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Synthesis and Radioprotective Properties of Chlorinated *o*-Dialkylaminopropionamido- and *o*-Dialkylaminopropylaminodiphenyl Sulphide Derivatives

ALFRED BURGER, JAMES G. BEASLEY and RICHARD B. MARGERISON

Department of Chemistry, University of Virginia

and

JOHN DOULL, VIVIAN PLZAK and JOHN F. NOBLE

U.S. Air Force Radiation Laboratory, University of Chicago

1. Introduction

One of the most time-honoured methods of varying the structure of a biologically active prototype compound consists of transforming aliphatic moieties into cyclic structures, and vice-versa. In many instances such ring openings or ring closures have provided analogues in which the preponderance of overlapping biological properties has been shifted, and side-effects have either been minimized or else have become the dominant characteristics of the new compound. The varied and useful biological activities of 10-dialkylaminoalkylphenothiazine derivatives have led several investigators to study analogues with the thiazine ring 'opened', both among diphenylamine and diphenyl sulphide derivatives. The first diethylaminoalkylaminodiphenyl sulphides were described in a patent by Pützer and Schönhöfer[1] who reported that some of them possessed amebicidal and anaesthetic properties. In another series of similar 2-substituted derivatives and the corresponding 2-dialkylaminoacyl diphenyl sulphides,[2,3] 2-(2-dimethylaminopropylamino) diphenyl sulphide prevented nicotine-caused tremors to the same extent as the cyclic analogue, 10-(2-diethylaminopropylamino)phenothiazine but lacked the antihistaminic properties of this drug.[3] A similar decrease of

antihistaminic effects without modification of parasympatholytic activity was also observed for 2-dimethylaminopropionamidodiphenyl sulphide while 2-(2-dimethylaminoethylamino)diphenyl sulphide retained some antihistaminic activity. This seems to indicate that the separation of the two nitrogen atoms by a three-carbon chain parallels the physiological behaviour of similar phenothiazines where 10-(3-dialkylaminopropyl) derivatives exhibit antiemetic and other CNS activities which are of minor significance in most 10-(2-dialkylaminoethyl)phenothiazines.

With this in mind, Burger and Stanmyer[4] synthesized a number of 2′-, 4- and 5-chloro- and 3′,4-, 4′,5-, and 4,4′-dichloro-2-(γ-dimethylaminopropylamino)diphenyl sulphide derivatives because the introduction of electron-attracting substituents into the 2-position of the analogous phenothiazines greatly increases CNS and antiemetic activities. One of the intermediate amides in these syntheses, i.e. 4′,5-dichloro-2-(3-dimethylaminopropionamido) diphenyl sulphide, significantly increased the survival time of male Carworth Farms mice irradiated with 800 r at a dose of 100 mg/kg. With the hope of improving this effect, a number of 4-chloro-, 4,4′- and 4′,5-dichloro-2-(3-pyrrolidino- and 3-piperidinopropylamino)diphenyl sulphide derivatives have now been synthesized via the corresponding pyrrolidino- and piperidinopropionamides because the analogous phenothiazine derivatives containing these groups had shown somewhat better radioprotective properties than dimethyl- or diethyl-aminopropyl compounds.

2. Chemical Synthesis

The three 2-aminodiphenyl sulphides which served as starting materials contained chlorine in positions 4′; 4,4′; and 4′,5. They were prepared as described previously,[4] and condensed with 3-chloropropionyl chloride to furnish the corresponding (3-chloropropionamido) derivatives; the yields ranged from 83–88 per cent. The terminal aliphatic chlorine atom was exchanged with pyrrolidino and with piperidino groups by refluxing the chloropropionamido derivatives with the respective amines in benzene solution, with or without pyridine as a neutralizing agent. The resulting γ-pyrrolidino- and piperidinopropionamides are listed in Table I together with their yields and physical and analytical data. The Table also contains data on long-chain homologues

prepared by the action of 8-bromooctanoyl chloride, and 9-bromononanoyl chloride on the three chlorinated 2-aminodiphenyl sulphides listed above, followed by reaction of the resulting ω-bromoamides with piperidine and pyrrolidine, respectively.

Reduction of the γ- and ω-pyrrolidino and piperidino amides with lithium aluminium hydride yielded oily 2-(*t*-aminoalkyleneamino)-chlorodiphenyl sulphide derivatives. These diamines are listed in Table II.

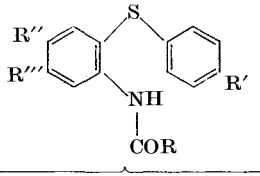
3. Experimental

Preparation of amides. A solution of 0·1 mole of the 2-aminodiphenyl sulphide derivative and 0·125 mole of dry pyridine in 300 ml of dry ether was cooled to 0°, and a solution of 0·105 mole of one of the acyl chlorides in 50 ml of ether was added in a thin stream with agitation. After standing for 2 h the mixture was treated with 100 ml of water containing 25 ml of 5 per cent hydrochloric acid. The solution was filtered from insoluble amide, and the acid filtrate was extracted with three 50 ml portions of ether. The combined ethereal extracts were concentrated. They deposited, on cooling, additional quantities of the amide which was filtered, washed with water, and recrystallized. For additional data see Table I.

Preparation of piperidino or pyrrolidino amides. A solution of 0·043 mole of the haloalkylamide, 0·121 mole of dry piperidine (or pyrrolidine), and 10·8 g of dry pyridine in 100 ml of dry benzene was refluxed for 24–48 h, and concentrated on a steam bath under reduced pressure. The residue was washed with 50 ml of 5 per cent sodium hydroxide solution, and extracted with three 50 ml portions of ether. The ether extracts were washed with water, dried over magnesium sulphate and evaporated to dryness. The residual amino amide was recrystallized. See Table I.

Reduction of the basic amides. A suspension of 0·658 mole of lithium aluminium hydride in 75 ml of dry ether was stirred and refluxed for 1 h, and then 0·27 mole of the respective pyrrolidino or piperidino amide, dissolved in 120 ml of dry ether, was added dropwise over a period of 25 min. The mixture was refluxed and stirred for 15 h, and then decomposed, with cooling, by dropwise addition of 7 ml of ethyl acetate, followed by 9 ml of

Table. I. Halogenoacyl, piperidinoacyl and pyrrolidinoacyl derivatives of chlorinated 2-aminodiphenyl sulphides

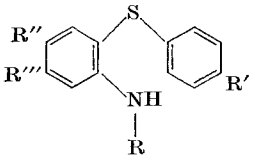


R	R′	R″	R‴	Yield, %	Appearance (crystals unless otherwise noted)	Solvent of crystallization	M.p., °C (corr.)	Empirical formula	Analysis calc. C	Analysis calc. H	Analysis found C	Analysis found H
$(CH_2)_2Cl$	Cl	H	H	88	Needles	MeOH	111·5–112·5	$C_{15}H_{13}Cl_2NOS$	55·22	4·02	55·23	4·22
$(CH_2)_8Br$	Cl	H	H	86	Plates	MeOH	86 –86·5	$C_{21}H_{25}BrClNOS$	55·44	5·54	55·71	5·44
$(CH_2)_2NC_5H_{10}$	Cl	H	H	63	Plates	abs. EtOH	80 –81	$C_{20}H_{23}ClN_2OS$	64·06	6·18	63·79	6·31
$(CH_2)_2NC_4H_8.HCl$	Cl	H	H	67	Plates	abs. EtOH	196 –197*	$C_{19}H_{22}Cl_2N_2OS$	57·42	5·58	56·89	5·43
$(CH_2)_8NC_5H_{10}.HCl.\frac{1}{2}H_2O$	Cl	H	H	80	Colourless	MeOH	91 – 91·5	$C_{26}H_{35}ClN_2OS$	61·89	7·39	61·86	7·44
$(CH_2)_8NC_4H_8$	Cl	H	H	66	Colourless	Hexane	65 – 67	$C_{25}H_{33}ClN_2OS$	67·46	7·47	68·07	7·07
$(CH_2)_8CO_2C_2H_5$	Cl	H	H	81	Light Tan	MeOH	55·5– 57·5	$C_{24}H_{30}ClNO_3S$	64·33	6·74	64·06	6·76
$(CH_2)_2NC_4H_8$	Cl	Cl	H	67	Colourless	abs. EtOH	74 – 74·5	$C_{19}H_{20}Cl_2N_2OS$	57·72	5·10	57·63	5·01
$(CH_2)_2NC_5H_{10}$	Cl	Cl	H	88	Colourless	abs. EtOH	95 – 97	$C_{20}H_{22}Cl_2N_2OS$	58·67	5·42	58·92	5·21
$(CH_2)_2NC_4H_8$	Cl	H	Cl	85	Colourless	abs. EtOH	85 – 87	$C_{19}H_{20}Cl_2N_2OS$	57·72	5·10	57·97	5·34
$(CH_2)_2NC_5H_{10}$	Cl	H	Cl	90	Colourless	abs. EtOH	83·5– 85·5	$C_{20}H_{22}Cl_2N_2OS$	58·67	5·42	58·49	5·68
$(CH_2)_7Br$	Cl	H	Cl	76	Colourless flakes	MeOH	77·5– 79	$C_{20}H_{22}BrCl_2NOS$	50·54	4·67	50·45	4·80
$(CH_2)_8Br$	Cl	H	Cl	82	Colourless flakes	MeOH	67·5– 69·5	$C_{21}H_{24}BrCl_2NOS$	51·54	4·94	51·53	5·21
$(CH_2)_7NC_4H_8.HCl$	Cl	H	Cl	74	Colourless	EtOAc–MeOH	108·5–110·5†	$C_{24}H_{31}Cl_3N_2OS$	57·42	6·23	57·41	6·32
$(CH_2)_7NC_5H_{10}.HCl$	Cl	H	Cl	77	Colourless	EtOAc–MeOH	146·5–148·5	$C_{25}H_{33}Cl_3N_2OS$	58·19	6·45	58·05	6·41
$(CH_2)_8NC_4H_8.HCl$	Cl	H	Cl	68	Colourless	EtOAc–MeOH	80 – 82	$C_{25}H_{33}Cl_3N_2OS$	58·19	6·45	58·44	6·36
$(CH_2)_8NC_5H_{10}.HCl$	Cl	H	Cl	96	Colourless	EtOAc–MeOH	112 –114	$C_{26}H_{35}Cl_3N_2OS$	58·92	6·66	58·58	6·32

* Melting point of base, 62–63°.

† The melting point changes to 123–124° on heating, or by heating in ethyl acetate.

Table II. 2-Piperidinoalkylamino and 2-pyrrolidinoalkylamino derivatives of chlorinated 2-aminodiphenyl sulphides

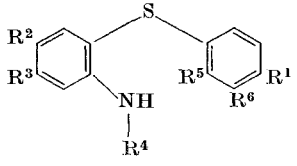


R	R′	R″	R‴	Yield, %	Appearance (colourless unless otherwise noted)	Solvent of crystallization	M.p., °C (corr.)	Empirical formula	Analysis calc. C	calc. H	found C	found H
$(CH_2)_3NC_5H_{10}.2HCl$	Cl	H	H	67	Plates	EtOAc–abs. EtOH	169·5–170·5	$C_{20}H_{27}Cl_3N_2S$	55·36	6·27	55·78	6·36
$(CH_2)_3NC_4H_8.2HCl$	Cl	H	H	53	Plates	EtOAc–abs. EtOH	159 –162·5	$C_{19}H_{25}Cl_3N_2S$	54·35	6·00	54·19	6·12
$(CH_2)_9NC_5H_{10}$	Cl	H	H		Yellow oil			$C_{26}H_{37}ClN_2S$	70·18	8·38	69·71	7·94
$(CH_2)_9NC_4H_8$	Cl	H	H	62	Yellow oil			$C_{25}H_{35}ClN_2S$	69·65	8·18	69·02	7·28
$(CH_2)_3NC_4H_8.HCl.\frac{1}{2}H_2O$	Cl	Cl	H	29	Colourless	EtOAc–MeOH	72·5– 75·5	$C_{19}H_{22}Cl_3N_2S.\frac{1}{2}H_2O$	53·46	5·67	53·91	5·44
$(CH_2)_3NC_5H_{10}.HCl$	Cl	Cl	H	31	Colourless	abs. EtOH	152 –157	$C_{20}H_{25}Cl_3N_2S$	55·62	5·84	55·30	5·70
$(CH_2)_3NC_5H_{10}.HCl.\frac{1}{2}H_2O$	Cl	H	Cl	52	Colourless	abs. EtOH–Et_2O	137 –139·5	$C_{20}H_{25}Cl_3N_2S.\frac{1}{2}H_2O$	54·86	6·30	54·84	6·10
$(CH_2)_3NC_4H_8.HCl$	Cl	H	Cl	35	Colourless	EtOAc–MeOH	155 –156·5	$C_{19}H_{23}Cl_3N_2S$	54·61	5·55	54·49	5·11
$(CH_2)_8NC_5H_{10}$·Picrate	Cl	H	Cl	66	Yellow	EtOH	113·5–114·5	$C_{25}H_{34}Cl_2N_2S.C_6H_3N_3O_7$	53·60	5·37	53·18	5·82
$(CH_2)_8NC_4H_8$·Picrate	Cl	H	Cl	57	Yellow	EtOH	104 –105·5	$C_{24}H_{32}Cl_2N_2S.C_6H_3N_3O_7$	52·94	5·18	52·83	5·47
$(CH_2)_9NC_4H_8.HCl.\frac{1}{2}H_2PtCl_6$	Cl	H	Cl	32	Tan		80 dec.	$C_{25}H_{34}Cl_2N_2S.HCl.\frac{1}{2}H_2PtCl_6$*	42·47	5·13	42·59	5·08
$(CH_2)_9NC_5H_{10}.HCl.\frac{1}{2}H_2PtCl_6$	Cl	H	Cl	40	Tan		80 dec.	$C_{26}H_{36}Cl_2N_2S.HCl.\frac{1}{2}H_2PtCl_6$†	45·62	5·45	45·27	5·09

* Pt, Calcd., 13·81; Found: 13·44. The amine was a colourless oil.

† Pt, Calcd., 14·26; Found: 13·41. The amine was a colourless oil.

Table III. Radioprotective activity of some 2-aminodiphenyl sulphide derivatives

Derivative of diphenyl sulphide							Solvent	Toxicity: approximate LD50, mg/kg	Radiation studies		
									dose,* mg/kg	change in survival time50,†‡ days	mortality, 30 days
	R^1	R^2	R^3	R^4	R^5	R^6					
2-Amino-2′-chloro-	H	H	H	H	Cl	H	PG§	over 300	100	+2	10/10
									150	+4	10/10
									300	+5	10/10
2-Amino-5-chloro- [.HCl.H_2O]	H	Cl	H	H	H	H	H_2O	over 400	200	+1	10/10
									300	−6	10/10
2-Amino-3′, 4-dichloro- [.HCl]	H	H	Cl	H	H	Cl	H_2O	over 400	200	0	10/10
									300	−4	10/10
2-Amino-4, 4′-dichloro-	Cl	H	Cl	H	H	H	PG§	over 200	100	+3	10/10
									200	+5	10/10
									250	0	10/10
2-Acetamido-4′-chloro-	Cl	H	H	$COCH_3$	H	H	PG§	over 400	200	+4	10/10
									300	+3	10/10
2-Acrylamido-4-chloro-	H	H	Cl	$COCH{=}CH_2$	H	H	H_2O	over 400	200	−2	10/10
									250	0	10/10
2-(3-Dimethylaminopropionamido)-4′, 5-dichloro-	Cl	Cl	H	$CO(CH_2)_2N(CH_3)_2$	H	H	PG§	100–200	50	0	10/10
									100	+9	10/10
									200	−5	10/10
2-(3-Pyrrolidinopropionamido)-4, 4′-dichloro-	Cl	H	Cl	$CO(CH_2)_2NC_4H_8$	H	H	PG§	over 1000	50	−5	10/10
									100	0	10/10
									750	+2	10/10
2-(3-Piperidinopropionamido)-4, 4′-dichloro-	Cl	H	Cl	$CO(CH_2)_2NC_5H_{10}$	H	H	PG§	100–200	10	−2	9/10
									50	+3	10/10
									100	+2	10/10

2-(3-Pyrrolidinoprop-pionamido)-4′, 5-dichloro-	Cl	Cl	H	$CO(CH_2)_2NC_4H_8$	H	H	PG§	200–300	20	−3	10/10
									100	−2	10/10
									200	+3	10/10
2-(3-Piperidinoprop-ionamido)-4′, 5-dichloro-	Cl	Cl	H	$CO(CH_2)_2NC_5H_{10}$	H	H	PG§	100–200	10	−3	10/10
									50	+2	10/10
									100	+5	10/10
2-(3-N, N-Dimethyl-aminopropylamino)-4, 4′-dichloro-	Cl	H	Cl	$(CH_2)_3N(CH_3)_2$	H	H	H_2O	100–150	50	−1	10/10
									100	−3	10/10
									150	−5	10/10
2-(3-N, N-Dimethyl-aminopropylamino)-4′, 5-dichloro-[.HCl]	Cl	Cl	H	$(CH_2)_3N(CH_3)_2$	H	H	H_2O	50–100	25	−4	10/10
									50	0	10/10
									75	−3	10/10
2-(3-Piperidino-propylamino)-4, 4′-dichloro- [.HCl.$\frac{1}{2}$ H_2O]	Cl	H	Cl	$(CH_2)_3NC_5H_{10}$	H	H	H_2O	200–300	10	+4	10/10
									20	−3	10/10
									50	−4	10/10
									200	−3	10/10
2-(3-Pyrrolidinopro-pylamino)-4′, 5-dichloro- [.HCl.$\frac{1}{2}$ H_2O]	Cl	Cl	H	$(CH_2)_3NC_4H_8$	H	H	H_2O	50–100	5	+2	10/10
									20	−3	10/10
									50	+1	10/10
2-(3-Piperidinopro-pylamino-4′, 5-dichloro- [.HCl]	Cl	Cl	H	$(CH_2)_3NC_5H_{10}$	H	H	H_2O	200–300	10	+4	10/10
									20	−3	10/10
									50	−2	10/10
									200	−4	10/10
Bis-(2-aminophenyl) disulphide							PG§	50–100	25	+3	10/10
									50	+3	8/10
									75	+3	10/10
10-(2-Dimethylamino-propyl)phenothiazine. HCl (Phenergan)							H_2O	50–100	10	+1	10/10
									50	−1	10/10
									75	−2	10/10

* Radiation dosage, 800 r; compounds administered 10–20 min before irradiation.
† + means prolongation of survival time beyond the median survival time of the irradiated controls.
‡ − means shortening of survival time.
§ Compound was dissolved in a 1 : 1 mixture of propylene glycol and water.

water. After vigorous stirring for 1 h, the mixture was filtered from granular lithium salts, and the precipitate was triturated twice with 25 ml portions of ether. The combined ethereal filtrates were dried over magnesium sulphate, filtered, and neutralized with ethereal hydrogen chloride. The gummy hydrochloride was rinsed with ether; it crystallized on scratching. If necessary, the ethereal solution of the diamine was chromatographed through an alumina column (24 cm length, 19 mm inside diameter). Two of the long-chain diamines (see Table II) gave no solid hydrochlorides, mucates, succinates, oxalates or picrates. For additional data, see Table II.

Pharmacology—(a) The approximate LD50 was determined by administering each compound intraperitoneally to small groups of mice in increasing doses, and recording the mortality for a period of ten days. Many of the compounds when given at the higher dosage levels caused a severe and persistent depression which, when combined with the fact that the mice are confined in plastic tubes during the radiation exposure period, resulted in the death of some of the röntgen-irradiated, drug-treated mice. Thus it was not possible to use dosage levels of these compounds as great as indicated by the toxicity studies. The approximate LD50 is recorded in Table III. (b) Adult male Carworth Farms (CF-1) mice weighing 18–24 g and housed in rooms at 65–67°C and fed with Rockland Mouse Pellets and water *ad libitum* were used in these studies. In the radiation screening studies each compound was injected intraperitoneally into at least ten mice and 10–20 min later the animals were exposed to 800 r of whole-body X-irradiation. At least ten control animals were given comparable injections of saline or propylene glycol, depending on whether the test compound was soluble in water or not. The solutions of the water-soluble compounds were adjusted to pH 7·0 before injection; the water-insoluble compounds were dissolved in a 1 : 1 mixture of propylene glycol and water. The concentrations of the solutions were so adjusted that no more than 2 per cent of their bodyweight was injected into the mice each time.

The röntgen ray exposures were given as a single whole-body exposure of 250 kVP, 15 mA at a dose rate of 40–43 r/min, determined with a Victoreen ionization thimble in air. The added

filtration consisted of 0·25 mm of copper and 1·0 mm of aluminium. The target distance was 75 cm. The animals were irradiated in individual plastic tubes placed radially on a rotating turntable so that each animal received an equal radiation dose. The animals were randomized before the exposure so that both control and test groups were irradiated simultaneously. The results of these studies are listed in Table III. At the end of this Table, similar data for two compounds are given whose structure relates them more or less to the diphenyl sulphide derivatives.

Summary. A series of 4-chloro, 4,4′- and 4′,5-dichloro-2-(3-pyrrolidino- and 3-piperidinopropylamino)diphenyl sulphide derivatives have been synthesized. Radioprotective tests of these compounds as well as of related propionamido and other amino- and amido-diphenyl sulphides are reported. None of these compounds appears to be sufficiently potent or non-toxic to provide a significant lead for further work in this series.

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