Synthesis of New 3-(Phenoxyphenyl)sydnones

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The title compounds were prepared by dehydrocyclization of corresponding substituted *N*-nitrosoglycines obtained from isomeric *o*-, *m*- and *p*-aminodiphenyl ether with ethyl bromoacetate and subsequent nitrosation of the intermediate *N*-arylsubstituted glycines.

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Since their first synthesis [1] sydnones have received much attention and have been reviewed by several authors [2]. Many of substituted sydnones and their derivatives have proved to possess valuable biological activity [3] and their pharmacological activity in some instances [3e] was found high enough for practical purposes. Among others, a number of cephalosporylsydnone derivatives has been prepared [4]. In an effort to prepare new sydnones of potential pharmacological activity, especially the combination of the sydnone moiety with some modern antibiotics as also some thyroxine-like compounds, we turned our attention to the preparation of phenoxy-substituted 3-phenylsydnones as a model reaction. Various phenyl-group substituted 3-phenylsydnones have been reported but there are not many examples with an etheral bond included.

In the present paper we wish to report preparation and identification of isomeric *o*-, *m*- and *p*-(3-phenoxyphenyl)-sydnones [5]. As the method of preparation we used a cyclodehydratation of α-aminoacid *N*-nitroso derivatives, the method which remains the sole useful synthetic route for preparation of sydnones since Earl and Mackney's synthesis of 3-phenylsydnone [1].

Isomeric phenoxyphenylglycines **IIa-c** were prepared by the reaction of 2-, 3- or 4-aminodiphenyl ether [7] with ethyl bromoacetate and subsequent alkaline hydrolysis [8] of esters **Ia-c** (Table I). Nitrosation of **Ia-c** according to the method of Eade and Earl [9] yielded *N*-nitroso-*N*-(*o*-, *m*- or *p*-phenoxy)phenylglycines **IIIa-c** [11], which were cyclized without previous isolation. The cyclodehydratation to sydnones **IVa-c** (Table II) was performed with acetic anhydride.

The light-sensitive crystalline compounds were identified by uv, ir and nmr spectra showing characteristics presented in Table II. The uv spectral data demonstrated the hypsochromic displacement of the absorption maxima of the phenoxy substituted compounds in comparison to the unsubstituted 3-phenylsydnone (λ max 310 nm) [12]. The phenyl group in position 3 of the sydnone ring is shown to possess a polar effect and a resonance interaction with the sydnone ring [12c]. In our examples the phenoxy group apparently diminishes the second one making plausible the highest effect for *para*-, **IVc**, and the smallest for *meta*-substitution, **IVb**. In the ir spectrum the very strong carbonyl stretching band falls in the range of 1736 and 1754 cm^{-1}. The proton nmr spectra of all three isomers taken in deuteriochloroform show a characteristic and clearly distinguishable singlet of the proton on the sydnone ring at 6.70, 6.75 and 6.93 ppm, respectively. Phenyl hydrogens are shifted downfield and appear in the range 6.9 and 7.7 ppm.

Scheme I

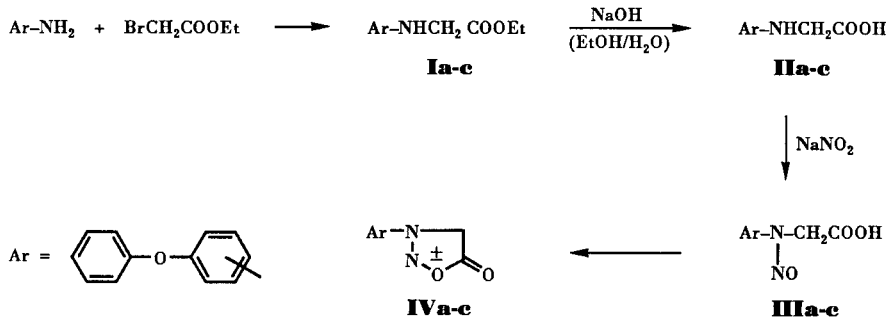
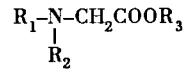


Table I

Phenoxyphenylglycines IIa-c, their Esters **Ia-c** and Nitrosoderivatives **IIIb-c**

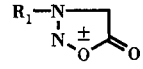


No	R_1	R_2	R_3	Yield %	Mp °C	Molecular Formula	Analysis %C	Calcd./Found %H	%N
Ia	2-C_6H_5-O-C_6H_4	H	C_2H_5	70	56-57	$C_{16}H_{17}NO_3$	70.83	6.32	5.16
							71.09	6.22	4.96
Ib	3-C_6H_5-O-C_6H_4	H	C_2H_5	51	43-44	$C_{16}H_{17}NO_3$	70.83	6.32	5.16
							71.12	6.29	5.09
Ic	4-C_6H_5-O-C_6H_4	H	C_2H_5	81	46-47	$C_{16}H_{17}NO_3$	70.83	6.32	5.16
							70.77	6.36	5.05
IIa	2-C_6H_5-O-C_6H_4	H	H	90	134-135	$C_{14}H_{13}NO_3$	69.12	5.39	5.76
							69.35	5.29	5.57
IIb	3-C_6H_5-O-C_6H_4	H	H	95	104-108	$C_{14}H_{13}NO_3$	69.12	5.39	5.76
							69.21	5.47	5.66
IIc	4-C_6H_5-O-C_6H_4	H	H	84	120-123	$C_{14}H_{13}NO_3$	69.12	5.39	5.76
							69.39	5.62	5.70
IIIb	3-C_6H_5-O-C_6H_4	NO	H	[a]	93-94 dec	$C_{14}H_{12}N_2O_4$	61.76	4.44	10.29
							62.00	4.47	10.08
IIIc	4-C_6H_5-O-C_6H_4	NO	H	[a]	98 dec	$C_{14}H_{12}N_2O_4$	61.76	4.44	10.29
							61.79	4.47	10.10

[a] Used in the cyclization step without isolation [11].

Table II

Phenoxyphenylsydones **IVa-c**



No	R_1	Yield %	Mp °C	Molecular Formula	Analysis %C	Calcd./Found %H	%N	UV [a] λ max (log ε)	IR [b] ν CO	NMR [c,d]
IVa	2-C_6H_5-O-C_6H_4	84	113-114 dec	$C_{14}H_{10}NO_3$	66.14	3.96	11.02	298 (3.91)	1736	6.93
					66.21	3.73	11.21			
IVb	3-C_6H_5-O-C_6H_4	84	109-110	$C_{14}H_{10}NO_3$	66.14	3.96	11.02	305 (3.83)	1739	6.75
					66.42	3.78	11.26			
IVc	4-C_6H_5-O-C_6H_4	76	155-157	$C_{14}H_{10}NO_3$	66.14	3.96	11.02	285 (4.13)	1754	6.70
					66.44	4.06	11.07			

[a] In ethanol. [b] In potassium bromide discs. The value given in cm^{-1}. [c] In deuteriochloroform. Chemical shift given in ppm (δ) relative to internal TMS. [d] Sydnone ring protons.

EXPERIMENTAL

The aminodiphenyl ethers were prepared by reduction of the corresponding nitrodiphenyl ethers [8]. Only general methods used will be described in this section. Data concerning individual compounds are tabulated. The melting points are uncorrected and were determined by the capillary method. Ultraviolet spectra were recorded on a Hitachi-Perkin-Elmer Model 124 double beam spectrophotometer. Infrared spectra were taken in potassium bromide pellets with a Perkin-Elmer 297 Infracord spectrophotometer. Proton nmr spectra were obtained using a Varian EM-360 spectrometer with tetramethylsilane as internal standard.

2-, 3- and 4-Phenoxyphenylglycines. **IIa-c.**

To the mixture of 2-, 3- or 4-aminodiphenyl ether (3.7 g, 0.02 mole) and an equimolar quantity of ethyl bromoacetate in dry ethanol (10 ml), 0.04 mole of freshly dried sodium acetate was added and the mixture was heated under reflux for 4-5 hours. The mixture was diluted with water (10 ml). After standing over-

night in the refrigerator crystalline esters **Ia-c** were obtained and purified by recrystallization from ethanol.

The alkaline solution obtained on boiling **Ia-c** (0.02 mole) with sodium hydroxide (0.03 mole) in 20 ml of ethanol/water 1:10 for 0.5 hour was cooled and acidified with hydrochloric acid. Pure products **IIa-c** (Table I) were obtained by recrystallization from either ethanol for **IIb,c** or from benzene for **IIa**.

3-(2-, 3- and 4-Phenoxyphenyl)sydnones **IVa-c**.

To a suspension of the corresponding phenoxyphenylglycines **IIa-c** (0.005 mole) in diluted acetic acid (1:1) a solution of sodium nitrite (0.0055 mole) was added at 0-3°. The mixture was stirred at this temperature for 3 hours and the *N*-nitroso-derivative obtained was extracted into benzene. The benzene solutions were dried over anhydrous magnesium sulphate.

To the dry crude benzene solution of *N*-nitroso-derivatives **IIIa-c** [10] an excess of acetic anhydride was added and refluxed for 2 hours. The reaction mixture was triturated with water, neutralized with 5% sodium carbonate and washed with water. The solvent from the benzene solution, dried over magnesium sulphate, was evaporated, yielding crystalline sydnones **IVa-c**. Pure compounds were obtained by recrystallization from diluted methanol (1:1) (Table II).

Acknowledgement.

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REFERENCES AND NOTES

[1] J. C. Earl and A. W. Mackney, *J. Chem. Soc.*, 899 (1935).

[2a] W. Baker and W. D. Ollis, *Quart. Rev. (London)*, **11**, 15 (1957); [b] F. H. C. Stewart, *Chem. Rev.*, **64**, 129 (1964); [c] M. Ohta and H. Kato, Non-benzenoid Aromatics, Vol **1**, Academic Press, New York 1969, p 117; [d] W. D. Ollis and C. A. Ramsden, *Adv. Heterocyclic Chem.*, **19**, 1 (1976); [e] C. G. Newton and C. A. Ramsden, *Tetrahedron*, **38**, 2965 (1982).

[3] See *e.g.* [a] *loc. cit.* [2b] , p 142; [b] L. B. Kier and E. B. Roche, *J. Pharm. Sci*, **56**, 149 (1967); [c] *loc. cit.* [2d], p 99; [d] Sh. B. Havanur, B. V. Badani and G. S. Puranik, *J. Heterocyclic Chem.*, **17**, 1049 (1980); [e] M. Bös and W. Fleischhacker, *Pharm. Unserer Zeit*, **13**, 51 (1984).

[4] See *e.g.* [a] M. Finland, C. Garner, C. Wilcox and D. L. Sabath, *Antimicrob. Agents Chemother.*, **9**, 11 (1976); *Chem. Abstr.*, **86**, 130823 (1976); [b] D. A. Berges, German Offen. 2558022 (1976); *Chem. Abstr.*, **86**, 72667 (1977); [c] *ibid.*, U. S. Patent 4093723 (1978); *Chem. Abstr.*, **89**, 180025 (1978); [d] *ibid.* U. S. Patent 4159373 (1979); *Chem. Abstr.*, **91**, 175374 (1979).

[5] One isomer *i.e.* 3-(4-phenoxy)phenylsydnone was mentioned among other variously substituted sydnones in the paper dealing with testing their inflamatory capacity [6], but reported details about the preparation and physical properties were scarce.

[6] H. Wagner and J. B. Hill, *J. Med. Chem.*, **17**, 1337 (1974).

[7] Aminodiphenylethers were known compounds [8].

[8] C. N. Suter, *J. Am. Chem. Soc.*, **51**, 2583 (1929).

[9] V. G. Jaschunskii, V. F. Vasilieva and N. Scheinker, *Zh. Obshch. Khim.*, **29**, 2715 (1959).

[10] R. A. Eade and J. C. Earl, *J. Chem. Soc.*, 2307 (1948).

[11] Pure **IIIb** and **IIIc** were obtained by evaporation of benzene and recrystallization of the residue from benzene/petroleum ether.

[12a] E. V. Borisov, L. E. Holodov and V. G. Jaschunskii, *Zh. Org. Khim.*, **4**, 2034 (1968); [b] J. M. Tien and J. M. Hunsberger, *J. Am. Chem. Soc.*, **83**, 178 (1961); [c] P. Zuman and J. Voaden, *Tetrahedron*, **16**, 130 (1961); [d] P. M. Weintraub and R. E. Bambury, *Tetrahedron Letters*, 579 (1969).