Synthesis of a Benzodiazepine Analogous Sydnotriazepine

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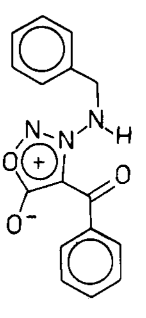
Received September 10, 1988

Starting from 3-benzylamino-4-benzoylsydnone (**1**) acylation to *N*-acetyl (**2a**), *N*-chloroacetyl (**2b**) and *N*-bromoacetyl (**2c**) derivatives was successful. Treatment of **2b** or **2c** with liquid ammonia resulted in cleavage of the *N*-acyl group to give sydnone imine **3** instead of cyclisation to sydnotriazepine **8**. Condensation of **1** with protected glycines **5a-5c** by dicyclohexylcarbodiimide yielded glycineamides **6a**, **6b** and **6c**. Compound **6c** was selectively deprotected and converted to sydnotriazepine **7**, a benzodiazepine analogous sydnotriazepine.

J. Heterocyclic Chem., **26**, 453 (1989).



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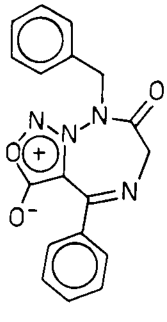

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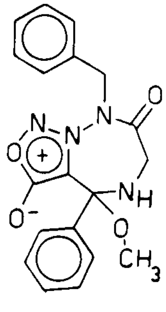

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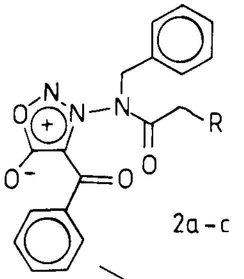
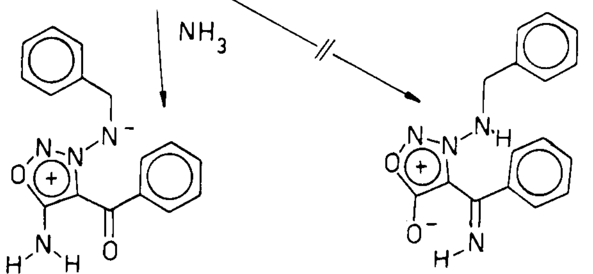


2a - c

	R
2a	H
2b	Cl
2c	Br



3

4

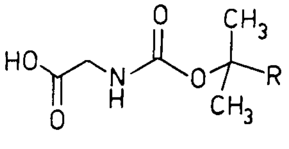
Previously [1] we reported a synthetic approach to 3-amino-4-benzoylsydnones as intermediates for the synthesis of fused 3-aminosydnones. Of special interest seemed to us the use of these intermediates to investigate an access to benzodiazepine analogous substances containing a sydnone ring instead of the usual benzene ring. Up to now, heterocycles like thiophene or pyrrole have been used as benzene ring analogues, and the corresponding substances demonstrate interesting pharmacological effects [2]. Therefore, synthesis of benzodiazepine analogous sydnotriazepines appeared as a rewarding objective for our investigations.

We started our examinations following the classical benzodiazepine synthesis of Sternbach [3]. Thus 3-benzylamino-4-benzoylsydnone **1** was treated with an excess amount of acetic anhydride, chloroacetyl chloride or bromoacetyl bromide in the presence of a catalytical amount of 4-dimethylaminopyridine to give *N*-acetyl (**2a**, 77%), *N*-chloroacetyl (**2b**, 68%) or *N*-bromoacetyl (**2c**, 80%) derivative. However, when equimolar amounts of the acylating agents were used in an inert solvent such as dichloromethane or chloroform, the acylation was not successful.

At 30° the ^{1}H-nmr spectra of **2a**, **2b**, and **2c** showed split signals and geminal coupling due to the acetyl and benzyl protons. If the ^{1}H-nmr spectra were recorded at 70° no splitting and coupling were observed. Obviously, free rotation hindrance of the bulky groups at the exocyclic nitrogen and amide mesomery caused splitting of signals. The ir absorption of the amide carbonyl bond in **2a**, **2b** and **2c** was detected at atypically large wave numbers (~ 1720 cm^{-1}). This location of absorption bands agree rather with that of an imide (~ 1725 cm^{-1}) than with normal amide carbonyl vibrations (1670-1630 cm^{-1}), according to the vinylogous principle. Postulated low basicity of the exocyclic nitrogen, caused by the association of the lone pair to the mesoionic ring [1], was confirmed and drastic formation conditions were explained by spectroscopic properties of **2a**, **2b** and **2c**.

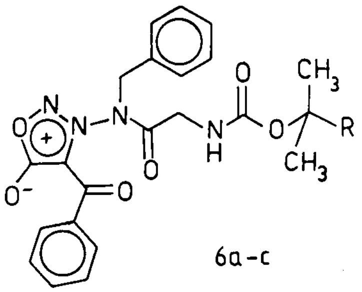
Substitution of the halogen at **2b** or **2c** by an amino group followed by cyclisation should give the desired sydnotriazepine **8**. But reaction of **2b** or **2c** in the classical manner [3] with liquid ammonia caused, in nearly quantitative yield, cleavage of the acyl group and transformation of the sydnone to sydnone imine **3**. The formation of another possible product **4** as not observed. Identification of the reaction product was possible by mass spectrometry, because a prominent fragment ion (m/z = 105, benzoyl cation) could only derive from isomer **3**. Formation of sydnone imine **3** is an unusual reaction within the sydnone series. Of course the scope of this transformation seems to be limited to *N*-acylated-3-aminosydnones, because 3-aminosydnone **1** remained unreacted under such conditions.

After recognizing the impossibility of sydnotriazepine synthesis from intermediates like **2b** or **2c**, an introduction of the nitrogen in one step with the acyl group was tried. Adequate reagents for this purpose are protected glycines like **5a**, **5b** and **5c**. Introduction at the exocyclic nitrogen of **1** was afforded by dicyclohexylcarbodiimide as the condensation agent to give compound **6a** (87%), **6b** (77%) and **6c** (98%) in quite good yields. Spectroscopic properties of **6a**, **6b** and **6c** were equal to those of **2a**, **2b** and **2c**.



5a-c

	R
5a, 6a	CH_3
5b, 6b	CH_2-C≡N
5c, 6c	Biphenyl



6a-c

Now deprotection of glycinamines **6a**, **6b** and **6c** followed by cyclisation to sydnotriazepine **8** should be investigated. Various hydrolysis conditions for protected glycineamides like **6a** (mild acidolysis) and **6b** (mild alkalic cleavage) has been published thus far [4,5]. By testing this approach with **6a** or **6b**, either unreacted starting material remained or cleavage of the whole acyl group at the exocyclic nitrogen was observed yielding **1**. Deprotection of glycineamides such as **6c** was obtained under extremely mild acidic conditions [4,5]. Reacting **6c** in dry acetic acid at 50° followed by chromatographic separation of by-products (derived from the cleaved protection group) with dichloromethane/methanol as the eluent gave the easily crystallizable sydnotriazepine **7** in moderate yield (45%).

Spectroscopic data proved the structure of **7** to be a methanol addition product of **8**. In spite of many tries, intermediate **8** could not be isolated by chromatography from the crude reaction product. Cleavage of methanol from sydnotriazepine **7** by heating in chloroform in the presence of a catalytic amount of acid also failed. We were contented with the isolation of **7**, because **8** seems to be too sensitive to traces of acid.

Further investigations in sydnotriazepine chemistry have been omited, because the lability of the lactam bond in such heterocycles prevent any suitability to pharmacological testing.

EXPERIMENTAL

All melting points were determined on a Kofler melting point apparatus and are uncorrected. The ^{1}H and ^{13}C-nmr were recorded on a Varian EM 390 and a Bruker AC 80, using tetramethylsilane as the internal standard. Infrared spectra were recorded on a Perkin Elmer 298 spectrophotometer. Mass spectra were detected on a MAT CH-7 by Dr. Nikiforov, Institut für Organische Chemie. Microanalyses were determined by Dr. Zak, Institut für Physikalische Chemie.

3-(*N*-Acetyl-*N*-benzylamino)-4-benzoylsydnone (**2a**).

3-Benzylamino-4-benzoylsydnone (**1**) (2 g, 6.8 mmoles) was stirred in acetic anhydride (10 ml) in the presence of a catalytic amount of 4-dimethylaminopyridine for 20 hours at 20°. Excess acetic anhydride was removed by evaporation at reduced pressure. The residue was dissolved in dichloromethane (50 ml), washed with 0.5*N* hydrochloric acid (3 x 50 ml) and saturated sodium bicarbonate solution (3 x 50 ml). The organic layer was dried (sodium sulfate) and evaporated to dryness. Crystallisation from methanol/ethylacetate afforded **2a** (1.76 g, 77%), mp 90°; ^{1}H nmr (deuteriochloroform): δ 7-8 (m, 10H, aromatic-H), 4.6-5.5 (m, 2H, benzylic-H), 2.2 (s, 3H, acetyl-H); ir (potassium bromide): 1787 cm^{-1} (sydnone carbonyl), 1720 cm^{-1} (amide carbonyl), 1650 cm^{-1} (ketone carbonyl); ms: 307 (M$^+$ -NO), 279 (M$^+$ -NO-CO).

Anal. Calcd. for $C_{18}H_{15}N_3O_4$: C, 64.09; H, 4.48; N, 12.46. Found: C, 63.98; H, 4.59; N, 12.26.

3-(*N*-Chloroacetyl-*N*-benzylamino)-4-benzoylsydnone (**2b**).

3-Benzylamino-4-benzoylsydnone (**1**) (2 g, 6.8 mmoles) was stirred in chloroacetyl chloride (10 ml) in the presence of a catalytic amount of 4-dimethylaminopyridine for 20 hours at 60°. Excess chloroacetyl chloride was removed by evaporation at reduced pressure. The residue was dissolved in dichloromethane (50 ml), washed with 0.5*N* hydrochloric acid (3 x 50 ml) and saturated sodium bicarbonate solution (3 x 50 ml). The organic layer was dried (sodium sulfate) and evaporated to dryness. Crystallisation from methanol/ether afforded **2b** (1.71 g, 68%, colourless prisms), mp 68°; ^{1}H-nmr (deuteriochloroform): δ 7-8 (m, 10H, aromatic-H), 5.25, 5.05 (AB-system, 2H, benzylic-H, J = 15 Hz), 4.3, 4.1 (AB-system, 2H, chloroacetyl-H, J = 13 Hz); ir (potassium bromide): 1775 cm^{-1} (sydnone carbonyl), 1725 cm^{-1} (amide carbonyl), 1643 cm^{-1} (ketone carbonyl); ms: m/z 343, 341 (1:3) (M$^+$ -NO); 315, 313 (1:3) (M$^+$ -NO-CO).

Anal. Calcd. for $C_{18}H_{14}ClN_3O_4$: C, 58.15; H, 3.80; N, 11.30; Cl, 9.54. Found: C, 57.81; H, 3.80; N, 11.18; Cl, 9.45.

3-(*N*-Bromoacetyl-*N*-benzylamino)-4-benzoylsydnone (**2c**).

3-Benzylamino-4-benzoylsydnone (**1**) (2 g, 6.8 mmoles) was stirred in bromoacetyl bromide (10 ml) in the presence of a catalytic amount of 4-dimethylaminopyridine for 20 hours at 60°. Excess bromoacetyl bromide was removed by evaporation at reduced pressure. The residue was dissolved in dichloromethane (50 ml), washed with 0.5*N* hydrochloric acid (3 x 50 ml) and saturated sodium bicarbonate solution (3 x 50 ml). The organic layer was dried (sodium sulfate) and evaporated to dryness. Crystallisation from methanol/ether afforded **2c** (2.25 g, 80%, colourless prism), mp 100°; ^{1}H-nmr (deuteriochloroform): δ 7-8 (m, 10H, aromatic-H), 5.2, 5.0 (AB-system, 2H, benzylic-H, J = 15 Hz), 4.05, 3.85 (AB-system, 2H, bromoacetyl-H, J = 12 Hz); ir (potassium bromide): 1785 cm^{-1}, 1775 cm^{-1} (sydnone carbonyl), 1722 cm^{-1} (amide carbonyl), 1643 cm^{-1} (ketone carbonyl); ms: m/z 387, 385 (1:1) (M$^+$ -NO); 359, 357 (1:1) (M$^+$ -NO-CO).

Anal. Calcd. for $C_{18}H_{14}BrN_3O_4$: C, 51.94; H, 3.39; N, 10.10; Br, 19.20. Found: C, 51.92; H, 3.36; N, 10.01; Br, 18.83.

3-Benzylamino-4-benzoylsydnone Imine (**3**).

3-(*N*-Bromoacetyl-*N*-benzyl)amino-4-benzoylsydnone (**2c**) (208 mg, 0.5 mmole) was dissolved in liquid ammonia (20 ml) at −78°. The solution was allowed to warm to room temperature and the remaining yellow crystals were recrystallised from dichloromethane to afford **3** (144 mg, 98%, yellow needles), mp 201-202°; ^{1}H-nmr (acetone-d$_6$): δ 7-8 (m, 10H, aromatic-H), 4.7 (s, 2H, benzylic-H); ^{13}C-nmr (DMSO-d$_6$): δ 163.03 (sydnone imine carbonyl), 160.75 (ketone carbonyl), 138.11, 131.38, 129.98, 128.68, 128.14, 127.98, 127.43, 126.94 (aromatic-C), 94.66 (sydnone imine ring-C), 55.16 (benzylic-C); ir (potassium bromide): 1725 cm^{-1}, 1710 cm^{-1} (sydnone imine), 1630 cm^{-1} (ketone carbonyl); ms: m/z 294 (M$^+$), 264 (M$^+$ -NO), 105 ($C_6H_5C\equiv O^+$).

Anal. Calcd. for $C_{16}H_{14}N_4O_2$: C, 65.30; H, 4.79; N, 19.04. Found: C, 65.15; H, 4.73; N, 18.94.

3-(*N-t*-Butyloxycarbonylaminoacetyl-*N*-benzylamino)-4-benzoylsydnone (**6a**).

Dicyclohexylcarbodiimide (5.16 g, 25 mmoles), *N-t*-butyloxycarbonylglycine (**5a**) (4.38 g, 25 mmoles) and 3-benzylamino-4-benzoylsydnone (**1**) (5 g, 17 mmoles) were suspended in dry THF (100 ml) and stirred in the presence of a catalytic amount of 4-dimethylaminopyridine for 20 hours at 20°. Precipitated dicyclohexylurea was filtered off and excess THF was removed by evaporation at reduced pressure. The residue was dissolved in dichloromethane (50 ml), washed with 0.5*N* (hydrochloric acid) (3 x 50 ml) and saturated sodium bicarbonate solution (3 x 50 ml). The organic layer was dried (sodium sulfate) and evaporated to dryness. Crystallisation from methanol afforded **6a** (6.66 g, 87%), mp 149-150°. ^{1}H nmr (deuteriochloroform): δ 7-8 (m, 10H, aromatic-H), 5.32 (m, 1H, N-H), 5.25, 4.95 (AB-system, 2H, benzylic-H, J = 13 Hz), 4.1 (m, 2H, glycine methylene-H), 1.43 (s, 9H, methyl-H); ^{13}C-nmr (DMSO-d$_6$): δ 180.10 (ketone carbonyl), 168.55 (amide carbonyl), 163.68 (sydnone carbonyl), 155.50 (urethane carbonyl), 135.02, 133.55, 128.41, 128.08 (aromatic-C), 104.95 (sydnone ring-C), 78.40 (glycine methylene-C), 54.02 (benzylic-C), 42.26 (*t*-butyl-C), 27.96 (methyl-C); ir (potassium bromide): 1795 cm^{-1} (sydnone carbonyl), 1734 cm^{-1} (urethane carbonyl), 1700 cm^{-1} (amide carbonyl), 1638 cm^{-1} (ketone carbonyl).

Anal. Calcd. for $C_{23}H_{24}N_4O_6$: C, 61.06; H, 5.35; N, 12.38. Found: C, 61.17; H, 5.41; N, 12.34.

3-[*N*-(2-Cyano-1,1-dimethylethyloxycarbonylaminoacetyl)-*N*-benzylamino]-4-benzoylsydnone (**6b**).

Dicyclohexylcarbodiimide (5.16 g, 25 mmoles), *N*-(2-cyano-1,1-dimethylethyloxycarbonyl)glycine (**5b**) (5 g, 25 mmoles) [6] and 3-benzylamino-4-benzoylsydnone (**1**) (5 g, 17 mmoles) were suspended in dry THF (100 ml) and stirred in the presence of a catalytic amount of 4-dimethylaminopyridine for 20 hours at 20°. Precipitated dicyclohexylurea was filtered off and excess THF was removed by evaporation at reduced pressure. The residue was dissolved in dichloromethane (50 ml), washed with 0.5*N* hydrochloric acid (3 x 50 ml) and saturated sodium bicarbonate solution (3 x 50 ml). The organic layer was dried (sodium sulfate) and evaporated to dryness. Crystallisation from methanol/ether afforded **6b** (6.19 g, 77%), mp 120°; ^{1}H nmr (deuteriochloroform): δ 7-8 (m, 10H, aromatic-H), 5.52 (m, 1H, N-H), 5.25, 4.95 (AB-system, 2H, benzylic-H, J = 14 Hz), 4.1 (m, 2H, glycine methylene-H), 2.93 (s, 2H, cyano methylene-H), 1.6 (s, 6H, methyl-H); ir (potassium bromide): 2260 cm^{-1} (nitrile), 1800 cm^{-1} (sydnone carbonyl), 1730 cm^{-1} (urethane carbonyl), 1700 cm^{-1} (amide carbonyl), 1628 cm^{-1} (ketone carbonyl).

Anal. Calcd. for $C_{24}H_{23}N_5O_6$: C, 60.37; H, 4.86; N, 14.67. Found: C, 60.50; H, 4.88; N, 14.76.

3-[*N*-(1-Biphenyl-1-methylethyloxycarbonylaminoacetyl)-*N*-benzylamino]-4-benzoylsydnone (**6c**).

Dicyclohexylcarbodiimide (10.5 g, 51 mmoles), *N*-(1-biphenyl-1-methylethyloxycarbonyl)glycine (**5c**) (15.96 g, 51 mmoles) [7] and 3-benzylamino-4-benzoylsydnone (**1**) (10 g, 34 mmoles) were suspended in dry THF (200 ml) and stirred in the presence of a catalytical amount of 4-dimethylaminopyridine for 20 hours at 20°. Precipitated dicyclohexylurea was filtered off and excess THF was removed by evaporation at reduced pressure. The residue was dissolved in dichloromethane (150 ml), washed with 0.5*N* hydrochloric acid (3 x 80 ml) and saturated sodium bicarbonate solution (3 x 80 ml). The organic layer was dried (sodium sulfate) and evaporated to dryness. Crystallisation from ether afforded **6c** (19.6 g, 98%), mp 153°; ^{1}H-nmr (deuteriochloroform): δ 7-8 (m, 19H, aromatic-H), 5.45 (t, 1H, N-H, J = 6 Hz), 5.15, 4.85 (AB-system, 2H, benzylic-H, J = 15 Hz), 4.06 (d, 2H, glycine methylene-H, J = 6 Hz), 1.75 (s, 6H, methyl-H); ir (potassium bromide): 1784 cm^{-1} (sydnone carbonyl), 1732 cm^{-1} (urethane carbonyl), 1713 cm^{-1} (amide carbonyl), 1645 cm^{-1} (ketone carbonyl).

Anal. Calcd. for $C_{34}H_{30}N_4O_6$: C, 69.14; H, 5.12; N, 9.49. Found: C, 68.88; H, 5.25; N, 9.56.

8-Benzyl-5,6,7,8-tetrahydro-4-methoxy-7-oxo-4-phenyl-4*H*-[1,2,5]triazepino[1,7-*c*][1,2,3]oxadiazolium-3-olate (**7**).

3-[*N*-(1-Biphenyl-1-methylethyloxycarbonylaminoacetyl)-*N*-benzylamino]-4-benzoylsydnone (**6c**) (2 g, 3.39 mmoles) was dissolved in acetic acid (10 ml) and warmed to 60° in an argon atmosphere for 2 hours. The cooled reaction mixture was poored to aqueous sodium carbonate solution (100 ml) and extracted with dichloromethane (3 x 50 ml). The organic layer was dried (sodium sulfate), concentrated to 50 ml, mixed with methanol (50 ml) and stirred with silica gel (5 g) for 2 hours. Silica gel was removed by filtration, the solvent was evaporated, and the residue crystallised from methanol to yield **7** (550 mg, 45%, yellow crystals), mp 138°; ^{1}H-nmr (deuteriochloroform): δ 7-8 (m, 10H, aromatic-H), 4.7 (s, 2H, benzylic-H), 4.0 (s, 2H, glycine methylene-H), 3.7 (s, 3H, methyl-H); ^{13}C-nmr (DMSO-d$_6$): δ 168.01 (amide carbonyl), 159.73 (sydnone carbonyl), 137.40, 130.68, 129.44, 128.57, 128.35, 128.19, 128.03, 127.87, 127.22, 126.89 (aromatic-C), 109.55 (acetal-C), 95.25 (sydnone ring-C), 54.78 (benzylic-C), 52.23 (methyl-C), 46.22 (glycine methylene-C); ir (potassium bromide): 1760 cm^{-1} (sydnone carbonyl), 1750 cm^{-1} (amide carbonyl); ms: m/z 336 (M$^+$ -NO), 308 (M$^+$ -NO-CO).

Anal. Calcd. for $C_{19}H_{18}N_4O_4$: C, 62.27; H, 4.96; N, 15.29. Found: C, 62.57; H, 4.91; N, 15.51.

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