Monomethylamination of Pyridazinium Halides with Dimethylamine

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In the course of other work it was observed that the 5-alkyl-6-halo-1-methyl-3-dimethylaminopyridazinium halides Ia-c reacted with liquid dimethylamine to give 5-alkyl-1-methyl-3-dimethylamino-6-methylaminopyridazinium halides IIa-c, respectively. Thus, these reactions amount to *mono*-methylamination of Ia-c with *di*-methylamine.

Again, when the 5-alkyl-1-methyl-3,6-*bis*-dimethylaminopyridazinium iodides IVa-c were allowed to react with liquid dimethylamine the salts IIa-c were formed, yet at a much lower rate.

An extensive review of alkylations with amines and ammonium salts is available,[1] and methyl group transfers from *exo*-trimethylammonium substituents to the ring nitrogen atoms of heteroaromatic bases have been described in some cases.[2,3] Furthermore, it has been shown [4] that certain polychloropyridazines react with trimethylamine to give, among other products, dimethylaminopyridazines. However, reactions strictly analogous to those here described are not apparent in the literature.

When sodium hydride was added to the salts IIa-c dissolved in dimethylsulfoxide, hydrogen evolved, and the pyridazonimines IIIa-c (a hitherto unknown class of pyridazine derivatives) could be isolated as reasonably stable oils. Treatment of the imines IIIa and IIIb with methyl iodide in refluxing benzene gave the 3,6-*bis*-dimethylaminopyridazinium iodides IVa and IVb in good yields. The reaction of IIIc with methyl iodide was extremely slow, probably due to the steric requirements of the *t*-butyl group. The imines III react with aqueous potassium iodide to re-form the pyridazinium iodides II.

Experimental. (See Table 1 for NMR data). The *5-alkyl-6-halo-1-methyl-3-dimethylaminopyridazinium halides Ia* (a mixture of Ia, X=Cl, Y=I and Ia, X=I, Y=Cl), *Ib* (X=I, Y=Cl), and *Ic* (X=I, Y=Cl) were prepared by reacting the parent pyridazine (6-chloro-3-dimethylamino-,[5] 6-chloro-5-methyl-3-dimethylamino-,[5] and 5-*t*-butyl-6-chloro-3-dimethylaminopyridazine,[6] respectively) with a large excess of methyl iodide in a suitable solvent under reflux. Removal of the solvent *in vacuo*, trituration with ethyl acetate, and filtration gave the crude salt ready for reaction with dimethylamine (*vide infra*). Solvent, reflux time, and yield of crude product (nearly pure according to NMR) were: Ia (methanol, 12 h, 96 %), Ib (methanol, 12 h, 98 %), and Ic (acetonitrile, 1.5 h, —).

NMR data of Ia (X=Cl, Y=I) and of Ib (X=Cl, Y=I) are known.[8] The structure of Ic is assigned on the basis of a comparison of the NMR spectrum with that of Ib.

1,5-Dimethyl-3-dimethylamino-6-methylaminopyridazinium iodide (IIb). The methchloride Ib (6.24 g) was slowly introduced into liquid dimethylamine (excess large enough to allow for evaporation) using effective magnetic stirring. After about 0.5 h of stirring, the mixture was kept in a refrigerator overnight, then stirred again for another 3—4 h. Filtration and evaporation *in vacuo* yielded a residue which was dissolved in water. The aqueous phase was extracted with chloroform, the chloroform solution dried (magnesium sulfate), and evaporated *in vacuo*. The residue was triturated with ethyl acetate to give 4.92 g (80 %, pure iodide assumed) of a product, which may have been a mixture of the chloride and the iodide. Neglecting the question of anion this product was nearly pure according to NMR.

The analytically pure iodide IIb was obtained by dissolving the pyridazonimine IIIb (*vide infra*) in a solution of excess potassium iodide in aqueous methanol. Extraction with chloroform, drying (magnesium sulfate) of the chloroform phase and evaporation *in vacuo* gave a residue. Recrystallization from acetonitrile:ethyl acetate 1:1 gave pure IIb, m.p. 181—84°. (Found: C 34.83; H 5.76; N 18.04; I 40.20. Calc. for $C_9H_{17}N_4I$: C 35.08; H 5.57; N 18.18; I 41.18). In spite of several trials the value for I is by far too low. The same phenomenon may be observed for the other iodides IIa and IIc (*vide infra*).

1-Methyl-3-dimethylamino-6-methylaminopyridazinium iodide (IIa) and *5-t-butyl-1-methyl-3-dimethylamino-6-methylaminopyridazinium iodide (IIc)* were obtained analogous to IIb. The reaction proceeded in both cases faster, but the yields of crude products (nearly pure according to NMR) were smaller: 35 % and 52 %, respectively.

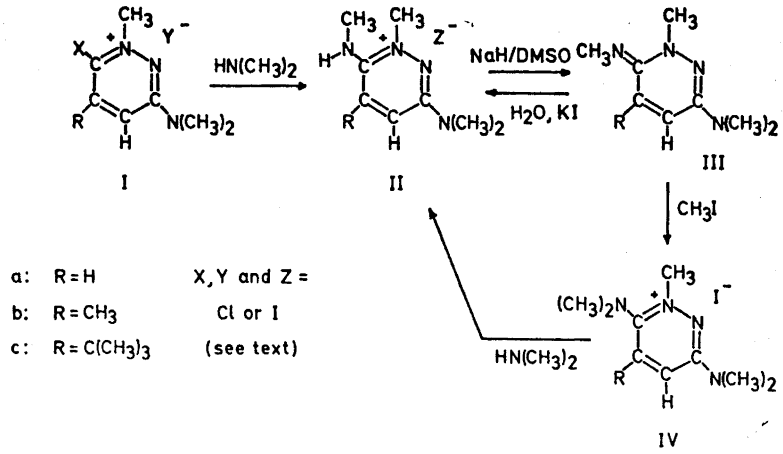

Table 1. NMR data.[a,b] δ in ppm, J in cps, (s)=singlet, (d)=doublet, (q)=quartet, (br)=broad.

Comp.	δ(1)	δ(3)	δ(4)	δ(5)	δ(NH)	δ(6)	J_{45}	J_{NH-CH_3}
IIa	4.16(s)	3.11(s)	7.83(d)[c]	7.72(d)[c]	7.77(br)	3.21(br)	10.0	—
IIb	4.20(s)	3.10(s)	7.52(br)	2.72(br)	7.11(q,br)	3.43(d)	—	5.3
IIc	4.19(s)	3.20(s)	7.31(s)	1.61(s)	6.08(q,br)	3.40(d)	—	5.4
IIIa	3.49(s)[c]	2.80(s)	6.88(d)[c]	6.77(d)[c]	—	3.00(s)[c]	10.0	—
IIIb	3.53(s)[c]	2.52(s)	6.08(q)	2.10(d)	—	3.45(s)[c]	1.3	—
IIIc	3.25(s)	2.56(s)	6.31(s)	1.49(s)	—	3.25(s)	—	—
IVb	4.22(s)	3.17(s)[c]	7.88(br)	2.62(br)	—	3.21(s)[c]	—	—

[a] The NMR spectra were recorded on a Varian A-60 spectrometer.

[b] Benzene was used as solvent for the compounds IIIb and IIIc, while deuterochloroform was used for IIa-c, IIIa, and IVb (tetramethylsilane as internal standard in all cases). No precautions were taken to keep operating conditions constant, so the δ-values given are only correct within $\pm$ 0.10 ppm.

[c] The assignment is arbitrary.

The pure iodides IIa and IIc were also prepared as described for IIb and recrystallized from acetone-ethyl acetate. Melting points and analytical data were: IIa, m.p. 192–93°. (Found: C 32.71; H 5.14; N 18.97; I 41.80. Calc. for $C_8H_{15}N_4I$: C 32.66; H 5.14; N 19.04; I 43.13). IIc, m.p. 169–71°. (Found: C 41.18; H 6.60; N 15.91; I 35.50. Calc. for $C_{12}H_{23}N_4I$: C 41.14; H 6.62; N 16.00; I 36.23).

1,6-Dihydro-1,5-dimethyl-3-dimethylamino-6-methyliminopyridazine (*IIIb*). To a solution of the methiodide IIb in dimethylsulfoxide was added a great excess of sodium hydride, cautiously and with effective magnetic stirring. After cessation of the hydrogen evolution the reaction mixture was filtered with suction and the filtrate thoroughly extracted with petroleum ether. The extract was filtered and evaporated *in vacuo*. The residue was again extracted with petroleum ether, the extract filtered and evaporated to give the pyridazonimine IIIb as a nearly pure oil (according to NMR).

1,6-Dihydro-1-methyl-3-dimethylamino-6-methyliminopyridazine (*IIIa*) and *5-t-butyl-1,6-dihydro-1-methyl-3-dimethylamino-6-methyliminopyridazine* (*IIIc*) were prepared as described for IIIb. The crude oil IIIa was contaminated with about equimolar amounts of dimethylsulfoxide. The yields were not determined and analytical data not obtained.

*1-Methyl-3,6-*bis*-dimethylaminopyridazinium iodide*[3,7] (*IVa*) and *1,5-dimethyl-3,6-*bis*-dimethylaminopyridazinium iodide* (*IVb*) were

prepared by reacting the corresponding pyridazonimines (IIIa and IIIb, respectively) with a large excess of methyl iodide in refluxing benzene for 0.5 h. The resulting suspensions were cooled and filtered to give nearly pure (IVa) and (IVb) directly. The over-all yield of crude (IVb) from the salt (IIb) was 70–75 %. Recrystallization from ethyl acetate-acetonitrile gave the pure salt, m.p. 150–52°. (Found: C 37.39; H 5.90; N 17.46; I 39.29. Calc. for $C_{10}H_{19}N_4I$: C 37.28; H 5.94; N 17.39; I 39.38).

The pyridazonimine IIIc reacted very slowly with excess methyl iodide in refluxing benzene. After 18 h, only about 1/3 of the imine had reacted. Analytical and NMR data of the methiodide (IVc) will be published in another paper.

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Ion Pair Extraction in Preparative Organic Chemistry

V. Alkylation of Dimethyl Benzoylmalonate

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Methyl ketones are conveniently prepared from a dialkyl malonate by acylation followed by hydrolysis of the intermediate dialkyl acylmalonate.[1] When this method is applied to alkylated dialkyl malonates the yield of the corresponding ketone is often very low due to a competing *O*-acylation in the first step. A logical method would be to alkylate the readily available dialkyl acylmalonates, since alkylation gives a higher yield of *C*-substitution than acylation.[2] The dialkyl acylmalonates, however, are rather strong acids and the corresponding anion thus a weak nucleophile. The alkylation would thus be a very slow process when conventional methods are used. The yields can also be expected to be very low due to side-reactions such as alcoholysis, which is rapid even in the cold.[3]

We have recently demonstrated that ion pairs of some enolates are very rapidly alkylated in a chloroform or methylene chloride solution.[4] We will now report that the same method can be used in the present case.

The tetrabutylammonium salt of dimethyl benzoylmalonate is readily extracted by chloroform from a water-solution, containing tetrabutylammonium hydroxide. It forms a crystallized salt, which can be readily alkylated in chloroform or methylene chloride. The alkylation with methyl iodide, for instance, is complete after about 10 min and gives a quantitative yield of dimethyl benzoylmethylmalonate. When the size of the alkyl group is increased the reaction rate is reduced and the yield of *O*-alkylated product increases. With isopropyl iodide *O*-alkylation is the main reaction.

In the present investigation the dimethyl ester was used in order to facilitate the quantitative analysis by NMR. The results are summarized in Table 1 and show the amount of *C*- and *O*-alkylated products in the mixture after alkylating the tetrabutylammonium salt of dimethyl benzoylmalonate.

Table 1.

Alkyl halide	*C*-alkylated product, %	*O*-alkylated product, %
Methyl iodide	100	0
Ethyl iodide	54	46
Butyl iodide	47	53
Isopropyl iodide	14	86