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Studies on Mesoionic Compounds. I. Synthesis of 3-Dialkylaminosydnonimines

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3-Dialkylaminosydnonimine salts (IV) were synthesized starting from 1,1-dialkylhydrazines (I) *via* II and III. IV exhibits a remarkable stability towards acids and could be obtained as crystals. Chemical and physicochemical properties of IV were similar to those of known sydnonimine salts. It should be mentioned that intermediary nitroso compounds (III) were rather unstable and spontaneously gave rise to unsaturated nitriles (III').

Since sydnonimines, a type of so-called mesoionic compounds, were first synthesized independently by Brookes, *et al.*[2a] and Ohta, *et al.*[2b] in 1957, a number of methods[3] for the synthesis of the compounds have been reported by many workers. However, none of the sydnonimines appearing in these reports possess the nitrogen atom at the 3 position of the ring system. This may be due to the fact that syntheses of these imines generally started with the corresponding primary amines. Moreover, sydnones and sydnonimines carrying electron donating groups at their 3 or 4 positions are considered unstable for the reason that a mesoionic ring is in excess of π-electrons and hence stabilized by donating its π-electrons to the exocyclic oxygen atom or the imino nitrogen to complete an aromatic sextet. It has been reported that an attempt to introduce an amino group to the 4 position of sydnone ring was unsuccessful;[4] while no one thus far recorded the synthesis of sydnones or sydnonimenes carrying a nitrogen atom attached directly to the 3 position of the ring.

On the other hand, it has been reported that certain sydnones and sydnonimines reveal a variety of pharmacological activities depending on the substituents. The correlation be-

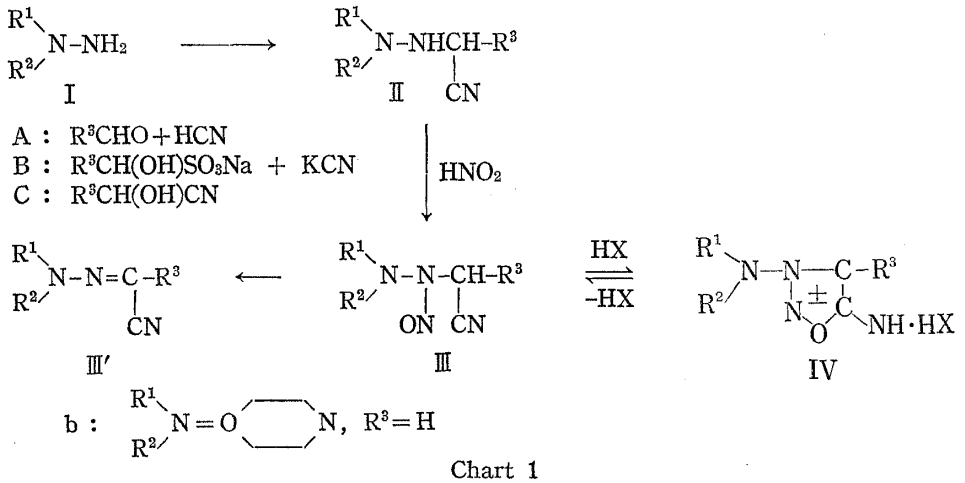


Chart 1

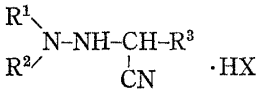
1) Location: *Juso-Nishino-cho, Higashiyodogawa-ku, Osaka.*
2) *a*) P. Brookes and J. Walker, *J. Chem. Soc.*, **1957**, 4409; *b*) H. Kato, M. Hashimoto and M. Ohta, *Nippon Kagaku Zasshi*, **78**, 707 (1957).
3) They are reviewed by F.H.C. Stewart, *Chem. Rev.*, **64**, 129 (1964).
4) H. Kato and M. Ohta, *Bull. Chem. Soc. Japan*, **32**, 282 (1959).

tween the type of substituents and the activity of these compounds, however, is not fully investigated.

These prompted us to synthesize 3-dialkylaminosydnonimines (IV) by employing hydrazines in place of primary amines as starting materials as shown in Chart 1.

Most 1,1-dialkyl-2-α-cyanoalkylhydrazines (II) were obtained by α-cyanoalkylation of 1,1-dialkylhydrazines (I) as depicted by the method A, although some were prepared by the method B or C. The nitriles thus obtained were purified by distillation with only one exception, the compound (IIj), which was obtained in crystalline. Nitrosation of II led to 1,1-dialkyl-2-nitroso-2-α-cyanoalkylhydrazines (III), most of which were unstable and began to decompose even at room temperature, and hence were cyclized to IV immediately after they had been synthesized. 3-Dialkylaminosydnonimines were isolated as their monohydrochlorides by the action of an excess of hydrochloric acid. As a cyclization reagent, an organic acid such as picric acid could also be used successfully.

Table I. 1,1-Dialkyl-2-α-cyanoalkylhydrazines and Their Salts

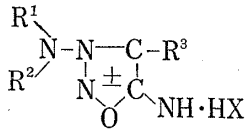


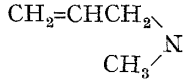
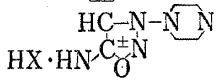
Compd. No.	R^1, R^2	R^3	Method	Yield (%)	bp of base (°C) (mmHg)	HX	Recryst. solvent
IIa		H	A	52	80— 89 (3)	HCl	EtOH–ether
IIb		H	A B	22 70	78— 80 (0.3)	HCl	MeOH
IIc		H	A	49	65— 67 (0.3)	HCl	EtOH–ether
IId		H	A	82	70— 80 (1)	picric acid	EtOH–ether
IIe	$(CH_3)_2N$	H	A B	48 69	53— 55 (2)	HCl	EtOH
IIf	$(C_4H_9)_2N$	H	A B C	0 17 37	85 (0.2)	—	—
IIg		H	B	40	101—105 (20)		
IIh		CH_3	A	36	60— 67 (6)	picric acid	EtOH–ether
IIi		C_3H_7	A	30	95—110 (1—2)	picric acid	EtOH–ether
IIj	$NCCH_2NHN$ 	H	B	59	mp 137—141	—	—

Compd. No.	mp of salt (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIa	157—158 (decomp.)	$C_7H_{14}N_3Cl$	47.86	8.03	23.92	47.64	8.06	24.06
IIb	178—181 (decomp.)	$C_6H_{12}ON_3Cl$	40.57	6.81	23.66	40.34	6.88	23.31
IIc	159—161 (decomp.)	$C_6H_{12}N_3Cl$	44.58	7.48	26.00	44.49	7.47	26.26
IId	138 (decomp.)	$C_{14}H_{18}O_7N_6$	43.86	5.00	21.93	43.65	4.85	22.22
IIe	125—127	$C_4H_{10}N_3Cl$	35.43	7.43	30.99	35.30	7.28	30.90
IIf	—	$C_{10}H_{21}N_3$	65.57	11.43	22.95	65.73	11.53	23.02
IIg								
IIh	131 (decomp.)	$C_{14}H_{18}O_7N_6$	43.98	4.75	21.98	44.01	4.95	21.97
IIi	107 (decomp.)	$C_{16}H_{22}O_7N_6$	46.82	5.40	20.48	46.53	5.26	20.65
IIj	—	$C_8H_{14}N_6$	49.47	7.26	43.27	50.09	7.30	43.02

When a sydnonimine hydrochloride (IV; X=Cl) was treated with sodium bicarbonate to remove the acid, III was obtained in good yield as is well known with other sydnonimines.[2b] However, the nitrosated hydrazines (III), in sharp contrast with the nitroso compounds which are precursor to ordinary sydnonimines, spontaneously gave rise to unsaturated nitriles (III')[5] with the evolution of nitrogen oxide. By this procedure N-cyanomethylenamino-morpholine (III'b) was isolated in crystalline in a good yield.

TABLE II. 3-Dialkylaminosydnonimine Salts



Compd. No.	R^1, R^2	R^3	HX	Yield (%)	Recryst. solvent
IVa		H	HCl	35	EtOH–ether
IVb		H	HCl	51	EtOH
IVc		H	HCl	—	EtOH
IVd		H	HCl	35	EtOH
IVe	$(CH_3)_2N$	H	HCl	50	EtOH
IVf	$(C_4H_9)_2N$	H	HCl	—	MeOH–ether
IVg		H	HCl	—	isoPrOH–ether
			picric acid	—	H_2O
IVh		CH_3	HCl	—	MeOH–ether
			picric acid	—	EtOH–ether
IVi		C_3H_7	HCl	—	
IVj		H	HCl	54	H_2O

Compd. No.	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IVa	163 (decomp.)	$C_7H_{13}ON_4Cl$	41.08	6.40	27.86	41.40	6.41	27.61
IVb	190—191 (decomp.)	$C_6H_{11}O_2N_4Cl$	34.87	5.37	27.12	34.83	5.04	26.99
IVc	180 (decomp.)	$C_6H_{11}ON_4Cl\cdot H_2O$	34.52	6.23	26.85	34.06	6.37	26.72
IVd	157 (decomp.)	$C_8H_{15}ON_4Cl$	43.94	6.91	25.62	43.45	7.08	26.16
IVe	180—181 (decomp.)	$C_4H_9ON_4Cl$	29.19	5.51	34.04	28.91	5.56	33.85
IVf	108[a]	$C_{10}H_{21}ON_4Cl$	48.28	8.51	22.52	48.29	8.50	22.47
IVg	109—112 (decomp.)[a]	$C_6H_{11}ON_4Cl$	37.80	5.82	29.39	37.76	6.03	29.02
	131—134	$C_{12}H_{13}O_8N_7$	37.60	3.42	25.58	37.36	3.56	25.50
IVh	167—170 (decomp.)	$C_8H_{15}ON_4Cl$	43.94	6.91	25.62	44.21	6.89	25.31
	148 (decomp.)	$C_{14}H_{17}O_8N_7$	40.88	4.17	23.84	41.02	4.23	23.58
IVi	oil							
IVj	242—243 (decomp.)	$C_8H_{14}O_2N_8Cl_2\cdot 2H_2O$	26.59	4.99	31.02	26.59	5.12	30.49

a) hygroscopic crystals

5) Y. Asahi, M. Nagaoka, K. Shinozaki discussed the formation of the nitriles at The 88th Annual Meeting of Pharmaceutical Society of Japan held in Tokyo, April 1968.

So far as being left in crystalline state or in acidic solutions, IV is not very unstable. In the IR spectral data, IV exhibits a close similarity to those of known sydnonimine salts especially to the spectra of 3-alkyl-sydnonimine salts (see Table III). This fact suggests that the electronic structure of the sydnonimine ring is little affected by introduction of an amino group at the 3 position in place of an alkyl group.

It is also worthy of note that some of these 3-dialkylaminosydnonimines exhibit the hypotensive activity in the animal tests.[6]

Table III. Spectral Data of Sydnonimine Hydrochlorides

	NMR[a]	IR[b]	UV[c]	λ_{max} (ε)
3-Piperidinosydnonimine hydrochloride (IVa)	2.24	1675	295	(0.98×10^4)
3-Morpholinosydnonimine hydrochloride (IVb)	2.13	1685	293	(1.04×10^4)
3-Pyrrolidinosydnonimine hydrochloride (IVc)	2.45	1680	290	(1.35×10^4)
3-Dimethylaminosydnonimine hydrochloride (IVe)	2.30	1670	290	(1.19×10^4)
3-Cyclohexylsydnonimine hydrochloride	2.25	1680	290	(3.20×10^4)

a) the nuclear magnetic resonance chemical shifts of sydnonimine-ring proton at 60 Mc in D_2O (τ)
b) the infrared absorption spectra of the imino groups of sydnonimine salts in KBr (cm^{-1})
c) the ultraviolet absorption spectra in H_2O ($m\mu$)

Experimental[7]

General Procedure for the Preparation of 1,1-Dialkyl-2-α-cyanoalkylhydrazines (II_{a-i})

Method A: To a solution of 1,1-dialkylhydrazine hydrochloride (I·HCl) (0.1 mole) in H_2O (20 ml) was added an aqueous solution of KCN (0.1 mole) and an aldehyde[8] (0.1 mole) with ice-cooling and stirring. The mixture was stirred for 7 hr at room temperature. The oily substance separated was extracted with ether or AcOEt, and the extract was dried over anhydrous $MgSO_4$ or K_2CO_3. After evaporation of the organic solvent *in vacuo*, the residue was submitted to distillation under reduced pressure to give II. The hydrochloride of II was prepared by the treatment with dry hidrogen chloride introduced into an ether solution of the purified base.

Method B: An aqueous solution of I (0.1 mole) and an aldehyde–sodium bisulfite (0.1 mole) was stirred for 1—2 hr at room temperature. To this was added KCN (0.1 mole), and stirring was further continued for 3—4 hr at 55—60°. The reaction mixture thus obtained was extracted with AcOEt, and the extract was worked up as described in method A.

Method C: A mixture of I (0.1 mole) and α-hydroxyalkylnitrile (0.1 mole) was set aside for about 15 hr at room temperature, during this period the solution went into two phases. After being separated from the lower aqueous layer, the organic layer was dried and submitted to distillation under reduced pressure to give II.

1,4-Bis(cyanomethylamino)piperazine (IIj)——To a solution of 1,4-diaminopiperazine dihydrochloride (3.8 g) in H_2O (30 ml) and $NaHCO_3$ (3.5 g) was added a solution of formaldehyde–sodium bisulfite monohydrate (6.1 g) dissolved in H_2O (20 ml). After being kept at 70° for 3 hr, the solution was evaporated to dryness. To the residue was added KCN (3.0 g) in H_2O (20 ml), and the mixture was warmed again at 60° for 1 hr to precipitate IIj in the form of colorless needle-like crystals[9] (2.3 g).

General Procedure for the Preparation of 3-Dialkylaminosydnonimine Salts (IV_{a-i})——To a solution of II (0.1 mole) in H_2O (20 ml) and conc.HCl (0.1 mole) was added dropwise a solution of $NaNO_2$ (0.1 mole) in H_2O (10 ml) with ice-cooling and stirring. An oily layer separated from the reaction mixture was extracted with ether. The extract was dried, and evaporated *in vacuo* to leave an yellow oil of III,[10] to which was added immediately an excess of methanolic hydrochloric acid. After being kept standing for a while, the solution was evaporated to dryness to give crude crystals[11] of sydnonimine hydrochloride, which were recrystallized from the solvent listed in Table II.

6) K. Kikuchi, M. Hirata, A. Nagaoka and Y. Aramaki, *Japan. J. Pharmacol.*, submitted.
7) All melting points are uncorrected.
8) Formalin (37%), MeCHO (80%), and PrCHO were used for the preparation of IIa—f, IIh, and IIi, respectively.
9) They were pure enough to be used for the subsequent reaction without further purification.
10) The nitroso compounds obtained from II_b and II_e solidified at low temperatures.
11) Syrupy sydnonimine hydrochlorides were successfully crystallized from dry ether.

1,4-(Sydnonimine-3,3′-diyl)piperazine Dihydrochloride (IVj)——To a solution of IIj (2.0 g) in H_2O (30 ml) and conc. HCl (2 ml) was added dropwise a solution of $NaNO_2$ (2.0 g) in H_2O (7 ml) to separate the nitroso compound in the form of white precipitate. The precipitate was collected by filtration, and to which were added conc. HCl (10 ml) and H_2O (50 ml). The mixture was then heated until the precipitate had dissolved in solution. From the solution, after being kept standing, was obtained IVj in colorless crystals which held 2 moles of water.

3-Piperidino-4-methylsydnonimine Picrate (IVh)——To an ether solution of the nitroso compound prepared as described above from IIh was added picric acid dissolved in ether–EtOH. The solvent was removed and the resulting oily substance was washed with ether to leave an yellow solid, which was recrystallized to give sydnonimine picrate.

Alkaline Decomposition of 3-Morpholinosydnonimine Hydrochloride (IVb)——A mixture of IVb (1.0 g) in H_2O (10 ml) and $NaHCO_3$ (0.5 g) was kept standing overnight to yield an oily substance,[12] which was positive in Lieberman's nitroso test and showed absorption bands in the infrared spectrum at 2270 cm^{-1} ($-CH_2CN$), 2230 cm^{-1} (=CHCN), and 1540 cm^{-1} (C=N), which suggested the substance to be a mixture of IIIb and III′b. After being kept standing for several weeks at room temperature, the crystals which separated from the reaction mixture were collected by filtration. The filtrate was extracted with AcOEt, and the extract was dried and evaporated to yield a brown crystalline residue, which was combined with the crystals previously collected. The combined crystalline material was recrystallized from petroleum benzine to give 390 mg (58%) of III′$_b$, mp 71—72°. NMR (in $CDCl_3$) τ: 3.75 (1H, singlet, –CH=N). *Anal.* Calcd. for $C_6H_9ON_3$: C, 51.79; H, 6.52; N, 30.20. Found: C, 51.67; H, 6.59; N, 30.40.

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12) This substance turned out to be negative in Lieberman's reaction when it was heated at 75—80° in EtOH for 26 hr.