Synthesis of 3-Aminosydnone Imines

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The synthesis and spectroscopic properties of 3-aminosydnone imines are described.

Sydnone imines are a class of compounds which have been widely investigated in recent years (2). Their pharmacology was discussed in detail (3). The sydnone imines described so far carry alkyl, aryl or aralkyl substituents in the 3-position and frequently also in the 4-position.

As part of a study of the pharmacological properties of mesoionic systems, 3-aminosydnone imines were synthesized. Sydnone imines with the direct attachment of a hetero atom to the 3-position were not known at the time this program was initiated. After completion of the experimental work (4) we became aware of a patent concerning the synthesis of 3-aminosydnone imines by K. Masuda and Y. Imashiro (5). 1,1-Disubstituted hydrazines react smoothly with aldehydes and cyanide ion to give the desired Mannich bases I. On nitrosation, the Mannich bases I form nitroso hydrazines, which, without prior isolation, were converted on acid treatment into the 3-aminosydnone imines II. The hydrochlorides of 3-aminosydnone imines are colourless and stable. Table I lists the compounds prepared. Acylation leads to the derivatives compiled in Table II.

IR Spectra.

3-Aminosydnone imine hydrochlorides show a strong absorption band at $1675 \pm 10 \text{ cm}^{-1}$. The hydrochlorides of the acylated 3-aminosydnone imines exhibit an amide

absorption at an unusually high frequency, close to 1715 cm⁻¹ and a second strong band at $1620 \pm 10 \text{ cm}^{-1}$. The amide band of the free bases appears at 1615 cm^{-1} , partially overlapping with the 1620 cm^{-1} band also present in the salts. A band close to 3170 cm^{-1} is characteristic for the majority of compounds in which $R_3 = H$.

UV Spectra.

The UV spectra of compounds carrying a hydrogen atom at C_4 show a maximum between 292 and 301 m μ , with a minor peak in the region 247-261 m μ , which in some instances is reduced to a shoulder. Exceptions are 17 (maximum = 307 m μ) and 19 (maximum = 305 m μ). Compounds with alkyl substituents in the 4-position exhibit only one maximum in the 312-318 m μ range. Acylation of N_6 causes a shift to longer wave lengths with one of the maxima now between 318 and 335 m μ . Exceptions are 24 (358 m μ), 34 (359 m μ), 37 (373 m μ) and 52 (340 m μ).

NMR Spectra.

The interpretation of the NMR spectra is facilitated by the large peak separation. Substituents at the nitrogen atom attached to position 3 have chemical shifts very similar to those of comparably disubstituted anilines. For instance, the N-Cll₃ groups of compound 1 exhibit a singlet at 3.12 ppm, the N-Cll₃ groups of dimethylaniline at 2.87 ppm. The positions of the N-Cll₂ groups of compound 6 or 7 at 3.94 and 3.83 ppm, respectively, are quite similar to those of the N-Cll₂ groups of diallylaniline at 3.75 ppm.

Alkyl or aralkyl substituents in the 4-position show the same chemical shifts as their counterparts in benzene chemistry. This is illustrated by the -CH₂-CH₂ group of compound 7; the deshielding caused by the benzene and mesoionic ring is identical, the four protons appear as a broad singlet at 2.93 ppm.

pK Values.

The pK values of several 3-aminosydnone imines were determined in 80% methylcellosolve. The compounds with R_3 =II were found to be slightly stronger bases than

TABLE 1

$$R_1 > N = N = C > R_3$$
 $R_2 > N = N = C > R_3$
 $Cl \hookrightarrow NH_2$

			0>-/	NH ₂		
	$\frac{R_1}{R_2} N$	R_3	Yield %	M.p., °C	Crystallization Solvent	Formula (6) HCl
1	CH ₃ N	II	79	178	Λ	$C_4H_8N_4O$
2	$C_2H_s \searrow N$ $C_2H_s \searrow N$	Н	64	135	Λ	$\mathrm{C_6H_{12}N_4O}$
3	CH ₃ HC≡CCH ₂ >N	Н	49	144-145	Α	$C_6H_8N_4O$
4	$\begin{array}{c} \text{CH}_2\text{=CHCH}_2\\ \text{CH}_2\text{=CHCH}_2 \end{array} \!$	Н	56	94-96	C	$C_8H_{12}N_4O$
5	$ \begin{array}{c} \operatorname{CH}_{2} \cdot \operatorname{CHCH}_{2} \\ \operatorname{CH}_{2} \cdot \operatorname{CHCH}_{2} \end{array} > N $	CH ₃	71	110-112	A	C ₉ H ₁₄ N ₄ O
6	$\frac{\text{CH}_2\text{CHCH}_2}{\text{CH}_2\text{CHCH}_2} > N$	C_2H_5	72	94-96	C	$\mathrm{C_{10}H_{16}N_{4}O}$
7	CH ₂ ÷CHCH ₂ CH ₂ ÷CHCH ₂	C ₆ H ₅ CH ₂ CH ₂	74	113-114	C	$C_{16}H_{20}N_4O$
8	$\left\langle \begin{array}{c} \\ \\ \end{array} \right\rangle$	н	35	182	Α	$C_6H_{10}N_4O$
9	\bigcap_{N}	н	. 53	162-163	Α	$\mathrm{C_7H_{12}N_4O}$
10		П	48	153-154	Α	$C_8H_{14}N_4O$
11	CH ₃	H	67	180	Α	$\mathrm{C_6H_{10}N_4O_2}$
12	$\binom{N}{N}$	н	59	187-188	D	C ₂ ll ₁₃ N₅O [2HCl]
13	CH ₃ C ₆ H ₃ CH ₂ N	11	41	160	A	$C_{10}H_{12}N_4O$
14	CH ₃ CH ₃ C ₆ H ₅ CH- N	Н	62	171	Α	$C_{11}H_{14}N_4O$
15	$\mathrm{C_6H_5CH_2CH_2N}$	Н	32	138-140	Λ	$C_{11}H_{14}N_4O$
16	$ \frac{p \cdot \text{CIC}_6 \text{H}_4 \text{CH}_2}{\text{CH}_3 \text{CH}_2 \text{CH}_2} \sim \text{N} $	Н	52	154	C	$C_{12}\Pi_{16}CIN_4O$
17	$\begin{array}{c} C_6H_5CH_2 \\ C_6H_5CH_2 \end{array} > N$	H	52	158-159	Α	$C_{16}\Pi_{16}N_4()$

TABLE 1 (Continued)

	$ \begin{array}{c} R_1 \\ R_2 \end{array} $ N	R ₃	Yield %	М.р., °С	Crystallization Solvent	Formula HCl
18	₩ N	н	52	155	Α	$\mathrm{C_{11}H_{12}N_4O}$
19	C_6H_5	Н	41	173-174	Λ	$C_{13}H_{16}N_4O$
20	CH.N	Ħ	38	155	В	C ₉ H ₁₁ N ₅ O [2 HCl]
21	CH ₂ N CH ₃	Ш	49	154	Λ	$C_{11}\Pi_{12}N_4O_3$

 $A = Methanol/ether. \ \ B = Ethanol/ether. \ \ C = lsopropanol/ether. \ \ D = Ethanol.$

TABLE II

			$R_1 > N - N = N = N = N = N = N = N = N = N =$	C-R ₃	⊙		
	$R_1 > N$	R ₃	R ₄	Yield %	М.р., ° С	Crystallization Solvent	Formula HCl
22	CH ₃ N	R	COCH3	76	173	A	$C_6H_{10}N_4O_2$
23	CH ₃ N	Н	COOC₂H₅	69	155	C	$\mathrm{C_7H_{12}N_4O_3}$
24	CH ₃ N	И	CO NO2	61	218-219	Α	$C_9 \Pi_9 N_5 O_5$ (free base)
25	CH ₃ N	Н	COCH₂CH₂C₀H₅	71	153-154	Α	$C_{13}H_{16}N_4O_2$
26	CH ₃ N	Н	co	81	178	Α	$C_{11}H_{12}N_4O_2$
27	CH ₃ N	Н	co—	57	198-199	Α	$\frac{C_{10}H_{11}N_{5}O_{2}}{[2~HCl]}$
28	CH ₃ N	Н	co—CI	76	184-185	Α	$\mathrm{C_{11}H_{11}ClN_4O_2}$
29	CH ₃ N	H	COCH ₂ C[CH ₃] ₃	56	180-181	Α	${ m C_{10}H_{18}N_4O_2}$
30	CH ₃ >N	Н	co	63	160-162	D	$C_{12}H_{14}N_4O_2$
			CH́₃				

TABLE II (Continued)

	$\frac{R_1}{R_2} > N$	R,	R.	Yield, %	M.p., °C	Crystallization Solvent	Formula HCl
31	$\frac{\text{CH}_3}{\text{CH}_3} > N$	П	CO	67	167-168	D	$C_{11}H_{11}Ch_{-4}O_2$
32	$CH_3 > N$	П	co—CI	59	187	D	$C_{11}H_{18}N_{4}O_{2}$
33	CH ₃ N	П	60—	48	181-184	В	$C_8\Pi_{12}N_4\Theta_2$
34	$CH_3 > N$	11	CO S NO2	57	185-187	Α	$C_9\Pi_9N_5O_4S$
35	CH ₂ +CHCH ₂ CH ₂ -CHCH ₂ N	11	COCH,	36	108-109	C	$C_{10}H_{14}N_4O_2$
36	CH₂=CHCH₂ CH₂=CHCH₂	C_2H_5	$\mathrm{COOC_2H_5}$	66	95-96	C	$C_{13}II_{20}N_4O_3$
37	CH ₂ =CHCH ₂ CH ₂ =CHCH ₂ N	CH ₃	CO S NO2	53	116-118	Α	$C_{14}H_{15}N_5O_4S$
38		11	COCH ₃	65	173	Α	$\mathrm{C_9H_{14}N_4O_2}$
39	$\bigcap_{\mathbf{N}}$	11	$COOC_2\Pi_{\mathfrak{s}}$	72	139-141	В	${ m C_{10}H_{16}N_4O_3}$
40	N	H	$COC_6\Pi_5$	76	149-150	Α	$\mathrm{C_{15}H_{18}N_4O_2}$
41	$\binom{N}{N}$	Н	co	73	158-159	C	$\mathrm{C}_{15}\mathrm{H}_{17}\mathrm{ClN}_4\mathrm{O}_2$
42	$\binom{N}{N}$	Н	CO CH ₃	58	140-142	C	$C_{16}H_{20}N_4O_2$
43	$\binom{N}{N}$	Н	co—	69	186	C	$\mathrm{C_{15}H_{24}N_4O_2}$
44	${N}$	Ħ	COCH ₃	62	153-154	C	$C_{10}H_{16}N_4O_2$
45	$\binom{0}{N}$	Н	co	78	168	C	$C_{13}H_{13}CIN_4O_3$

TABLE II (Continued)

	$\frac{R_1}{R_2} > N$	R ₃	R_4	Yield, %	M.p.,°C	Crystallization Solvent	Formula HCl
46	$\binom{0}{N}$	11	co	74	166-167	Λ	${\rm C_{14} H_{16} N_4 O_3}$
47	$\binom{0}{N}$	П	CO-CH3	61	187	D	$C_{13}H_{20}N_4O_3$
48		п	CO-	72	142-144	CHCl ₃ (petroleum ether)	$\frac{\mathrm{C_{18}H_{14}CIN_4O_2}}{\mathrm{(free\ base)}}$
49		11	co-Cl'	47	142	CHCl ₃ (ether)	$\mathrm{C_{18}H_{22}N_4O_2}$
50	$\begin{array}{c} C_6H_5CH_2 \\ CH_3 \end{array} N$	н	co-<	59	156	C	$C_{17}H_{22}N_4O_2$
51	$\frac{C_6H_5CH_2}{CH_3} > N$	H	(:0-	57	140-141	Α	$\mathrm{C_{17}H_{15}CIN_4O_2}$
52	CH ₃ CH ₃ C ₆ H ₅ CH-N	H	co — N	75	176	Α	$C_{17}H_{17}N_5O_2$
53	CH ₃ CON N	Н	сосн _з	54	179	Α	$C_{11}H_{17}N_5O_3$

 $A = Methanol/ether, \quad B = Ethanol/ether, \quad C = Isopropanol/ether, \quad D = Ethanol/petroleum \ ether.$

those carrying a substituent at the 4 position. All titration curves are simple curves. This result is in agreement with the observation that the UV maxima of the monohydrochlorides in ethanol remain unchanged on the addition of perchloric acid. Since acylation of N_6 reduces the pK values considerably, protonation is taking place at N_6 and not at the nitrogen atom attached to position 3. The striking difference of the amide band position in the IR spectra of the acylated 3-aminosydnone imines versus the corresponding salts also points to N_6 as site of protonation.

Typical examples of the physical properties of the compounds described are summarized in Table III.

EXPERIMENTAL

The NMR spectra were determined on a Varian A-60 in deuterated DMSO. UV spectra were recorded on a Bausch and Lomb 505 in ethanol solution and the IR spectra on a Perkin-Elmer Infracord 237 B in potassium bromide.

The hydrazines employed as starting materials were either

commercial samples, used without further purification or prepared by nitrosation of the appropriate amine, followed by lithium aluminum hydride reduction.

Preparation of 3-Aminosydnone Imine Hydrochlorides.

To a solution of 0.5 mole of the 1,1-disubstituted hydrazine in 120 ml. of water or water-ethanol, 0.5 mole of potassium cyanide in 70 ml. of water was added under stirring at 5° in the course of 10 minutes, followed by 0.5 mole of aldehyde in the course of one hour. The mixture was stirred for one hour at room temperature, cooled to 5° and 50 ml. of concentrated hydrochloric acid and 0.5 mole of sodium nitrite in 75 ml. of water was added dropwise. The pH of the solution was kept acidic by gradual addition of hydrochloric acid. The nitroso hydrazine was extracted into chloroform. The solution was dried and evaporated to dryness in vacuo. The residue was stirred into 10 times its weight of methanol and saturated with hydrogen chloride. The solution was evaporated in vacuo at room temperature. The residue was either crystallized or, if impure, chromatographed on silicic acid. On elution with 20-50% methanol in chloroform, the desired product was obtained.

Preparation of Acylated 3-Aminosydnone Imine Hydrochlorides.

The acylation of the 3-aminosydnone imine hydrochloride

TABLE III

1	CH, NN—CH CH, CHO	IR (cm ⁻¹) 3180 1680	UV λ max, mμ 294 258	ε 10 000 3 800	NMR (ppm) 3N-CH ₃ :3.12 s 4C-H :8.07 s	р <i>К</i> 8.85
22	CH ₃ NN—CH CH ₃ //⊕ \\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	3155 1712 1625	316 297 243	9 300 10 700 6 600	$\begin{array}{l} 3N{-}CH_{3}; 3.30 \; s \\ 4C{-}H & : 9.02 \; s \end{array}$	4.50
6	$\begin{array}{c} \text{CH}_2\text{=CHCH}_2 \\ \text{CH}_2\text{=CHCH}_2 \end{array} \begin{array}{c} \text{NN}_{\bigoplus} \text{C} - \text{CH}_2\text{CH}_3 \\ \text{NH}_2 \text{ Cl} \\ \end{array}$	1675	312	8 600	3N-CH ₂ :3.94 d 4C-CH ₂ :2.78 q	8.20
7	$\begin{array}{c} \text{CH}_2\text{=CHCH}_2\\ \text{CH}_2\text{=CHCH}_2 \end{array} \begin{array}{c} \text{NN-C-CH}_2\text{CH}_2\\ \text{NH}_2 \end{array} \begin{array}{c} \alpha \\ \beta \\ \text{NH}_2 \end{array} \begin{array}{c} \beta \\ \text{CH}_2\text{-CHCH}_2 \end{array}$	1670	318	6 400	3N-CH ₂ :3.83 d 4α -CH ₂ : 2.93 s β -CH ₂ :	8.15
36	$\begin{array}{c} \text{CH}_2\text{=CHCH}_2 \\ \text{CH}_2\text{=CHCH}_2 \end{array} \begin{array}{c} \text{NN-C-CH}_2\text{CH}_3 \\ \text{NHCOOC}_2\text{H}_3 \end{array} \begin{array}{c} \text{CI}^{\bigodot} \end{array}$	1745 1645	335 235	12 900 15 000	3NCH ₂ :3.96 d 4CCH ₂ :2.77 q	3.30
13	CH ₃ NN—CH PhCH ₂ NO—CH VO—NH ₂ CIO	1670	298 257	8 500 3 500	3N-CH ₃ :3.05 s 3N-CH ₂ :4.68 s 4C-H ::8.32 s	
51	CH ₃ NN—CH PhCH ₂ NN—CH O NHCO	1710 1615	330 250	22 000 12 100	3N-CH ₃ :3.37 s 3N-CH ₂ :5.00 s 4C-H :9.45 s	

was achieved by two methods.

Method A.

To a mixture of 150 ml. of acetic anhydride and 150 ml. of pyridine, 3-aminosydnone imine hydrochloride (0.1 mole) was added. The mixture was warmed for a few minutes to 60° and left under exclusion of light for 3 days at room temperature. The crystalline material was removed by filtration through a Büchner funnel and recrystallized.

Method B.

To 120 ml. of pyridine, 3-aminosydnone imine hydrochloride (0.1 mole) was added under stirring. Acyl chloride (0.15 mole) was introduced in small portions at -10° . The mixture was

stirred at room temperature for 3 hours, cooled to 5° and 500 ml. of water was added. The solution was extracted four times with chloroform, the combined extracts were washed with water, dried and evaporated to dryness. The residue was dissolved in the alcohol of choice and hydrogen chloride was introduced at 10° to slightly acidic pH. On addition of ether the crystalline material separated.

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