Synthesis and Antimicrobial Activity of 3-(Substituted-phenyl)-sydnones

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3-(3 or 4-Acetylphenyl)-sydnones **7**, **8** have been synthesized by formation of the glycines **3**, **4**, followed by nitrosation to **5**, **6** and cyclization with acetic anhydride to sydnones. Sydnone derivatives carrying chalcone moieties **15**, **16** were prepared by formation of the chalcone analogues **11**, **12** through condensation of the glycines **3**, **4** with the appropriate aldehydes, followed by the reactions applied for the preparation of **7**, **8**. The sydnone derivatives were screened for antimicrobial activities.

Synthese und antimikrobielle Aktivität von 3-(substituierten-Phenyl) sydnon-Derivaten

3-(3- oder 4-Acetylphenyl)sydnone **7**, **8** wurden aus den Glycin-Derivaten **3**, **4** durch Nitrosieren zu **5**, **6** und Cyclisieren mittels Essigsäureanhydrid aufgebaut. Die Sydnon-Derivate **15**, **16**, die Chalkon-Teile tragen, wurden analog aus den Chalkonen **11**, **12** hergestellt. Die Sydnon-Derivate wurden auf antimikrobielle Aktivität geprüft.

Sydnone derivatives have been evaluated for varied biological properties[1,2]. Several publications have reported the antimicrobial activity of substituted aryl-sydnones[3-5]. Chalcone analogues are known to have antibacterial activity[6,7]. Therefore, we synthesized substituted aryl-sydnones, in addition to a series of compounds containing both sydnone and chalcone moieties.

Chemistry

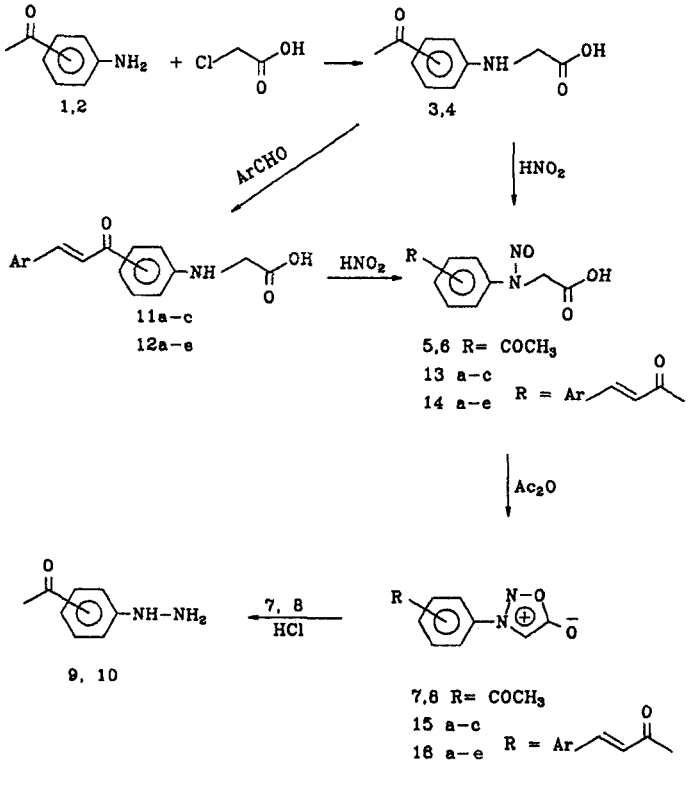
N-(3 or 4-acetylphenyl)-glycine **3**, **4** were obtained by the reaction of neutralized chloroacetic acid with 3 or 4-aminoacetophenone **1**, **2** respectively (Scheme 1). *N*-nitrosation of **3**, **4** with nitrous acid at 0-5°C yielded **5**, **6** which were cyclized to the corresponding sydnones **7**, **8** by acetic anhydride. Sydnones were successfully used as intermediates in the preparation of hydrazine derivatives[2,3,8,9]. Consequently, by subjecting compounds **7**,**8** to acid hydrolysis, 3- and 4-acetylphenylhydrazines **9**, **10** were obtained. Compound **9** was only stable for a few h, while compound **10** was stable for several days. However, it was reported that compound **10** obtained by reduction of *p*-acetylphenyl diazonium chloride was unstable and underwent intermolecular condensation between the NH_2 and CO groups[10].

Sydnone derivatives hybridized with chalcones **15**, **16** were prepared by initial formation of the corresponding chalcones **11**, **12** by base catalyzed reaction of the glycines **3**, **4** with the appropriate aldehydes. Compounds **11**, **12** were then subjected to nitrosation (**13**, **14**), followed by cyclization to the corresponding sydnones **15**, **16**, as described for compounds **7**, **8** (Scheme 1).

Treatment of compound **16d** with 3 Br_2 yielded the tribromo derivative **20** (Scheme 2), in which Br_2 is added to the double bond of the α,β unsaturated ketone moiety and the 4-position of the sydnone nucleus. No bromination occured in the two deactivated aryl nuclei[7,11]. Compound **20** was also indirectly prepared by stepwise pathway: Bromination of **12d** yielded the dibromo derivative **17**, which was subjected to *N*-nitrosation to give **18**, followed by cyclization with acetic anhydride to the sydnone derivative **19**. Reaction of **19** with one equivalent of Br_2 yielded **20**.

Preliminary antimicrobial screening

The antimicrobial activity of the twelve sydnone derivatives **7**, **8**, **15a-c**, **16a-e**, **19**, and **20** was determined by the agar diffusion technique[12]. The organisms tested were *Staphylococcus aureus* (gram positive), *Escherichia coli* (gram negative), and *Candida albicans* (pathogenic fungi). The agar media were inoculated with the test organisms and a solution of the tested compound in DMSO (1 mg/ml) was placed separately in cups (8 mm diameter) in the agar medium. A 0.1% solution of streptomycin was used as a reference. The inhibition zones were measured after 24 h incubation.



Scheme 1: For Ar and a-e see Table 1.
Odd numbered compounds are meta-substituted, while even numbered compounds ara para-substituted.

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Table 1: *N*-[3- or 4-(Substituted cinnamoyl)phenyl]glycines **11a-c**, **12a-e**; *N*-Nitroso-*N*-[3- or 4-(substituted cinnamoyl)phenyl]glycines **13a-c**, **14a-e**, and 3-[3- or 4-(substituted cinnamoyl)phenyl]sydnones **15a-c**, **16a-e**.

Comp. No.	Ar	Yield %	m.p. °C	Molecular Formula	Analysis % (Calcd./Found) C	H	N
11a	4-ClC_6H_4	77	125-7	$C_{17}H_{14}ClNO_3$ (315.7)	64.6 64.8	4.47 4.3	4.4 4.6
11b	4-BrC_6H_4	85	117-8	$C_{17}H_{14}BrNO_3$ (360.2)	56.6 56.7	3.92 4.0	3.8 4.0
11c	4-$NO_2C_6H_4$	88	173-4	$C_{17}H_{14}N_2O_5$ (326.3)	62.5 62.5	4.32 4.6	8.5 8.3
12a	4-ClC_6H_4	75	206-8	$C_{17}H_{14}ClNO_3$ (315.7)	64.6 64.8	4.47 4.3	4.4 4.7
12b	2-BrC_6H_4	65	199-201	$C_{17}H_{14}BrNO_3$ (360.2)	56.6 56.3	3.92 4.1	3.8 3.6
12c	3-$NO_2C_6H_4$	80	213-4	$C_{17}H_{14}N_2O_5$ (326.3)	62.5 62.3	4.32 4.5	8.5 8.3
12d	4-$NO_2C_6H_4$	85	208-10	$C_{17}H_{14}N_2O_5$ (326.3)	62.5 62.6	4.32 4.6	8.5 8.4
12e	4-$CH_3OC_6H_4$	56	170-2	$C_{18}H_{17}NO_4$ (311.3)	69.4 69.2	5.51 5.8	4.5 4.5
13a	4-ClC_6H_4	55	112-4	$C_{17}H_{13}ClN_2O_4$ (344.7)	59.2 59.0	3.80 4.1	8.1 8.3
13b	4-BrC_6H_4	65	103-5	$C_{17}H_{13}BrN_2O_4$ (389.2)	52.4 52.6	3.37 3.4	7.2 7.5
13c	4-$NO_2C_6H_4$	70	175-7	$C_{17}H_{13}N_3O_6$ (355.3)	57.4 57.7	3.69 3.9	11.8 11.9
14a	4-ClC_6H_4	55	175-7	$C_{17}H_{13}ClN_2O_4$ (344.7)	59.2 59.5	3.80 4.1	8.1 8.3
14b	2-BrC_6H_4	50	75-7	$C_{17}H_{13}BrN_2O_4$ (389.2)	52.4 52.3	3.37 3.5	7.2 7.5
14c	3-$NO_2C_6H_4$	65	185-7	$C_{17}H_{13}N_3O_6$ (355.3)	57.4 57.7	3.69 3.8	11.8 11.9
14d	4-$NO_2C_6H_4$	72	180-2	$C_{17}H_{13}N_3O_6$ (355.3)	57.4 57.4	3.69 3.8	11.8 11.7
14e	4-$CH_3OC_6H_4$	62	156-8	$C_{18}H_{16}N_2O_5$ (340.3)	63.5 63.7	4.74 4.8	8.2 8.4

All the tested compounds exhibited high activity against *S. aureus*, especially, **12d**, **19**, and **20** (inhibition zones 18-25 mm). Only compounds **19** and **20** show low activity against *E. coli* (inhibition zones 14 mm). No significant inhibition was shown by any of the tested compounds against *C. albicans*.

In conclusion, all the tested compounds were active against gram positive bacteria, especially, the sydnone derivatives combined with the chalcone moieties. Compounds with nitro and bromo substitution were weakly active against gram negative bacteria. No activity was observed against *C. albicans*. However, none of the tested compounds showed superior activity than the reference streptomycin.

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Experimental Part

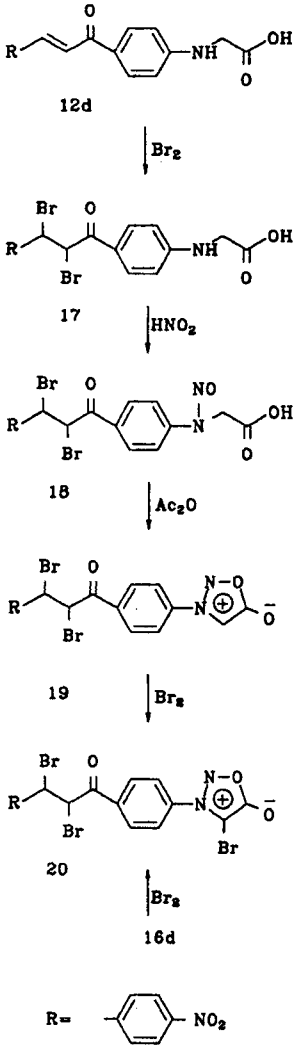
Melting points: uncorrected, Hiene melting point apparatus.- IR spectra (KBr, $\tilde{\nu}$ in cm^{-1}): Pye-Unicam SP 1000 spectrophotometer.- ^{1}H-NMR: Varian Jemini-200 and Joel FX 90Q spectrometers, TMS as internal standard, DMSO-D_6, chemical shift: δ (ppm).- Analytical data: Microanalytical Unit, Faculty of Science, Cairo University, Egypt.

N-(3-Acetylphenyl)glycine (**3**)

3-Aminoacetophenone (**1**) (13.5 g, 0.1 mole) was dissolved in hot water (500 ml) and neutralized chloroacetic acid (10.5 g, 0.1 mole) was then

Table 1: Cont.

Comp. No.	Ar	Yield %	m.p. °C	Molecular Formula	Analysis % (Calcd./Found) C	H	N
15a	$4\text{-}ClC_6H_4$	78	193-4	$C_{17}H_{11}ClN_2O_3$ (326.7)	62.4 62.7	3.39 3.5	8.5 8.7
15b	$4\text{-}BrC_6H_4$	70	182-3	$C_{17}H_{11}BrN_2O_3$ (371.2)	55.0 55.2	2.99 3.1	7.5 7.7
15c	$4\text{-}NO_2C_6H_4$	70	220-2	$C_{17}H_{11}N_3O_5$ (337.3)	60.5 60.3	3.29 3.4	12.4 12.6
16a	$4\text{-}ClC_6H_4$	68	125-7	$C_{17}H_{11}ClN_2O_3$ (326.7)	62.4 62.5	3.39 3.4	8.5 8.7
16b	$2\text{-}BrC_6H_4$	60	112-4	$C_{17}H_{11}BrN_2O_3$ (371.2)	55.0 54.8	2.99 3.2	7.5 7.6
16c	$3\text{-}NO_2C_6H_4$	68	228-30	$C_{17}H_{11}N_3O_5$ (337.3)	60.5 60.7	3.29 3.5	12.4 12.1
16d	$4\text{-}NO_2C_6H_4$	74	206-8	$C_{17}H_{11}N_3O_5$ (337.3)	60.5 60.5	3.29 3.5	12.4 12.4
16e	$4\text{-}CH_3OC_6H_4$	64	170-3	$C_{18}H_{14}N_2O_4$	67.0 66.8	4.38 4.5	8.6 8.8



Scheme 2

added under stirring. The mixture was heated under reflux for 6 h. After cooling, the solid separated was crystallized from acetic acid, yield 83%, m.p. 134-136°C.- IR: 3420 (NH), 2900 (CH), 1740 (C=O), 1650 (COO).- ^{1}H-NMR: 2.7 (s, 3H, CH_3), 4.0 (s, 2H, CH_2), 6.95 (v.br.s., 1H, OH, D_2O exchange), 7.35 (br.s., 4H, Ar-H).- $C_{10}H_{11}NO_3$ (193.2) Calcd. C 62.2 H 5.74 N 7.3 Found C 62.2 H 5.6 N 7.5.

N-(4-Acetylphenyl)glycine (**4**)

4-Aminoacetophenone (**2**) (13.5 g, 0.1 mole) dissolved in water (500 ml) and neutralized chloroacetic acid (63.0 g, 0.6 mole) were reacted together as mentioned under **3** and by applying 40 h reflux time. The solid separated was recrystallized from acetic acid, yield 76%, m.p. 217-219°C.- IR: 3390 (NH), 2910 (CH), 1725 (C=O), 1600 (COO).- ^{1}H-NMR: 2.4 (s, 3H, CH_3), 3.95 (s, 2H, CH_2), 6.65 (d, J = 9 Hz, 2H, Ar-H), 6.8 (v.br.s., 1H, OH, D_2O exchange), 7.75 (d, J = 9 Hz, 2H, Ar-H).- $C_{10}H_{11}NO_3$ (193.2) Calcd. C 62.2 H 5.74 N 7.3 Found C 62.3 H 5.8 N 7.4.

N-Nitroso-N-(acetylphenyl)glycines **5, 6**

Method **A**

The glycine **3** or **4** (1.93 g, 0.01 mole) in glacial acetic acid (20 ml) was cooled to 0-5°C. $NaNO_2$-solution (0.7 g in 10 ml water) was added portionwise over a period of 30 min during stirring. The stirring was continued for 1 h. The solid separated was washed several times with cold water, dried and crystallized from methanol-water. **5**: yield 82%, m.p. 133-135°C. **6**: yield 60%, m.p. 157-159°C.

Method **B**

A mixture of **3** or **4** (1.93 g, 0.01 mole) in methanol (10 ml) and 18% HCl (20 ml) was cooled to 0-5°C. $NaNO_2$-solution (0.7 g in 10 ml water) was added portionwise, then it was continued as mentioned in method **A**.

5: yield 70%.- IR: 2910 (CH), 1725 (C=O), 1600 (COO), 1450 (NO).- ^{1}H-NMR: 2.85 (s, 3H, CH_3), 4.97 (s, 2H, CH_2), 7.5-7.9 (m, 4H, Ar-H).- $C_{10}H_{10}N_2O_4$ (222.2) Calcd. C 54.0 H 4.54 N 12.6 Found C 54.3 H 4.3 N 12.5.

6: yield 73%.- IR: 2910 (CH), 1725 (C=O), 1600 (COO), 1430 (NO).- ^{1}H-NMR: 2.65 (s, 3H, CH_3), 4.85 (s, 2H, CH_2), 7.85 (d, J = 9 Hz, 2H, Ar-H), 8.15 (d, J = 9 Hz, 2H, Ar-H).- $C_{10}H_{10}N_2O_4$ (222.2) Calcd. C 54.0 H 4.54 N 12.6 Found C 54.2 H 4.3 N 12.8.

3-(Acetylphenyl)sydnones **7, 8**

The nitroso compound **5** or **6** (0.222 g, 0.001 mole) was heated with acetic anhydride (10 ml) on the water bath for 30 min. The solvent was removed i.vac. and the residue left was triturated with cold water and crystallized from methanol.

7: yield 75%, m.p. 141-143°C.- IR: 3130 (CH-syd.), 1780 (CO-syd.), 1725 (CO), 1650 (N-N).- ^{1}H-NMR: 2.6 (s, 3H, CH_3), 7.55 (s, 1H, CH-syd.), 7.7 (t, J = 9 Hz, 1H, Ar-H), 8.1 (m, 2H, Ar-H), 8.3 (br.s., 1H, Ar-H).- $C_{10}H_8N_2O_3$ (204.2) Calcd. C 58.8 H 3.95 N 13.7 Found C 59.0 H 4.2 N 13.8.

8: yield 70%, m.p. 177-178°C.- IR: 3120 (CH-syd.), 2920 (CH), 1780 (CO-syd.), 1725 (CO), 1650 (N-N).- ^{1}H-NMR: 2.7 (s, 3H, CH_3), 7.9 (s, 1H, CH-syd.), 8.15 (d, J = 9 Hz, 2H, Ar-H), 8.25 (d, J = 9 Hz, 2H, Ar-H).- $C_{10}H_8N_2O_3$ (204.2) Calcd. C 58.8 H 3.95 N 13.7 Found C 59.0 H 4.2 N 13.5.

3- or 4-Acetylphenylhydrazines **9, 10**

The sydnone **7** or **8** (0.2 g, 0.001 mole) was heated in 18% HCl (20 ml) on a water bath for 2 h. After cooling, the solution was basified with ammonia and the solid separated was extracted with ether. Ether was evaporated and the residue was collected without crystallization.

9: yield 45%, m.p. 85-87°C (dec.).- IR: 3450 (NH), 3320 (NH_2), 1725 (CO).- $C_8H_{10}N_2O$ (150.2) Calcd. C 63.9 H 6.7 Found C 63.5 H 6.9.

10: yield 58%, m.p. 96-98°C.- IR: 3450 (NH), 3300 (NH_2), 1725 (CO).- ^{1}H-NMR: 2.5 (s, 3H, CH_3), 3.7 (br.s., 3H, NH, NH_2, D_2O exchange), 7.3-7.9 (m, 4H, Ar-H).- $C_8H_{10}N_2O \cdot 1/2\ H_2O$ (159.2) Calcd. C 60.3 H 6.96 N 17.6 Found C 60.0 H 6.7 N 17.9.

N-[4-(Substitutedcinnamoyl)phenyl]glycines **11a-c, 12a-e**

To a mixture of compound **3** or **4** (1.35 g, 0.01 mole) and the appropriate aldehyde (0.01 mole) in ethanol (20 ml), sufficient volume of 3% alcoholic NaOH was added to render the solution alkaline. The mixture was stirred at room temp. for 2 h. After neutralization with 10% HCl, the solid separated was recrystallized from methanol (nitro derivatives were recrystallized from acetic acid); Table 1.

11: IR: 3400 (NH); 2940 (CH); 1725 (CO); 1650 (CH=CH); 1600 (COO); 1540; 1380 (NO_2, for **11c**).- ^{1}H-NMR: **11a**: 3.80 (s, 2H, CH_2), 4.2 (br.s., 1H, NH, D_2O exchange), 6.8 (d, J = 12 Hz, 1H, CHCO), 7.6-8.1 (m, 9H, Ar-H, Ar-CH=).- **11c**: 3.85 (s, 2H, CH_2), 4.1 (br.s., 1H, NH, D_2O exchange), 7.2 (d, J = 12 Hz, 1H, CHCO), 7.7-8.3 (m, 9H, Ar-H, Ar-CH=).- **12**: IR: 3400 (NH); 2940 (CH); 1725 (CO); 1650 (CH=CH); 1600 (COO); 1540; 1380 (NO_2, for **12c, 12d**).- ^{1}H-NMR: **12a**: 3.7 (s, 2H, CH_2), 4.1 (br.s., 1H, NH, D_2O exchange), 6.65 (d, J = 12 Hz, 1H, CHCO), 7.4-8.15 (m, 8H, Ar-H), 8.35 (d, J = 13.5 Hz, 1H, Ar-CH=).- **12d**: 3.75 (s, 2H, CH_2), 4.3 (br.s., 1H, NH, D_2O exchange), 6.65 (d, J = 12 Hz, 1H, CHCO), 7.5-8.25 (m, 9H, Ar-H, Ar-CH=).- **12e**: 3.5 (s, 2H, CH_2), 3.9 (s, 3H, CH_3), 4.6 (br.s., 1H, NH, D_2O exchange), 6.2 (hump, 1H, OH, D_2O exchange), 6.6 (d, J = 12 Hz, 1H, CHCO), 7.1-8.15 (m, 9H, Ar-H, Ar-CH=).

N-Nitroso-N-[4-(substituted cinnamoyl)phenyl]glycines **13a-c, 14a-e**

Method **A** and **B** applied for the preparation of **5** and **6** were used for the nitrosation of compounds **11a-c** and **12a-e**, respectively. All products were recrystallized from ethanol; Table 1.- **13**: IR: 2940 (CH); 1725 (CO); 1650 (CH=CH); 1600 (COO); 1450 (NO); 1050 (N-N); 1540; 1380 (NO_2, for **13c**).- ^{1}H-NMR: **13a**: 4.85 (s, 2H, CH_2), 7.45 (d, J = 12 Hz, 1H, CHCO), 7.75-8.3 (m, 9H, Ar-H, Ar-CH=).- **13c**: 4.85 (s, 2H, CH_2), 7.75-8.45 (m, 10 H, Ar-H, CH=CH).- **14**: IR: 2940 (CH); 1725 (CO); 1650 (CH=CH); 1600 (COO); 1450 (NO); 1050 (N-N); 1540; 1380 (NO_2, for **14c, 14d**).- ^{1}H-NMR: **14a**: 4.85 (s, 2H, CH_2), 6.7 (d, J = 12 Hz, 1H, COCH), 7.5-8.34 (m, 10 H, Ar-H, Ar-CH=).- **14d**: 4.85 (s, 2H, CH_2), 6.7 (d, J = 12 Hz, 1H, COCH), 7.7-8.4 (m, 9H, Ar-H, Ar-CH=).- **14e**: 3.9 (s, 3H, CH_3), 4.8 (s, 2H, CH_2), 6.7 (d, J = 12 Hz, 1H, CHCO), 7.2-8.15 (m, 9H, Ar-H, Ar-CH=).

3-[4-(Substitutedcinnamoyl)phenyl]sydnones **15a-c, 16a-e**

The method adopted for the preparation of the compounds **7** and **8** was applied. The products were crystallized from ethanol, Table 1.- **15**: IR: 3130 (CH-syd.); 2940 (CH); 1780 (CO-syd.); 1725 (CO); 1650 (CH=CH); 1540; 1380 (NO_2, for **15c**).- ^{1}H-NMR: **15a**: 7.45-8.75 (m, 11 H, CH-syd., CH=CH, Ar-H).- **15c**: 7.8 (s, 1H, CH-syd.), 7.85-8.65 (m, 10 H, CH=CH, Ar-H).- **16**: IR: 3130 (CH-syd.); 2940 (CH); 1780 (CO-syd.); 1725 (CO); 1650 (CH=CH); 1540; 1380 (NO_2, for **16c, 16d**).- ^{1}H-NMR: **16a**: 7.35 (s, 1H, CH-syd.), 7.45-8.5 (m, 10 H, Ar-H).- **16d**: 7.8 (s, 1H, CH-syd.), 7.9-8.6 (m, 10 H, CH=CH, Ar-H).- **16e**: 3.9 (s, 3H, CH_3), 7.2-8.4 (m, 11 H, CH-syd., CH=CH, Ar-H).

N-[4-[3-(4-Nitrophenyl)-2,3-dibromopropionyl]phenyl]glycine **(17)**

To **12d** (0.33 g, 0.001 mole) in acetic acid (10 ml), Br_2 (0.32 g, 0.002 mole) in acetic acid (5 ml) was added dropwise at room temp. with stirring. The mixture was left overnight and the solid separated was recrystallized from acetic acid, yield 65%, m.p. 196-198°C.- IR: 3410 (NH), 2920 (CH), 1725 (CO), 1600 (COO), 1540, 1380 (NO_2).- ^{1}H-NMR: 3.7 (s, 2H, CH_2), 4.2 (m, 1H, NH, D_2O exchange), 5.75 (d, J = 12 Hz, 1H, CHCO), 6.65 (d, J = 13 Hz, 1H, Ar-CHBr), 7.5 (d, J = 9 Hz, 2H, Ar-H), 7.85 (d, J = 9 Hz, 2H, Ar-H), 8.25-8.45 (m, 4H, Ar-H).- $C_{17}H_{14}Br_2N_2O_5$ (486.1) Calcd. C 42.0 H 2.90 N 5.76 Found C 41.7 H 3.1 N 5.9.

N-Nitroso-N-[4-[3-(4-nitrophenyl)-2,3-dibromopropionyl]phenyl]glycine **(18)**

17 (0.486 g, 0.001 mole) was subjected to nitrosation (cf. **12**). Crystallization from acetic acid, yield 55%, m.p. 180-182°C.- IR: 2920 (CH), 1725 (CO), 1600 (COO), 1450 (NO), 1040 (N-N).- ^{1}H-NMR: 4.85 (s, 2H, CH_2), 4.2 (br.s., 1H, NH, D_2O exchange), 5.8 (d, J = 12 Hz, 1H, CHCO), 6.70 (d, J = 13 Hz, 1H, Ar-CHBr), 7.6-8.5 (m, 8H, Ar-H).- $C_{17}H_{13}Br_2N_3O_6$ (515.1) Calcd. C 39.6 H 2.54 N 8.2 Found C 39.8 H 2.8 N 7.8.

3-[4-[3-(4-Nitrophenyl)-2,3-dibromopropionyl]phenyl]sydnone **(19)**

18 was treated with acetic anhydride (0.515 g, 0.001 mole) as described for the preparation of **15** and **16**. The product was crystallized from ethanol, yield 53%, m.p. 195-197°C.- IR: 3130 (CH syd.), 2940 (CH), 1780 (CO syd.), 1725 (CO), 1545, 1380 (NO_2).- ^{1}H-NMR: 6.05 (d, J = 12 Hz, 1H, CHCO), 7.1-8.5 (m, 10H, CH-syd., Ar-H, Ar-CHBr).- $C_{17}H_{11}Br_2N_3O_5$ (497.1) Calcd. C 41.1 H 2.23 N 8.45 Found C 40.8 H 2.3 N 8.3.

4-Bromo-3-[4-[3-(4-nitrophenyl)-2,3-dibromopropionyl]phenyl]sydnone **(20)**

Method **A**

To **19** (0.497 g, 0.001 mole) in ethanol (15 ml) and $NaHCO_3$ (0.5 g, in 10 ml of water) Br_2 (0.159 g, 0.001 mole) in ethanol (10 ml) was added during stirring at room temp. Stirring was continued for 1 h, then the mixture was poured onto water and the solid separated was crystallized from ethanol, yield 58%.

Method **B**

To a suspension of **16d** (0.337 g, 0.001 mole) in acetic acid (15 ml) was added sodium acetate (5 g) at room temp. The mixture was cooled in ice

and Br_2 (0.48 g, 0.003 mole) in acetic acid (15 ml) was added dropwise with stirring. Stirring was continued for 2 h and the mixture kept overnight. Then it was diluted with water and the precipitate was crystallized from ethanol, yield 53%; m.p. 133-135°C.- IR: 2940 (CH), 1785 (CO syd.), 1725 (CO), 1540, 1380 (NO_2).- ^{1}H-NMR: 6.0 (d, J = 12 Hz, 1H, CHCO), 7.4-8.55 (m, 9H, Ar-H, Ar-CHBr).- $C_{17}H_{10}Br_3N_3O_5$ (576.0) Calcd. C 35.5 H 1.75 N 7.3 Found C 35.7 H 2.0 N 7.3.

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