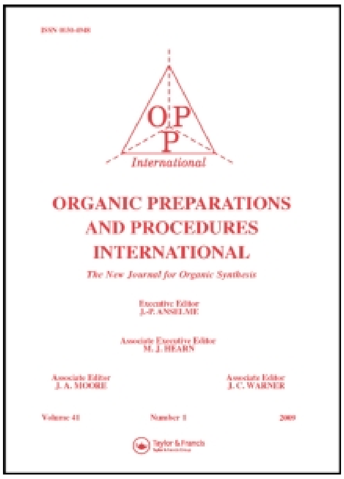

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SOME DERIVATIVES OF 3-CARBOXYMETHYLSYDNONE

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To cite this Article Stewart, F. H. C.(1970) 'SOME DERIVATIVES OF 3-CARBOXYMETHYLSYDNONE', Organic Preparations and Procedures International, 2: 1, 11 — 17

To link to this Article: DOI: 10.1080/00304947009458411

URL: http://dx.doi.org/10.1080/00304947009458411

ORGANIC PREPARATIONS AND PROCEDURES 2(1), 11-17 (1970)

SOME DERIVATIVES OF 3-CARBOXYMETHYLSYDNONE

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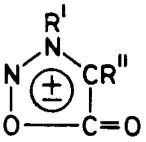
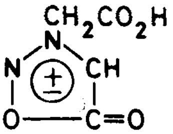
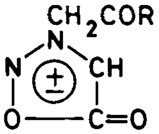
Sydnones (I) are produced by the action of certain reagents, notably acetic anhydride, on the N-nitroso derivatives of N-aryl or alkyl α-amino acids[1,2]. In view of the relationship of these heterocyclic compounds to amino acids, the synthesis of peptides containing a sydnone ring is being investigated. Exploratory preparative experiments in this direction have been carried out with 3-carboxymethylsydnone (II)[3], which is derived from iminodiacetic acid, an isomer of aspartic acid.



(I)



(II)



(III)

3-Carboxymethylsydnone (II) was converted into various ester and amide derivatives (III) using procedures routinely employed in peptide synthesis. The products included the 2,4,6-trimethylbenzyl (III; R = OTMB)[4,5], *p*-nitrobenzyl (III; R = ONB)[6], *p*-nitrophenyl (III; R = ONP)[7], and pentachlorophenyl (III; R = OPCP)[8] esters. The *p*-nitrophenyl active ester decomposed on standing, but the pentachlorophenyl analog was a more stable compound.

N,N'-Dicyclohexylcarbodiimide coupling of the sydnone (II) with benzylamine gave the amide (III; R = NHBzl). The glycine derivative (III; R = Gly-OBzl) was prepared in the same way from glycine benzyl ester *p*-toluenesulfonate. A similar reaction with glycine ethyl ester hydrochloride gave a substantial amount of the N-acylurea (III; R = $N(C_6H_{11})CONHC_6H_{11}$). The ethyl ester (III; R = Gly-OEt) was obtained by an active ester coupling with the pentachlorophenyl derivative (III; R = OPCP). Condensation of the *p*-nitrophenyl analog with the sodium salt of L-phenylalanine in aqueous dimethylformamide - chloroform in the presence of triethylamine[9] produced the acylamino acid (III; R = Phe-OH).

The proton magnetic resonance spectra of the compounds (III) gave chemical shift values (τ) for the sydnone ring proton and the 3-methylene protons in the regions 2.81 - 3.14 and 4.17 - 4.84, respectively[10]. Absorptions corresponding to the various types of proton in the R moieties in (III) were also present at the appropriate positions except in the case of the pentachlorophenyl ester (III; R = OPCP), which has no protons other than those in the vicinity of the sydnone nucleus.

Experimental

The microanalyses were carried out by the Australian Microanalytical Service, Melbourne. Melting points are uncorrected. Infrared spectra were obtained with KBr disks. The 60 Mc proton magnetic resonance spectra were run in dimethylsulfoxide-d_6 with a Varian A-60D spectrometer. For amino acid analysis, weighed samples were hydrolysed in 6N HCl at 110° for 24 hours under vacuum.

3-Carboxymethylsydnone 2,4,6-Trimethylbenzyl Ester (III; R = OTMB): A solution of 3-carboxymethylsydnone[3] (144 mg), triethylamine (0.14 ml), and chloromethylmesitylene[4] (169 mg) in dimethylformamide (0.5 ml) was kept overnight at room temperature, and then diluted with water. The solid product was washed with water, dried (236 mg; 85%), and recrystallized from ethanol, m.p. 172.5 - 173.5°; ν_{max} 3120 (sydnone ring CH)[2], 1720 cm^{-1} (very strong, combined sydnone and ester CO); τ 2.95 (sydnone ring proton), 3.14 (aromatic protons), 4.51 (3-methylene protons), 4.74 (benzylic protons).

Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.8; H, 5.8; N, 10.1.

Found: C, 60.6; H, 5.9; N, 10.0.

3-Carboxymethylsydnone *p*-Nitrobenzyl Ester (III; R = ONB):

Obtained in 96% yield as for the 2,4,6-trimethylbenzyl analog using *p*-nitrobenzyl bromide, and recrystallized from dimethylformamide - ethanol, m.p. 147.5 - 149.5°; ν_{max} 3150 (sydnone ring CH), 1750 cm^{-1} (combined CO); τ 1.69 and 2.30 ($A_2'X_2'$ pattern), 2.87 (sydnone ring proton), 4.35 (3-methylene protons), 4.55 (benzylic protons).

Anal. Calcd. for $C_{11}H_9N_3O_6$: C, 47.7; H, 3.2; N, 15.0.

Found: C, 47.6; H, 3.8; N, 14.8.

3-Carboxymethylsydnone *p*-Nitrophenyl Ester (III; R = ONP):

N,N'-Dicyclohexylcarbodiimide (2.06 g) was added to a stirred solution of 3-carboxymethylsydnone (1.44 g) and *p*-nitrophenol (1.67 g) in dry acetonitrile (20 ml) at 0°. After 1 - 2 hours at this temperature, the mixture was kept overnight at 5°, and then filtered. Removal of the solvent gave the product as an oil which solidified on trituration with ether (yield, 2.46 g; 92%). The compound decomposed on keeping, and should be prepared and recrystallized from ethanol in small batches shortly before use, m.p. 134 - 134.5°; ν_{max} 3120 (sydnone ring CH), 1770 - 1740 cm^{-1} (plateau, unresolved sydnone and NP ester CO); τ 1.63 and 2.46 ($A_2'X_2'$ pattern), 2.81 (sydnone ring proton), 4.17 (3-methylene protons).

Anal. Calcd. for $C_{10}H_7N_3O_6$: C, 45.3; H, 2.6; N, 15.8.

Found: C, 45.5; H, 2.7; N, 16.3.

3-Carboxymethylsydnone Pentachlorophenyl Ester (III; R = OPCP): Obtained in 81% yield as for the *p*-nitrophenyl ester, but using dimethylformamide as the solvent, followed by dilution with water after filtration. The compound was recrystallized from ethanol, m.p. 188 - 189°; ν_{max} 3110 (sydnone ring CH), 1795 (PCP ester CO), 1755 cm^{-1} (sydnone CO); τ 2.95 (sydnone ring proton), 4.65 (3-methylene protons). Variable intensity impurity peaks at 2.69 and 3.77 were observed with different samples, and, in view of their location and the absence of upfield absorption, are tentatively ascribed to traces of the symmetrical anhydride of (II).

Anal. Calcd. for $C_{10}H_3Cl_5N_2O_4$: C, 30.6; H, 0.8; N, 7.1; Cl, 45.2.
Found: C, 30.9; H, 1.2; N, 7.1; Cl, 44.9.

3-Carboxymethylsydnone Benzylamide (III; R = NHBzl): A mixture of 3-carboxymethylsydnone (288 mg), benzylamine (0.22 ml), and N,N'-dicyclohexylcarbodiimide (412 mg) in acetonitrile (8 ml) was stirred for 1 - 2 hours at 0°, and then at room temperature. The initial copious precipitate of the benzylamine salt of the sydnone dissolved gradually, and was replaced by the finer precipitate of N,N'-dicyclohexylurea. Removal of the latter, and evaporation of the solvent gave the oily product, which solidified on treatment with water (yield, 406 mg; 87%). The compound was recrystallized from ethyl acetate - cyclohexane, m.p. 145 - 146°; ν_{max} 3120 (sydnone ring CH), 1725 (sydnone CO), 1680 (amide I), 1550 cm^{-1} (amide II); τ 2.70 (phenyl protons), 3.00 (sydnone ring proton), 4.80 (3-methylene protons), 5.65 (doublet, benzylic protons).

Anal. Calcd. for $C_{11}H_{11}N_3O_3$: C, 56.7; H, 4.7; N, 18.0.
Found: C, 56.4; H, 4.9; N, 17.8.

3-Sydnonylacetylglycine[11] Benzyl Ester (III; R = Gly-OBzl): 3-Carboxymethylsydnone (3-sydnonylacetic acid) (144 mg), glycine benzyl ester *p*-toluenesulfonate (337 mg), and triethylamine (0.14 ml) in acetonitrile (4 ml) at 0° were treated with N,N'-dicyclohexylcarbodiimide

(206 mg). The crystalline product (267 mg; 92%) was obtained as in the previous example, and recrystallized from ethyl acetate - cyclohexane, m.p. 133.5 - 135°; ν_{max} 3120 (sydnone CH), 1730 (combined CO), 1670 (amide I), 1555 cm^{-1} (amide II); τ 2.65 (phenyl protons), 3.02 (sydnone ring proton), 4.75 (3-methylene protons), 4.85 (benzylic protons), 5.98 (doublet, glycyl protons). Amino acid analysis gave the glycine content as 3.24 mmole/g (calcd. 3.43 mmole/g).

Anal. Calcd. for $C_{13}H_{13}N_3O_5$: C, 53.6; H, 4.5; N, 14.4.
Found: C, 53.4; H, 4.3; N, 14.3.

3-Sydnonylacetylglycine Ethyl Ester (III; R = Gly-OEt): A mixture of glycine ethyl ester hydrochloride (109 mg), triethylamine (0.11 ml), and the pentachlorophenyl ester (III; R = OPCP) (300 mg) in dimethylformamide (1.5 ml) was kept for several days at room temperature, and then diluted with water. The precipitated pentachlorophenol (198 mg; 98%) was separated, and the filtrate saturated with sodium chloride and extracted with ethyl acetate. The dried, combined extracts were evaporated, and the residue treated with ether, whereupon solidification ensued (yield, 93 mg; 54%). The product was recrystallized from ethyl acetate - cyclohexane, m.p. 110 - 110.5°; ν_{max} 3150 (sydnone CH), 1740 and 1725 (very strong, combined CO), 1670 (amide I), 1565 cm^{-1} (amide II); τ 3.03 (sydnone proton), 4.78 (3-methylene proton), 5.90 (ethyl quartet), 6.07 (doublet, glycyl protons), 8.84 (ethyl triplet). The glycine content was 4.44 mmole/g (calcd. 4.37 mmole/g).

Anal. Calcd. for $C_8H_{11}N_3O_5$: C, 41.9; H, 4.8; N, 18.3.
Found: C, 42.2; H, 5.4; N, 18.3.

Attempted preparation of this compound by the carbodiimide procedure used for the benzyl ester gave N-3-sydnonylacetyl N,N'-dicyclohexylurea in 34% yield. The product was recrystallized from ethyl acetate - cyclohexane, m.p. 183 - 184°; ν_{max} 3140 (sydnone CH), 2930 and

2850 (strong, alicyclic CH), 1770 and 1695 (acylamide system), 1750 (shoulder, sydnone CO), 1660 (amide I), 1545 cm^{-1} (amide II); τ 3.02 (sydnone ring proton), 4.65 (3-methylene protons), 7.90 - 9.10 (alicyclic protons). No glycine was detected by amino acid analysis.

Anal. Calcd. for $C_{17}H_{26}N_4O_4$: C, 58.3; H, 7.4; N, 16.0.

Found: C, 58.1; H, 7.6; N, 15.7.

N-3-Sydnonylacetyl-L-phenylalanine (III; R = Phe-OH): L-Phenylalanine (165 mg) was dissolved in 4N NaOH (0.25 ml). Triethylamine (0.14 ml), dimethylformamide (1.0 ml), and chloroform (0.5 ml) were added, followed by the *p*-nitrophenyl ester (III; R = ONP) (265 mg)[9]. The mixture was stirred at room temperature for 24 hours, diluted with chloroform, and extracted with water. Acidification gave the product, which was taken up in ethyl acetate. The compound was finally washed with ether (yield, 191 mg; 66%), and recrystallized from ethanol, m.p. 207.5 - 208.5° decomp.; $[\alpha]_D^{20}$ + 15.0° (c. 0.5; DMF); ν_{max} 3150 (sydnone CH), 1750 - 1660 (strong, broad combined CO), 1550 cm^{-1} (amide II); τ 2.74 (phenyl protons), 3.14 (sydnone ring proton), 4.84 (3-methylene protons), 5.47 (one-proton multiplet), 6.99 (two-proton multiplet). Amino acid analysis gave the phenylalanine content as 4.99 mmole/g (calcd. 5.24 mmole/g).

Anal. Calcd. for $C_{13}H_{13}N_3O_5$: C, 53.6; H, 4.5; N, 14.4.

Found: C, 53.6; H, 4.6; N, 14.2.

Acknowledgments

The author is indebted to Mr. N.M. McKern for technical assistance, to Mr. D.J. Gale for the proton magnetic resonance spectra, and Mr. P.W. Nicholls for the amino acid analyses.

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5. Abbreviations used are:- TMB, 2,4,6-trimethylbenzyl; NB, *p*-nitrobenzyl; NP, *p*-nitrophenyl; PCP, pentachlorophenyl; Bzl, benzyl; Et, ethyl; DMF, dimethylformamide.

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11. The term 3-sydnonyl is used for the radical comprising the sydnone ring (I; R" = H) joined to another moiety R' at the 3-nitrogen atom.

(Received July 31, 1969)