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3-HYDROXYSYDNONE IMINES

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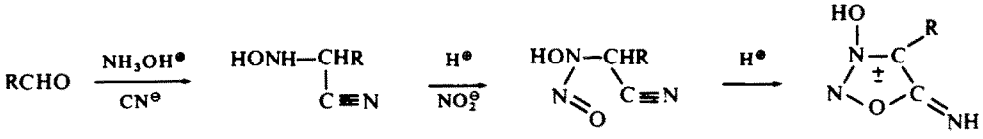
Abstract—Condensation of aldehydes, hydroxylamine and cyanide resulted in the formation of Mannich bases, which were nitrosated, to form 3-hydroxysydnone imines on acid treatment. A novel mesoionic betaine structure was assigned to these compounds on spectral evidence.

WHILE sydnone imines have been known since 1957,[1] 3-aminosydnone imines were only described recently.[2] The pronounced blood pressure lowering effect of 3-aminosydnone imines[3] led to the synthesis of the appropriate 3-hydroxysydnone imines, reported in this paper.

Synthesis

The Mannich reaction products (**1**) were the desired starting materials. A literature survey showed that compounds **1** (R = alkyl) were previously prepared under Mannich conditions.[4] As expected, the reaction could be extended to include products with R = aralkyl. On nitrosation of **1** nitrosohydroxylamines (**2**) were obtained. which were converted, without prior characterization, into the 3-hydroxysydnone imines (**3**) (Scheme 1):



1 **2** **3**

a: R = $CH_2CH_2CH_3$
b: R = $CH_2C_6H_5$
c: R = $CH_2CH_2C_6H_5$

The final products (**3**) were white, stable and highly crystalline solids. **3a** dissolved with ease in ether and water, **3b** and **3c** were water insoluble. The 3-hydroxysydnone imines (**3**) could not be converted into salts by mineral acid, in contrast to 3-aminosydnone imines.[2] This behaviour and spectral evidence suggested that gross structure **3** does not account for the properties of 3-hydroxysydnone imines.

Structure

The structure assignment is based on the spectra of 3-hydroxysydnone imines and of several derivatives, listed in Table 1. To facilitate the discussion of the spectral data

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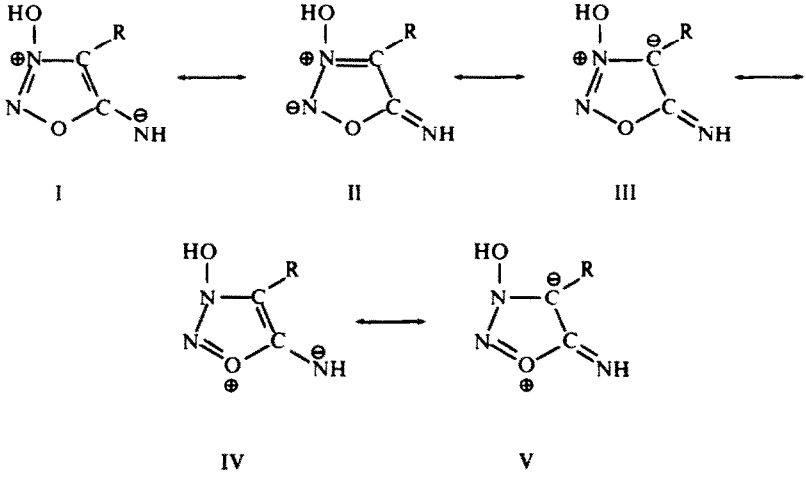
the resonance structures of this mesoionic system are recorded (I–V). It will be shown in the sequel, that these structures fail to describe the properties of **3**. The UV spectrum of **3a** in aqueous solution proved to be particularly useful in the structure assignment.



I II III

IV V

In the pH range of 1·7–10 the curve remained unchanged with the major absorption band at 281 mμ. At pH 11·9 the 281 mμ extinction started to decrease and a new long wave band at 315 mμ emerged. On neutralization of the aqueous solution the original UV curve was reestablished. The UV change at pH 11·9 was therefore not caused by destruction of the mesoionic system, but by partial deprotonation. Of special importance was the finding, that the UV spectrum remained unaltered in acidic solution. Since the exocyclic nitrogen is known to be basic in related sydnone imines,[1, 2] intramolecular protonation must have taken place, prohibiting protonation by external acid. Compounds **3** represent therefore a new betaine system. The properties of the betaine system are best expressed by one of the resonance structures as depicted in Table 1, arising from I by intramolecular protonation. It is necessary, however, to bear in mind the partial double bond character of the exocyclic imide. In fact, the presence of the imide band in the IR spectrum of **3a** at 1680 cm^{-1} provides additional evidence for the betaine structure, since it coincides with the imide band of 3-aminosydnone imine *hydrochlorides*[2a]. These results explain the unexpected reluctance of 3-hydroxysydnone imines to salt formation.

The aromatic character of the mesoionic system is further demonstrated by the characteristic NMR shifts of the methylene protons in position 4, which are very similar to benzenoid shifts and almost identical with those observed for 3-aminosydnone imine hydrochlorides[2a].

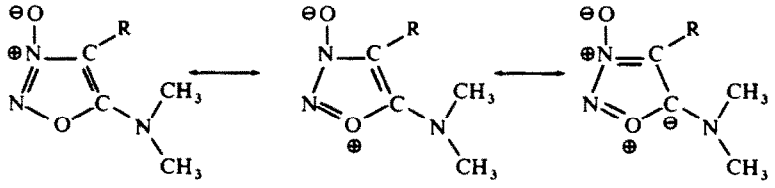
Reactions

Compound **3a** was stable to dilute mineral acid even at reflux temperature, to base at room temperature.

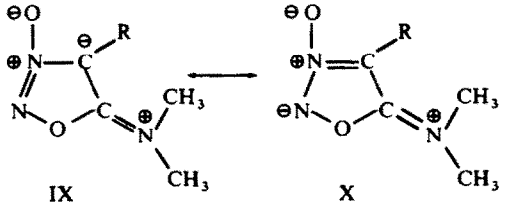
On reflux of **3a** with acetic anhydride a mixture of mono (**4**) and diacetylation product (**5**) was obtained, easily separable on column chromatography. Reaction of **3a** with phenyl isocyanate similarily yielded compounds **6** and **7**.

Of interest was now the investigation of the "phenolic" character of **3**. All attempts to alkylate the "phenolate" by methyliodide, diazomethane or methanol/hydrogen chloride failed under the usual reaction conditions. Therefore, a pronounced electron delocalization towards the neighbouring nitrogen has to be postulated. A similar electron delocalization was previously observed with 3-aminosydnone imines[2a] and 3-aminomünchnone imines.[5] In these cases the 3-amino group could not be protonated even with strong mineral acids.

Dialkylation of **3c** and **4** was finally achieved with methyliodide in the presence of sodium hydride. The obvious assumption of O,N-alkylation of **3c** proved erroneous on inspection of the NMR spectrum. Both methyl groups—of **8** and **9**—showed identical chemical shifts, giving rise to a sharp peak. The Me groups remained indistinguishable in the presence of deuterated trifluoroacetic acid, suggesting a common binding site. The UV spectra of **8** and **9** remained unaltered in the pH range 1·6–12, lending further support to dialkylation on the nitrogen. These results are in agreement with the mass spectrum of **9**, which shows a signal at m/e 189 (M^+—$(CH_3)_2N$). No signal for M^+—14 or 15 was observed, which excludes loss of CH_3 or CH_2 from CH_3O followed by loss of CH_3N. The dimethylation products **8** and **9** are represented in Table 1 by the resonance structure VI. The volatility of **9**—the mass spectrum was recorded at 40° inlet temperature—indicates, that resonance structure VI, with minimal charge separation, is the major contributor.



VI VII VIII



IX X

The dialkylation of **4** necessitates the loss of the acetyl group, otherwise the molecule cannot retain its mesoionic character, as indicated in **11**. Monomethylation of **4** leaves, however, the mesoionic structure intact, without loss of the acetyl group. Compound **10** was indeed isolated from the mother liquors of **9** as a colorless liquid.

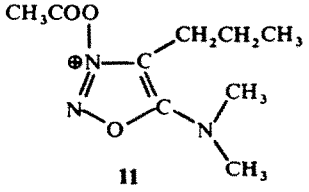


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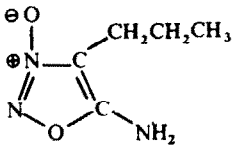
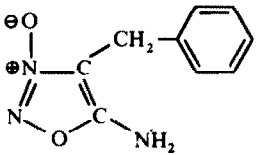
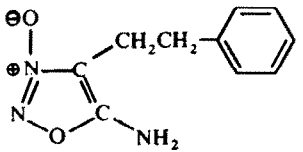
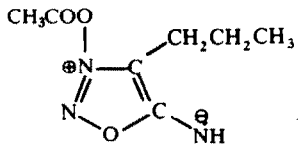
TABLE 1.

		IR (KBr) cm^{-1}	UV (Ethanol) λ_{max}, mμ	ε	NMR (DMSO) ppm (δ)
3a		3310 3250 3160 3080 1680	281 239	10250 3450	$4\underline{CH_3}CH_2CH_2$: 0·86 t $4CH_3\underline{CH_2}CH_2$: 1·52 sext. $4CH_3CH_2\underline{CH_2}$: 2·30 t $5NH_2$: 7·14 s ex.
3b		3280 3235 3120 1675 1610	279 239	8200 2500	$4CH_2$: 3·84 s arom. H : 7.25 s $5NH_2$: 7·77 s ex.
3c		3380 3290 3240 3120 1675 1610	281 239	10250 3360	$4CH_2CH_2$: 2·82 s arom. H : 7·22 s $5NH_2$: 7·54 s ex.
4		3260 3200 3150 1730 1660	305 272 240	1200 sh 10000 5200 sh	$4\underline{CH_3}CH_2CH_2$: 0·87 t $4CH_3\underline{CH_2}CH_2$: 1·55 sext. $4CH_3CH_2\underline{CH_2}$: 2·58 t $3CH_3CO$: 2·16 s 6NH : 11·40 s ex.

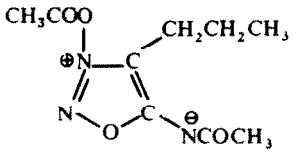
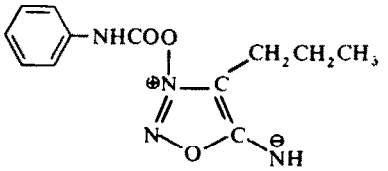
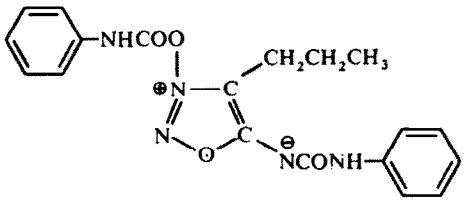
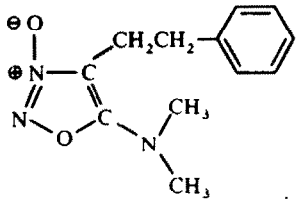
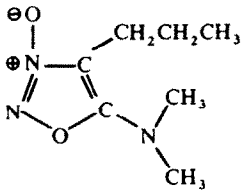
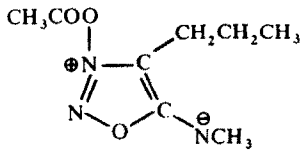
5		1745 1720 1680	 272 230	 4100 3000	$4\underline{CH_3}CH_2CH_2$: 0·98 t $4CH_3\underline{CH_2}CH_2$: 1·67 sext. $4CH_3CH_2\underline{CH_2}$: 2·50 t $3CH_3CO$, $6CH_3CO$: 2·44 s
6		3350 1730 1710 1660	314 277 238	11500 24300 23100	$4\underline{CH_3}CH_2CH_2$: 0·90 t $4CH_3\underline{CH_2}CH_2$: 1·61 sext. $4CH_3CH_2\underline{CH_2}$: 2·64 t arom H : 7·03–7·58 6NH, 3CONH : 9·21 s, 10·66 s ex.
7		3280 1740 1675 1652	306 244	9100 16600	$4\underline{CH_3}CH_2CH_2$: 0·88 t $4CH_3\underline{CH_2}CH_2$: 1·60 sext. $4CH_3CH_2\underline{CH_2}$: 2·55 t arom H : 7·05–7·47 3 and 6 : arom. region CONH : 10·63 s ex.
8		1655 1595	243 291	2670 10800	$4CH_2CH_2$, $5N(CH_3)_2$: 2·90 s arom H : 7·22–7·35

TABLE 1—*continued*

		IR (KBr) cm^{-1}	UV (Ethanol) λ_{max}, mμ	ε	NMR (DMSO) *m* ppm (δ)
9		1670	240 291	2600 10900	$4\underline{CH_3}CH_2CH_2$: 0·93 t $4CH_3\underline{CH_2}CH_2$: 1·55 sext. $4CH_3CH_2\underline{CH_2}$: 2·65 t $5N(CH_3)_2$: 3·11 s
10		1705 1670 ($CHCl_3$)	305 272	1300 6600	$4\underline{CH_3}CH_2CH_2$: 0·92 t $4CH_3\underline{CH_2}CH_2$: 1·60 sext. $4CH_3CH_2\underline{CH_2}$: 2·57 t $3CH_3CO$: 2·13 s $6CH_3N$: 3·27 s

Since alkylation of the oxygen function of 3 could not be achieved as a final synthetic step an attempt was made to prepare these compounds by using O-alkyl- and O-aralkylhydroxylamines as starting materials, in place of hydroxylamine. The nitrosation and subsequent acid treatment of the nitroso compounds met, however, with failure. Apparently, the nitroso compounds are highly unstable[6] in contrast to the nitroso compounds derived from hydroxylamine, which could be handled without special precautions.*

The compounds described in this paper were devoid of noteworthy pharmacological activity.

EXPERIMENTAL

The NMR spectra were determined on a Varian A-60, UV spectra recorded on a Bausch and Lomb 505, IR spectra on a Perkin–Elmer Infracord 237 B.

3-Hydroxy-4-n-propyl sydnone imine (**3a**). Compound **1a**[4] (11·4 g, 0·1 mole) in 400 ml 50% ethanol/water was cooled to 0° and $NaNO_2$ (6·9 g, 0·1 mole) in 14 ml water was dropwise added under vigorous stirring. With conc HCl the pH was maintained slightly acidic. The aqueous phase was extracted with chloroform, the combined chloroform extracts were washed with water, dried over Na_2SO_4 and added to 500 ml ice cold MeOH, saturated with HCl. The solvents were removed *in vacuo* and the residue chromatographed on silicic acid. **3a** was eluted with 5% MeOH/chloroform and crystallized from ether/light petroleum, 9 g (63%), m.p. 87·5–88·5°. (Found: C, 42·14; H, 6·69; N, 29·00. Calc. for $C_5H_9N_3O_2$ (143·1): C, 41·95; H, 6·34; N, 29·36%).

1-Hydroxylamino-2-phenyl propionitrile (**2b**). Phenylacetaldehyde (120 g, 1 mole) was treated with $NaHSO_3$ (104 g, 1 mole) in 250 ml water followed by addition of hydroxylamine hydrochloride (70 g, 1 mole) in 200 ml water in the course of 1 hr. The mixture was adjusted to pH4 with 2N NaOH and left overnight at room temp. KCN (72·6 g, 1·1 mole) in 150 ml water was introduced and the mixture was heated to 70° for 6 hr. The substance was extracted into chloroform, the solvent evaporated *in vacuo*, 140 g dark oily residue.

4-Benzyl-3-hydroxysydnone imine (**3b**). To crude **2b** (140 g), in 400 ml EtOH, $NaNO_2$ (69 g, 1 mole) in 150 ml water was dropped in below 0°, maintaining the pH slightly acidic by addition of HCl. The aqueous phase was repeatedly extracted with chloroform, the solvent was evaporated *in vacuo*. The residue was poured into 1.5 l ice cold MeOH, saturated with HCl. After 1 hr at 0° the mixture was evaporated to dryness *in vacuo* at room temp. On chromatography on silicic acid **3b** was eluted with 2·5% MeOH in chloroform and crystallized from acetone/light petroleum, 16·2 g (8·5%, based on aldehyde), m.p. 159–161°. (Found: C, 56·41; H, 5·10; N, 21·82. Calc. for $C_9H_9N_3O_2$ (191·2): C, 56·54; H, 4·75; N, 21·98%).

3-Hydroxy-4(2-phenethyl)-sydnone imine (**3c**). Like **2b** starting with dihydrocinnamaldehyde (134 g, 1 mole). On chromatography on silicic acid **3c** was eluted with 5% MeOH in chloroform and crystallized from MeOH/ether, 21·5 g (10·5%), m.p. 141–144°. (Found: C, 58·67; H, 5·59; N, 20·50. Calc. for $C_{10}H_{11}N_3O_2$ (205·2): C, 58·53; H, 5·40; N, 20·48%).

3-Acetoxy-4-n-propyl sydnone imine (**4**) *and 3-Acetoxy-N-acetyl-4-n-propyl sydnone imine* (**5**). Compound **3a** (14·3 g, 0·1 mole) was refluxed in 150 ml Ac_2O for 45 mins. The mixture was evaporated to dryness *in vacuo*. The residue was dissolved in benzene and chromatographed on silicic acid. On elution with 2·5% MeOH in chloroform **5** was isolated, on elution with 10% MeOH **4**, 0·9 g (4·8%), m.p. 62–64°. (Found: C, 48·00; H, 6·09; N, 18·42. Calc. for $C_9H_{13}N_3O_4$ (227·2): C, 47·57; H, 5·77; N, 18·49%); **5**, 16·2 g (71%), m.p. 89–92°. (Found: C, 45·57; H, 6·17; N, 22·49. Calc. for $C_7H_{11}N_3O_3$ (185·2): C, 45·40; H, 5·99; N, 22·69%).

3-Phenylcarbamoyloxy-4-propyl sydnone imine (**6**) *and 3-Phenylcarbomoyloxy-N-phenylcarbamoyl-4-propyl sydnone imine* (**7**). Compound **3a** (7·2 g, 0·05 mole) and 15 ml phenylisocyanate were heated to 100° for 8 hr. The mixture was poured into 150 ml 2N HCl, extracted with chloroform and the dried chloroform extracts were evaporated to dryness. The residue was chromatographed on silicic acid, **7** was eluted with chloroform, **6** with 10% MeOH in chloroform; **6** crystallized from acetone/light petroleum 3·2 g (24%).

* Compounds **3**, **8** and **9** which possess the same structural elements as the "methoxazonyl" group described by Woodward and Wintner[6] differ however by the absence of a pronounced band at 1500 cm^{-1} in the IR.

m.p. 141–144°. (Found: C, 54·86; H, 5·39; N, 21·19. Calc. for $C_{12}H_{14}N_4O_3$ (262·3): C, 54·95; H, 5·38; N, 21·37%); **7** crystallized from acetonitrile/ether, 6·7 g (35%), m.p. 165–167°. (Found: C, 60·05; H, 5·15; N, 18·52. Calcd. for $C_{19}H_{19}N_5O_4$ (381·4): C, 59·83; H, 5·02; N, 18·36%).

Alkylation attempts of **3a** *and* **3c**

(*a*) *By means of methyliodide.* A mixture of **3a** (3 g), MeCN (25 ml) and MeI (30 g) was refluxed for 132 hr. After evaporation, the residue was chromatographed on silicic acid. On elution with 10% MeOH in chloroform starting material was recovered in almost quantitative yield.

(*b*) *By means of diazomethane.* Ether (30 ml) containing diazomethane (approximately 0·1 mole) and **3a** (7 g, 0·05 mole) in 25 ml ether and 2 ml MeOH was mixed and kept at room temp. for 24 hr. On evaporation starting material was recovered in quantitative yield.

(*c*) *By means of methanol/hydrogen chloride.* A soln of **3c** (1·1 g) in 25 ml MeOH was saturated with HCl kept for one week at room temp, warmed to 50° for 8 hr and concentrated to dryness *in vacuo*. Starting material was recovered in quantitative yield.

Identity was established in all cases by UV, IR and NMR spectra, by TLC, m.p. and m.m.p.

Acid treatment of 3-hydroxy-4-propylsydnone imine (**3a**). Compound **3a** (200 mg) was refluxed for 5 hr in 25 ml 2N HCl. The aqueous soln was extracted repeatedly with chloroform. The combined chloroform extracts were dried and evaporated to dryness *in vacuo*. The residue was treated with acetone/ether.

A crystalline ppt was filtered off, which proved to be ammonium chloride (25 mg). The mother liquors were concentrated and crystallized from ether/light petroleum, 151 mg, m.p. 85–89°.

The substance was identical with starting material by IR, UV and NMR.

Base treatment of 3-hydroxy-4(2-phenethyl)sydnone imine (**3c**). Compound **3c** (1·1 g) was warmed for a short time with 10 ml 2N NaOH to effect soln. The clear soln remained for 24 hr at room temp. An aliquot was worked up. TLC and UV spectra showed unchanged starting material. After heating for 8 hr to 100° no identifiable material could be isolated.

N-Dimethyl-3-oxo-4(2-phenethyl)sydnone imine (**8**). Compound **3c** (1 g, 0·005 mole) was methylated as described for **9**. The substance was recrystallized from ether/light petroleum, 0·8 g (70%), m.p. 92–93°. (Found: C, 61·75; H, 6·47; N, 17·65. Calc. for $C_{12}H_{15}N_3O_2$ (233·2): C, 61·78; H, 6·48; N, 18·02%); Mass spectrum: $M^+ = 233$, 5%; $m/e = 189$, 4% ($M^+ - N(CH_3)_2$), $m/e = 142$, 100% ($M^+ - C_7H_7$).

N-Dimethyl-3-oxo-4-propylsydnone imine (**9**) *and 3-acetoxy-N-methyl-4-propylsydnone imine* (**10**). To **4** (6·0 g, 0·032 mole) in 30 ml DMF, NaH (2·5 g, 0·05 mole) was portionwise added under stirring at room temp. MeI (14·1 g, 0·05 mole) in 20 ml DMF was dropped in at 5° over a 35 min interval. The mixture was stirred for 1 day, poured into cold water and repeatedly extracted with chloroform. The residue of the dried chloroform extract crystallized from EtOH on cooling in dry ice/acetone. Recrystallized for analysis from ether/light petroleum, 0·9 g (16%), m.p. 60–61°. (Found: C, 49·30; H, 7·67; N, 24·41. Calc. for $C_7H_{13}N_3O_2$ (171·2: C, 49·11; H, 7·65; N, 24·55%).

On chromatography of the mother liquor on silica gel compound **10** was eluted with 10% IPA in light petroleum. **10** was distilled at 150°/0·05 mm Hg. Colorless liquid, 1·4 g (22%). (Found: C, 48·57, 47·91; H, 6·74, 6·67; N, 21·44, 21·43. Anal. Calc. for $C_8H_{13}N_3O_3$ (199·2): C, 48·23; H, 6·58; N, 21·09%).

The NMR of **10** indicates the presence of **9** as minor impurity.

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