TABLE I

Nitrosoanilines	Solvent	Formula	Carbon[a] Calcd.	Carbon[a] Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Metal Calcd.	Metal Found	Yield, %
N,N'-Diphenylethylenediamine	H_2O	$C_{14}H_{12}N_3O_6Na_2$	38.68	38.62	2.8	3.3	25.81	25.71	10.48	9.96	48
N-Phenyl-1-naphthylamine	H_2O	$C_6H_{11}N_4O_2Na$	60.90	61.23	3.34	3.58	—	—	6.3	6.78	24
β-Anilinopropionic acid sodium salt	H_2O	$C_9H_8N_4O_5Na_2$	36.25	36.08	2.69	3.09	18.79	19.08	15.42	15.31	42
2-Nitrodiphenylamine	H_2O	$C_{12}H_8O_5N_5Na$	44.30	44.87	2.49	2.84	—	—	7.0	6.78	40
Ethyl-1-naphthylamine	CH_3OH	$C_{12}H_{11}N_4O_3Na$	—	—	—	—	—	—	8.14	8.48	18
N-Ethyl-*m*-toluidine	H_2O	$C_9H_{11}N_4O_3Na$	—	—	—	—	—	—	9.34	9.43	23
N-Phenyl	H_2O	$C_{12}H_9N_4NaO_3$	51.43	51.53	3.24	3.58	20.0	19.93	8.21	8.09	58
N-Methyl	H_2O	$C_7H_7N_4NaO_3$	38.54	38.86	3.24	3.44	25.68	25.59	—	—	—
							Chlorine				
N-2-Chloroalkylaniline	CH_3OH	$C_9H_8N_4O_3ClNa$	—	—	—	—	12.85	12.43	8.25	8.08	31

[a] Galbraith Laboratories, Knoxville, Tenn.

filtrate until the cloud point was reached; the mixture was cooled, and 0.55 g. of crystalline solid was isolated. An analytical sample was prepared by recrystallization from methanol, m.p. 142–144° dec.

Anal. Calcd. for: $C_{13}H_{12}N_4O_3$; C, 57.35; H, 4.44; N, 20.58. Found: C, 57.40; H, 4.22; N, 20.48.

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The Preparation of Some *N*-Alkylsydnones Containing a Functional Group in the Side Chain

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Most investigations on the sydnones (I) have been concerned with derivatives in which the substituent R is an aromatic or heteroaromatic moiety.[1,2] *N*-Alkylsydnones, on the other hand, have been studied less extensively,[3] and the main interest in them has been their cleavage by strong acid to give otherwise rather inaccessible alkylhydrazines.[4,5]

A number of *N*-alkylsydnones have also been examined for biological activity. Brookes and Walker[7] prepared several *N*-methylsydnones (I. R = CH_3, R' = alkyl) as possible antagonists of the natural amino acids, while Daeniker and Druey[8] found that *N,N'*-ethylenebissydnone (II) exhibited slight antitumor activity. It has also been claimed that various simple sydnones possess ascaricidal action.[9]

The present work describes the preparation of several *N*-alkylsydnones of structure III, in which a short aliphatic side chain is terminated by a functional group R. Sydnones of this type have not been reported previously and could be of interest as potential biologically active agents, or as precursors of such agents.

The sydnones (III) have been obtained by the normal synthetic procedure,[10] that is, nitrosation

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(5) A long-chain alkyl sydnone (I. R = $C_{16}H_{33}$, R' = H) has been prepared in order to examine the effect of the mesoionic sydnone nucleus on the behavior of a unimolecular film.[6]
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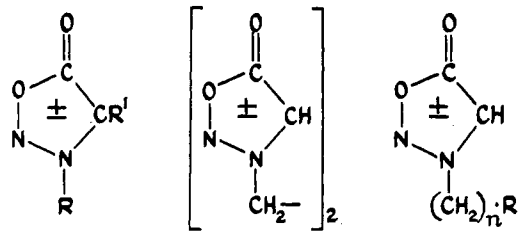

(I) (II) (III)

Figure 1

of the appropriate *N*-alkylglycine followed by treatment of the *N*-nitroso derivative with acetic anhydride. In some cases slight modifications in the usual experimental procedure were necessitated by the high solubility of the products in water.

In this way *N*-β-cyanethylglycine[11] was converted into *N*-β-cyanethylsydnone (III. n = 2, R = CN), and *N*-carboxymethyl-β-alanine[12] into *N*-β-carboxyethylsydnone (III. n = 2, R = CO_2H). Similarly, *N*-γ-methoxypropylsydnone (III. n = 3, R = OCH_3) was obtained from *N*-γ-methoxypropylglycine. The latter compound, as its hydrochloride, was prepared from commercially available γ-methoxypropylamine.

In the case of the *N*-nitroso derivative of *N*-β-hydroxyethylglycine[13] acetylation of the hydroxyl group accompanied sydnone formation. The crude acetyl derivative (III. n = 2, R = $OCOCH_3$) thus obtained was an oil which decomposed extensively on attempted distillation. Selective hydrolysis of the acetoxy group without cleaving the sydnone nucleus was effected using either a strong acid or strong base ion-exchange resin as catalyst, and *N*-β-hydroxyethylsydnone (III. n = 2, R = OH) obtained as a viscous oil. The sydnone was isolated as the crystalline *p*-toluenesulfonyl derivative (III. n = 2, R = $OSO_2C_7H_7$).

An attempt to prepare *N*-γ-bromopropylsydnone (III. n = 3, R = Br) was unsuccessful. *N*-γ-Bromopropylglycine hydrobromide was obtained by refluxing *N*-γ-methoxypropylglycine hydrochloride with hydrogen bromide in acetic acid. Nitrosation of the hydrobromide gave an unstable *N*-nitroso derivative, which, on treatment with acetic anhydride, yielded a dark resinous product. This material apparently contained the sydnone nucleus, but could not be purified.

EXPERIMENTAL

The microanalyses were carried out by the Australian Microanalytical Service, University of Melbourne. All melting points are uncorrected.

N-β-*Cyanethyl-N-nitrosoglycine*. A solution of 5.0 g. of *N*-β-cyanethylglycine[11] in 10 ml. of water was saturated with nitrous fumes (from dilute sulfuric acid and sodium nitrite) at room temperature. The course of the reaction was followed by diluting a drop of the solution with acetone at intervals until the absence of a precipitate or turbidity indicated that nitrosation was complete. Extraction with hot ethyl acetate followed by evaporation of the dried extract *in vacuo* gave the product as an oil which soon solidified. It was recrystallized from ethyl acetate, m.p. 117.5–118.5°, yield 2.3 g. (38%).

Anal. Calcd. for $C_5H_7N_3O_3$: C, 38.2; H, 4.5; N, 26.0. Found: C, 38.4; H, 4.4; N, 25.9.

N-β-*Cyanethylsydnone* (III. n = 2, R = CN). The foregoing nitroso compound (1.9 g.) was treated with 8 ml. of acetic anhydride for 4 days at room temperature. The resultant clear solution was diluted with ether, and the precipitated sydnone collected and recrystallized from ethyl acetate. The compound formed clusters of needles, m.p. 81.5–82.5°, yield 1.0 g. (60%). λ_{max}^{Nujol} 3.19 (sydnone CH), 4.42 (CN), and 5.76 μ (sydnone CO).

Anal. Calcd. for $C_5H_5N_3O_2$: C, 43.2; H, 3.6; N, 30.2. Found: C, 43.6; H, 3.8; N, 30.3.

N-Carboxymethyl-N-nitroso-β-alanine. An aqueous solution of 5.0 g. of *N*-carboxymethyl-β-alanine[12] was treated with nitrous fumes as described for the cyano analog to give 4.1 g. (68%) of the nitroso derivative, which formed colorless needles from water, m.p. 124.5–125.5°.

Anal. Calcd. for $C_5H_8N_2O_5$: C, 34.1; H, 4.6; N, 15.9. Found: C, 33.7; H, 4.6; N, 15.8.

In earlier experiments a low-melting form of this compound, m.p. 85.5–86.5°, was obtained.

N-β-*Carboxyethylsydnone* (III. n = 2, R = CO_2H). Treatment of 3.9 g. of the nitroso compound with 17 ml. of acetic anhydride for 4 days at room temperature, followed by hydrolysis with water, and evaporation to dryness *in vacuo*, gave the sydnone as a solid, which was recrystallized from ethanol–petroleum ether. The compound formed colorless needles, m.p. 135.5–136.5°, yield 2.9 g. (83%). λ_{max}^{Nujol} 3.19 (sydnone CH), 5.80 (sydnone CO), 5.91 (carboxyl CO), and in the region 3.57–4.00 μ (carboxyl bonded OH).

Anal. Calcd. for $C_5H_6N_2O_4$: C, 38.0; H, 3.8; N, 17.7. Found: C, 37.8; H, 4.0; N, 17.6.

The silver salt formed moderately soluble, colorless, needles from water, m.p. 186.5–187.5° dec.

Anal. Calcd. for $C_5H_5AgN_2O_4$: C, 22.7; H, 1.9; N, 10.6 Found: C, 22.6; H, 2.1; N, 10.6.

The *p*-nitrobenzyl ester was obtained by refluxing an aqueous ethanolic solution of the sodium salt with *p*-nitrobenzyl bromide and formed slightly yellow needles from ethyl acetate, m.p. 92–93°.

Anal. Calcd. for $C_{12}H_{11}N_3O_6$: C, 49.1; H, 3.8; N, 14.3. Found: C, 49.3; H, 3.9; N, 14.1.

Ethyl N-γ-methoxypropylglycinate. A solution of 26.7 g. of γ-methoxypropylamine (American Cyanamid Co.) and 30 g. of triethylamine in 200 ml. of benzene was treated with 47.5 g. of ethyl bromoacetate in 100 ml. of benzene according to the general procedure of Speziale and Jaworski.[14] The ester was obtained as a colorless, mobile liquid, b.p. 150–152°/15 mm., yield 23.5 g. (45%).

Anal. Calcd. for $C_8H_{17}NO_3$: C, 54.9; H, 9.7. Found: C, 55.1; H, 9.5.

N-γ-Methoxypropylglycine hydrochloride. Twenty grams of the ethyl ester were refluxed for 30 min. with a solution of 5.5 g. of sodium hydroxide in 25 ml. of water, and the mixture evaporated to small bulk. Concd. hydrochloric acid (27 ml.) was added cautiously, and the mixture evaporated to dryness *in vacuo*. The residue was extracted with hot ethanol. After filtration and dilution with ether the product was obtained as colorless needles, yield 19.5 g. (93%). This material was contaminated with sodium chloride, but was satisfactory for

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the next stage. For analysis it was recrystallized several times from acetic acid–ether, and then from ethanol–ether, m.p. 142–143°.

Anal. Calcd. for $C_6H_{14}ClNO_3$: C, 39.2; H, 7.6; N, 7.6. Found: C, 38.8; H, 7.4; N, 7.2.

N-γ-Methoxypropyl-N-nitrosoglycine. A solution of 4.6 g. of the foregoing hydrochloride in 15 ml. of water was cooled in ice, and 1.9 g. of sodium nitrite in 5.0 ml. of water added slowly with stirring. After 30 min. the clear solution was extracted with warm ethyl acetate. Evaporation of the dried extract *in vacuo* gave the nitroso compound as an oil which solidified on scratching, yield 2.8 g. (64%). It was recrystallized twice from ethyl acetate–petroleum ether, and formed slightly yellow needles, m.p. 70.5–71.5°.

Anal. Calcd. for $C_6H_{12}N_2O_4$: C, 40.9; H, 6.8; N, 15.9. Found: C, 41.1; H, 6.9; N, 15.8.

N-γ-Methoxypropylsydnone (III. n = 3, R = OCH_3). Treatment of 1.5 g. of the nitroso compound with 7.0 ml. of acetic anhydride in the usual way gave the sydnone as a slightly yellow oil, b.p. 164–165°/1 mm., yield 0.8 g. (60%). The compound solidified at −14°. Evidently slight decomposition occurred on distillation for the infrared spectrum contained a broad band at 2.86 μ, as well as the expected maxima at 3.20 μ (sydnone CH) and 5.76 μ (sydnone CO).

Anal. Calcd. for $C_6H_{10}N_2O_3$: C, 45.6; H, 6.3; N, 17.7. Found: C, 46.1; H, 6.4; N, 17.8.

N-β-Hydroxyethylglycine. Twenty one grams of *N-β*-hydroxyethylacetonitrile (prepared by the condensation of ethanolamine and hydroxyacetonitrile[15]) were refluxed for 2–3 hr. with 49.8 g. of barium hydroxide octahydrate in 160 ml. of water. The barium was removed by addition of a slight excess of sulfuric acid, and the filtered solution evaporated to small bulk and again filtered. Addition of ethanol precipitated the glycine as a colorless crystalline solid, m.p. 174–175°, yield 17.5 g. (70%). Kipriyanov and Kipriyanov[13] report m.p. 174–175°.

N-β-Hydroxyethyl-N-nitrosoglycine. A solution of 12.0 g. of sodium nitrite in 15 ml. of water was added slowly to an ice cold mixture of 17.5 g. of *N-β*-hydroxyethylglycine and 12.7 ml. of concd. hydrochloric acid in 10 ml. water. After keeping for 1–2 hr. at 0° the solution was extracted repeatedly with warm ethyl acetate. The nitroso compound was finally obtained as an oil which solidified on scratching. The product was washed with ether and dried, m.p. 73–75°, yield 8.3 g. (38%). Continuous extraction of the solution furnished more of the nitroso compound, but extensive resinification also occurred. For analysis the compound was recrystallized from ethyl acetate as almost colorless needles, m.p. 78.5–79.5°.

Anal. Calcd. for $C_4H_8N_2O_4$: C, 32.4; H, 5.4; N, 18.9. Found: C, 32.3; H, 5.7; N, 18.4.

The nitroso compound was also obtained in 41% yield by the action of nitrous fumes on an aqueous solution of *N-β*-hydroxyethylglycine, but the product was of inferior quality and very difficult to recrystallize.

N-β-Hydroxyethylsydnone (III. n = 2, R = OH). The foregoing nitroso compound (8.3 g.) was treated with 35 ml. of acetic anhydride for 4 days at room temperature, the mixture hydrolyzed with water, and then evaporated to dryness *in vacuo*. The residue was dissolved in ethyl acetate, and the solution shaken with concd. potassium carbonate solution, and dried over sodium sulfate. Evaporation gave the acetyl derivative (III. n = 2, R = $OCOCH_3$) as an oil which failed to solidify at −14°, and which decomposed extensively on distillation giving a black, tarry residue.

Treatment of the crude acetyl derivative with *p*-toluenesulfonyl chloride and pyridine failed to yield a *p*-toluenesulfonyl derivative (see below), thus indicating the absence of *N-β*-hydroxyethylsydnone in the product. The material also gave a strong Liebermann reaction, and probably contains the parent nitroso compound. In addition, it is possible that lactonization between the β-hydroxyl and the carboxyl groups may have occurred to some extent under the reaction conditions used.

A solution of 3 g. of the crude acetyl derivative (III. n = 2, R = $OCOCH_3$) in 20 ml. of water was refluxed with 9 g. of Zeo-Karb 225 acidic resin for 1 hr. The filtered solution was evaporated *in vacuo*, the residue dissolved in ethyl acetate and the dried solution evaporated. Crude *N-β*-hydroxyethylsydnone (III. n = 2, R = OH) was obtained as a viscous, almost colorless, oil. λ_{max}^{film} 2.94 (OH), 3.18 (sydnone CH), and 5.76 μ (sydnone CO).

An ice cold solution of the crude sydnone in 4 ml. of pyridine was treated dropwise with a solution of 2.7 g. of *p*-toluenesulfonyl chloride in pyridine. After 1 hr. the mixture was diluted with water, and the precipitated *p*-toluenesulfonyl derivative (III. n = 2, R = $OSO_2C_7H_7$) was collected and washed, yield 1.7 g. (27% overall), m.p. 118–120°. The compound formed colorless needles from ethanol, m.p. 120–121°. For analysis it was again recrystallized from ethanol, m.p. 120.5–121.5°. λ_{max}^{Nujol} 3.15 (sydnone CH), 5.73 (sydnone CO), 6.25 (benzene nucleus), 7.38 and 8.50 μ (sulfonate).

Anal. Calcd. for $C_{11}H_{12}N_2O_5S$: C, 46.5; H, 4.2; N, 9.9. Found: C, 46.4; H, 4.4; N, 9.7.

The *p*-toluenesulfonyl derivative was also obtained in 21% yield from crude *N-β*-hydroxyethylsydnone produced by selective hydrolysis of the acetyl derivative with Amberlite IRA-400 basic resin in water at room temperature for 12 hr.

N-γ-Bromopropylglycine hydrobromide. A mixture of 4.1 g. of *N-γ*-methoxypropylglycine hydrochloride, 40 ml. of 48% hydrobromic acid, and 100 ml. of glacial acetic acid was refluxed for 5 hr., and evaporated to dryness *in vacuo*. The residue was extracted with hot acetic acid and the filtered extract diluted with ethyl acetate. The hydrobromide separated as needles, and was recrystallized from ethanol–ether, m.p. 173.5–174.5°, yield 3.6 g. (59%). For analysis it was repeatedly recrystallized from ethanol–ether, but, nevertheless, failed to give very satisfactory analytical results.

Anal. Calcd. for $C_5H_{11}Br_2NO_2$: C, 21.7; H, 4.0; N, 5.1. Found: C, 22.6; H, 4.2; N, 4.5.

N-γ-Bromopropyl-N-nitrosoglycine. An ice-cooled solution of 3.4 g. of *N-γ*-bromopropylglycine hydrobromide in 9.0 ml. of water was treated dropwise with 1.0 g. of sodium nitrite in 4.0 ml. of water. The nitroso compound soon began to crystallize, and was collected after 30 min., and dried over phosphorus pentoxide *in vacuo*. It was recrystallized from ethyl acetate–petroleum ether, m.p. 87–88° dec., yield 1.1 g. (40%). The compound was unstable, and resinified readily. For analysis it was recrystallized from ether–petroleum ether when it formed colorless needles, m.p. 91.5–92.5°, which, however, slowly decomposed even on storage at 0°.

Anal. Calcd. for $C_5H_9BrN_2O_3$: C, 26.7; H, 4.0; N, 12.4. Found: C, 27.4; H, 4.1; N, 11.6.

Treatment of the nitroso compound with acetic anhydride in the cold for several days gave a red solution from which a dark brown, ether-insoluble, tacky material was isolated. This failed to solidify at −14°, and decomposed on heating. The infrared spectrum, however, contained distinct maxima at 3.20 and 5.79 μ indicating the probable presence of the sydnone nucleus.

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Halogen Reactivity in α-Fluoroanthraquinones

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In searching for better "leaving groups" for displacement reactions in the anthraquinone system,