 30.09). Principal bands in IR-spectrum (cm^{-1}): 3072(w), 1568(m), 1536(m), 1450(s), 1379(s), 1253(m), 1215(m), 1191(s), 1116(m), 772(m). The dry column was extracted exhaustively with alcohol which was evaporated *in vacuo* The residue was recrystallised from benzene containing 30 % light petrol yielding 0.62 g of IXa, m.p. 186°. (Found: C 64.01; H 5.34; N 28.39. Calc. for $C_{10}H_{10}N_4$: C 64.50; H 5.41; N 30.09). Principal bands in IR-spectrum (cm^{-1}): 3110(w), 2240(m), 1577(s), 1524(s), 1474(s), 1441(s), 1423(s), 872(m), 806(s), 775(s), 610(m).

3-Methyl-5-bromo-6,7-dihydro-dipyridazino[2,3-a:4,3-d]pyrrole (Ve). Vb was brominated (quantitatively) and purified as described above for Vc. M.p. 165°—170° (decomp.). (Found: C 45.81; H 3.40; N 20.62; Br 30.00. Calc. for $C_{10}H_9N_4Br$: C 45.30; H 3.42; N 21.13; Br 30.14). Principal bands in IR-spectrum (cm^{-1}): 3034(w), 2922(w), 1552(m), 1431(s), 1398(s), 1372(m), 1250(m), 1179(s), 1111(m), 910(m).

3-Methyl-dipyridazino[2,3-a:4,3-d]pyrrole (VIIIb). Ve (0.30 g) was refluxed in 10 ml of *o*-dichlorobenzene for 1 h. After cooling and addition of ether the precipitate was filtered. The product was neutralised by treatment with a sodium hydrogen carbonate solution and extracted with chloroform which was dried (potassium carbonate) and evaporated. The residue was recrystallised from benzene, 0.18 g. M.p. 163°—164°. (Found: C 62.36; H 4.15; N 30.09. Calc. for $C_{10}H_8N_4$: C 65.21; H 4.38; N 30.42). Principal bands in IR-spectrum (cm^{-1}): 3046(w), 1576(s), 1497(m), 1328(s), 1255(m), 1180(m), 1109(m), 800(s), 709(m), 682(m).

3-Methyl-6-(β-carbethoxyethyl)-7H-pyrrolo[2,3-c]pyridazine (IXc). IXa (0.71 g) was hydrolysed with boiling N sodium hydroxide (15 ml) for 6 h. The solution was neutralised to pH 7 with hydrochloric acid and the solvent removed *in vacuo*. The residue was extracted with absolute alcohol which was then saturated with hydrogen chloride and refluxed for 1 h. The alcohol was evaporated *in vacuo* and the residue chromatographed on a short column of alumina with alcohol as eluent. The eluate was evaporated and the residue recrystallised from benzene, 0.67 g, m.p. 157°, subl. 145°/0.1 mm. (Found: C 61.78; H 6.25; N 18.20. Calc. for $C_{12}H_{15}N_3O_2$: C 61.78; H 6.48; N 18.01). Principal bands in IR-spectrum (cm^{-1}): 3170(m), 3030(m), 1735(s), 1580(m), 1535(m), 1425(s), 1330(m), 1260(m), 1190(s), 1155(m), 780(s).

3-Methyl-5-bromo-6-(β-carbethoxyethyl)-7H-pyrrolo[2,3-c]pyridazine (IXd). IXc was brominated by heating in glacial acetic acid with equimolar amounts of bromine for 3 h. The hydrobromide of the product was precipitated with ether. The purification of the product was analogous to the purification of Vc and VIIIc. M.p. 202° (benzene). (Found: C 46.58; H 4.47; N 13.33; Br 25.65. Calc. for $C_{12}H_{14}N_3O_2Br$: C 46.14; H 4.52; N 13.46; Br 25.60). Principal bands in IR-spectrum (cm^{-1}): 3078(m), 2980(s), 1728(s), 1440(s), 1422(m), 1380(m), 1290(m), 1194(s), 1031(m), 775(m).

4,4a,5,5a,6,7-Hexahydro-3-methyl-8-chloro-dipyridazino[2,3-a:4,3-d] pyrrole (VII). Va (1.0 g) was reduced in a citric acid buffer, pH 2.5, containing potassium chloride at a cathode potential of −0.85 V *vs.* S.C.E. The reduction consumed approximately four electrons per molecule. The reduction completed, the solution was made alkaline with sodium carbonate. A precipitate was filtered, and the filtrate extracted with chloroform which was then dried and evaporated *in vacuo*. The precipitate and the residue was dissolved in chloroform and purified on a column of alumina using chloroform as eluent. Yield 0.5 g, m.p. 179°. (Found: C 53.69; H 5.84; N 24.81; Cl 15.78. Calc. for $C_{10}H_{13}N_4Cl$: C 53.46; H 5.83; N 24.94; Cl 15.78). Principal bands in IR-spectrum (cm^{-1}): 2935(m), 1707(m), 1619(s), 1590(s), 1415(s), 1301(m), 1178(m), 1099(m), 1060(m), 1000(m). Signals in NMR-spectrum: $\delta = 1.5-2.2$ (m), $\sum H = 2$; $\delta = 1.42$(s), $\sum H = 3$; $\delta = 2.3-2.7$ (m), $\sum H = 2$; $\delta = 2.7-3.2$ (m), $\sum H = 4$; $\delta = 3.3-3.8$ (m), $\sum H = 1$; $\delta = 4.1-4.6$ (m), $\sum H = 1$.

6,7-Dihydro-3-ethyl-5-methyl-8-chloro-dipyridazino[2,3-a:4,3-d]pyrrole (Vd). 3-Chloro-6-ethylpyridazine (1.0 g) dissolved in nitrobenzene (20 ml) containing a small amount

of hydrogen chloride was heated under nitrogen in a closed vessel to 120° for 8 h. After being cooled the solution was treated with dry ether. The precipitate formed was filtered, dissolved in water which was made alkaline with sodium carbonate, and extracted with chloroform. The chloroform was dried and evaporated and the residue purified on a column of alumina using a 1:1 mixture of chloroform and light petrol as eluent. The first orange fraction contained a small amount of the aromatic dipyridazinopyrrole and the light yellow second one Vd, 0.40 g, m.p. 183° (benzene). (Found: C 58.45; H 5.16. Calc. for $C_{12}H_{13}N_4Cl$: C 57.95; H 5.27). Principal bands in IR-spectrum (cm^{-1}): 2962 (m), 1571(m), 1440(s), 1380(m), 1204(m), 1082(w), 1060(m), 898(m), 873(m), 730(m).

1-(3'-Phenylpyridazino-6')-3-phenylpyridazone-6 (XII). Equimolar amounts of 3-chloro-6-phenylpyridazine and its hydrochloride were dissolved in nitrobenzene and heated to 120° under nitrogen in a closed vessel for 48 h. After being cooled, the nitrobenzene solution was extracted with dilute hydrochloric acid, which was washed with ether and made alkaline with sodium carbonate solution. The alkaline solution was extracted with chloroform which was dried and evaporated. The residue was purified on a short column of alumina with chloroform used as eluent. The product was recrystallised from benzene; m.p. 190°. (Found: C 73.06; H 4.19. Calc. for $C_{20}H_{14}N_4O$: 73.60; H 4.32). Principal bands in IR-spectrum (cm^{-1}): 3050(m), 1670(s), 1594(s), 1410(s), 1316(m), 840(m), 769(m), 743(m), 681(s), 600(m). Signals in NMR-spectrum: $\delta = 7.4-8.4$ (m), $\sum H = 12$; $\delta = 9.00$ (d), $\sum H = 1$, $J = 9.5$; $\delta = 9.30$ (d), $\sum H = 1$, $J = 9.5$.

6,7-Dihydro-3-methyl-8-chloro-dipyridazino[2,3-a:4,3-d]pyrrole-N-oxide. Va (0.50 g) was dissolved in chloroform (15 ml) and *m*-chloroperbenzoic acid (1 g) was added. The solution was kept at 35° for 24 h. Ether was added and the resultant precipitate, 425 mg, filtered, dissolved in chloroform, and precipitated with ether, m.p. 226—228°. (Found: C 49.68; H 4.36; N 23.20. Calc. for $C_{10}H_9N_4OCl$: C 50.74; H 3.83; N 23.68). Principal bands in IR-spectrum (cm^{-1}): 3080(w), 1495(s), 1435(s), 1406(s), 1323(s), 1254(s), 1205(s), 1051(s), 704(m), 639(m). Signals in NMR-spectrum: $\delta = 2.99$(s), $\sum H = 3$; $\delta = 3.1-3.8$(m), $\sum H = 4$; $\delta = 6.80$(s), $\sum H = 1$; $\delta = 8.27$(s), $\sum H = 1$.

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Received May 16, 1966.