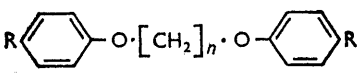
579. *Synthesis of Bis-*[p-*di*-(2-*chloroethyl*)*aminophenoxy*]*alkanes.*

By F. Bergel and E. Reiner.

A homologous series of compounds based on the structure mentioned in the title has been prepared from the corresponding primary diamines *via* the hydroxyethylamino-derivatives.

In recent years, attention of a number of research teams has centred on schistosomicidal drugs derived from diphenoxyalkanes, particularly those (I) substituted in the *p*-positions with primary, secondary, and tertiary amino-groups.[1-3] This structure has served as a basis for our synthesis of a homologous series, carrying two " nitrogen mustard " groups [I; R = $(Cl\cdot CH_2\cdot CH_2)_2N$; n = 2—10 and 12]. We were hoping to find differences in biological behaviour with variations in polymethylene chain length; in the literature examples of such variations have been reported in relation to pharmacodynamic,[4,5] enzymic,[6] anti-protozoal,[7] as well as anti-tumour [8] and anti-leukæmic [9] properties.



(I)

Starting materials were αω-polymethylene dibromides and *p*-nitrophenoxide (formed *in situ* from *p*-nitrophenol and anhydrous potassium carbonate) which, in ethyl methyl ketone and in presence of potassium iodide,[10] gave the dinitro-compounds in high yields (I; R = NO_2; n = 1—12). Of these, some have been reported with analyses in the

[1] Raison and Standen, (*a*) *Trans. Roy. Soc. Trop. Med. Hyg.*, 1954, **48**, 446; (*b*) *Brit. J. Pharmacol.*, 1955, **10**, 191.
[2] Collins, Davis, and Hill, *Chem. and Ind.*, 1954, 1072.
[3] Ashley, Collins, Davis, and Sirett, *J.*, 1958, 3298.
[4] Barlow and Ing, *Brit. J. Pharmacol.*, 1948, **3**, 298.
[5] Paton and Zaimis, *ibid.*, 1949, **4**, 381.
[6] Blaschko and Duthie, *Biochem. J.*, 1945, **39**, 347.
[7] King, Lourie, and Yorke, *Ann. Trop. Med. Parasit.*, 1938, **32**, 177.
[8] Kon and Roberts, *J.*, 1950, 978.
[9] Haddow and Timmis, *Lancet*, 1953, I, 207.
[10] Everett, " Recent Advances in the Field of Chemotherapy of Cancer," Dissertation presented in support of Application for Fellowship, Royal Inst. of Chem., 1955, p. 215.

literature;[11] the others have been quoted with incomplete data in patents[12a,b,c] and are presented in Table 1. The dinitro-compounds were catalytically reduced to the corresponding diamines (I; R = NH_2; n = 1—12) of which those not previously recorded in full[3,10,11,12b,c] or only described as salts or derivatives of the free bases[3] are assembled in Table 2. Interaction with ethylene oxide in aqueous acetic acid[13] produced the bis-[di-(2-hydroxyethyl)amino]-derivatives [I; R = $(HO{\cdot}CH_2{\cdot}CH_2)_2N$; n = 1—12]. Of these (Table 3), the C_2 and C_3 analogues have been described by Everett[10] and some of the others have been mentioned with m. p. only in patents.[12c,d] The hydroxyethyl derivatives, with the exception of the compounds (I; n = 1 and 11), were in turn transformed into " nitrogen mustard " compounds (Table 4).

In view of maximum schistosomicidal activities of the corresponding amino-derivatives (I; R = Me_2N; n = 3—8)[1b] three compounds [I; R = $(Cl{\cdot}CH_2{\cdot}CH_2)_2N$; n = 2, 6, 7] were tested on the Walker rat carcinoma 256. Of these the C_7 compound (CB 3214) at 500 mg./kg. (non-toxic dose) produced a slight hold-up of the tumour but the C_6 analogue (CB 3139) at the same dose level showed no inhibition. In our experiments toxic effects on the retina of the animals were absent, although such effects have been reported for mainly primary diamines in carnivores and primates.[14]

Experimental.—αω-Polymethylene dibromides. The dibromoalkanes with one to five carbon atoms as well as decamethylene bromide were obtained from commerical sources.

Hexa- and nona-methylene dibromides were prepared from their respective glycols.[15] Pimelic ester was reduced with lithium aluminium hydride[16] to its glycol which was in turn converted into the C_7 dibromide.[15] The C_8 dibromide was obtained from 1,8-dimethoxyoctane by the general method of Nineham.[17] The C_{11} dibromide (yield 69%) was prepared from the glycol which was obtained by reduction of diethyl undecanedioate.[16] The last compound was

TABLE 1. *Nitro-compounds* (I; R = NO_2).

		Yield		Found (%)			Required (%)			
n	M. p.	(%)	Formula	C	H	N	C	H	N	Ref.
5	102—104 [a]	57	$C_{17}H_{18}N_2O_6$	58·7	5·3	8·1	58·9	5·2	8·1	12*a*
6	106—108 [b]	90	$C_{18}H_{20}N_2O_6$	60·1	5·8	7·6	60·0	5·6	7·8	12*b*
7	114—116 [a]	90	$C_{19}H_{22}N_2O_6$	61·3	5·9	7·5	61·0	5·9	7·5	12*c*
11	79·5—81·5 [c]	96	$C_{23}H_{30}N_2O_6$	63·9	7·0	6·2	64·2	7·0	6·5	

Solvents: *a*, ethyl acetate; *b*, ethanol; *c*, propan-2-ol; *d*, benzene–light petroleum.

TABLE 2. *Amines* (I; R = NH_2).

		Yield		Found (%)			Required (%)			
n	M. p.	(%)	Formula	C	H	N	C	H	N	Ref.
5	80—82° [b, d]	91	$C_{17}H_{22}N_2O_2$	71·5	7·7	9·7	71·3	7·7	9·8	12*b*
6	146—147·5 [b]	94	$C_{18}H_{24}N_2O_2$	71·6	8·0	9·3	71·9	8·05	9·3	12*b*
7	78—79·5 [d]	97	$C_{19}H_{26}N_2O_2$	72·8	8·6	8·7	72·6	8·3	8·9	12*c*
11	72—74 [c]	97	$C_{23}H_{34}N_2O_2$	74·5	9·1	7·6	74·6	9·3	7·6	

[b, d] See Table 1.

synthesised from the C_9 dibromide and sodium cyanide as described by Chuit[18] with subsequent hydrolysis and esterification. The C_{12} dibromide was obtained either by catalytic reduction

[11] Weddige, *J. prakt. Chem.*, 1880, **21**, 127; Kinzel, *Arch. Pharm.*, 1898, **236**, 260; Wilson and Baker, *J.*, 1931, 1765; Partridge and Short, *J.*, 1947, 391; McMillan, *J. Amer. Chem. Soc.*, 1952, **74**, 5229; Wagner, *J. prakt. Chem.*, 1883, **27**, 206.

[12] (*a*) B.P. 758,382/1956; (*b*) B.P. 749,923/1956; (*c*) B.P. 761,888/1956; (*d*) B.P. 770,410/1957.

[13] Everett, Roberts, and Ross, *J.*, 1953, 2386.

[14] Edge, Mason, Wien, and Ashton, *Nature*, 1956, **178**, 806; Goodwin, Richards, and Udall, *Brit. J. Pharmacol.*, 1957, **12**, 468; Collins, Davis, Edge, and Hill, *ibid.*, 1958, **13**, 238.

[15] *Org. Synth.*, 1955, Coll. Vol. III, p. 227.

[16] *Org. Reactions*, 1951, **6**, 469.

[17] Nineham, *J.*, 1953, 2601.

[18] Chuit, *Helv. Chim. Acta*, 1926, **9**, 264.

of 1,12-di-*o*-methoxyphenoxydodec-6-ene followed by cleavage and bromination or by esterification of dodecanedioic acid with subsequent reduction to the glycol and bromination of the latter.

Di(p-*nitro- and -amino-phenoxy*)*alkanes.* *p*-Nitrophenol (2 equiv.), anhydrous potassium carbonate (2 equiv.), αω-polymethylene dibromide (1 equiv.), and potassium iodide (0·02 equiv.)

TABLE 3. *Di-2-hydroxyethylamino-compound* [I; R = $(HO{\cdot}CH_2{\cdot}CH_2)_2N$]

				Found (%)			Required (%)		
n	M. p.	Yield (%)	Formula	C	H	N	C	H	N
1	143—145° [a]	86	$C_{21}H_{30}N_2O_6$	61·7	7·4	6·9	62·05	7·4	6·9
2	112·5—113·5 [b]	56	$C_{22}H_{32}N_2O_6$	62·6	7·7	6·7	62·8	7·7	6·7
3	107—109 [b, c]	71	$C_{23}H_{34}N_2O_6$	63·9	8·1	6·5	63·6	7·9	6·5
4	130—131·5 [a]	74	$C_{24}H_{36}N_2O_6$	64·1	8·2	6·4	64·3	8·1	6·3
5	113·5—115·5 [a]	58	$C_{25}H_{38}N_2O_6$	64·6	8·1	6·1	64·9	8·3	6·1
6	109·5—111·5 [a]	84	$C_{26}H_{40}N_2O_6$	65·1	8·4	5·9	65·5	8·5	5·9
7	105·5—107 [d]	82	$C_{27}H_{42}N_2O_6$	65·9	8·6	5·8	66·1	8·6	5·7
8	108—110 [a]	75	$C_{28}H_{44}N_2O_6$	66·3	8·9	5·6	66·6	8·8	5·6
9	102·5—104 [d]	56	$C_{29}H_{46}N_2O_6$	67·0	8·9	5·3	67·15	8·9	5·4
10	108—110 [d]	70	$C_{30}H_{48}N_2O_6$	67·3	9·3	5·5	67·6	9·1	5·3
11	105—106·5 [a]	64	$C_{31}H_{50}N_2O_6$	68·1	9·5	5·3	68·1	9·2	5·1
12	112—114 [a]	46	$C_{32}H_{52}N_2O_6$	68·1	9·3	5·0	68·5	9·35	5·0

Solvents: (*a*) MeOH–light petroleum; (*b*) MeOH; (*c*) water; (*d*) chloroform–light petroleum.

TABLE 4. *Di-2-chloroethylamino-compounds* [I; R = $(ClCH_2CH_2)_2N$].

				Found (%)				Required (%)				Hydrolysis
n	M. p.	Yield (%)	Formula	C	H	N	Cl	C	H	N	Cl	(%)
2	78—79° [a]	27	$C_{22}H_{28}O_2N_2Cl_4$	53·8	5·8	5·6	28·5	53·5	5·7	5·7	28·7	—
3	51—52 [b]	26—75	$C_{23}H_{30}O_2N_2Cl_4$	54·4	6·0	5·5	27·2	54·3	5·9	5·5	27·9	50
4	99·5—100·5 [b]	61	$C_{24}H_{32}O_2N_2Cl_4$	55·3	6·2	5·2	26·4	55·3	6·2	5·4	27·2	—
5	59·5—61·5 [b]	13	$C_{25}H_{34}O_2N_2Cl_4$	56·2	6·6	5·1	26·6	56·0	6·4	5·2	26·4	70
6 *	67—69 [a]	61	$C_{26}H_{36}O_2N_2Cl_4$	56·9	6·6	5·2	26·1	56·7	6·6	5·1	25·8	77
7	48—50 [b]	45	$C_{27}H_{38}O_2N_2Cl_4$	57·9	6·7	4·7	24·8	57·4	6·7	5·0	25·1	51
8	73—74 [a]	57	$C_{28}H_{40}O_2N_2Cl_4$	58·0	6·9	5·1	24·2	58·1	7·0	4·8	24·5	36
9	52—54 [a]	36	$C_{29}H_{42}O_2N_2Cl_4$	58·8	7·2	4·7	23·8	58·8	7·5	4·6	23·5	51
10 †	75—76 [c]	25	$C_{30}H_{44}O_2N_2Cl_4$	59·6	7·4	4·7	23·0	59·4	7·3	4·6	23·4	41
12 ‡	55—56 [d]	27	$C_{32}H_{48}O_2N_2Cl_4$	60·5	7·3	4·0	22·0	60·7	7·6	4·4	22·3	—
*	140	Dipicrate	$C_{36}H_{42}O_{16}N_8Cl_4$	45·0	4·2	10·7		45·2	4·2	11·1		
†	110	Dipicrate	$C_{42}H_{50}O_{16}N_8Cl_4$	47·5	4·9	10·2		47·3	4·7	10·5		
‡	91	Dipicrate										

Solvent: (*a*) cyclohexane; (*b*) benzene–pentane; (*c*) pentane; (*d*) ethanol.

were suspended in ethyl methyl ketone, and heated under reflux with stirring for 24 hr. (cf. Everett [10]). After cooling, the mixture was extracted with benzene which was washed with water, dried (Na_2SO_4), and evaporated *in vacuo*. The compounds were purified by recrystallisation (charcoal) (Table 1), and (0·01—0·02 mole) reduced catalytically (platinum oxide; 0·1 g.) in ethyl acetate or ethyl acetate–ethanol. The free bases after recrystallisation (charcoal) were obtained as yellowish prisms or plates (Table 2).

Bis-[p-*di-*(2-*hydroxyethyl- and* 2-*chloroethyl*)*aminophenoxy*]*alkanes.* The above amines (0·01 equiv.) were shaken with chilled acetic acid–water (1 : 1) (20 ml.) and ethylene oxide (4—5 equiv.) for 3—4 hr. After being kept for a further 12 hr. the mixture was gently heated on a water-bath, and the excess of ethylene oxide removed. The remaining solution was made alkaline with ammonia solution or saturated aqueous sodium carbonate, and the usually very hydrophilic precipitate was dried and purified by crystallisation (Table 3).

Each of the tetrahydroxyethyl compounds (0·01 mol.) was suspended in benzene (20 ml.), and phosphorus oxychloride (1—2 ml.) was added to the refluxing mixture. After 0·5 hour's heating on the water-bath most of the solvent was removed *in vacuo*, and further phosphorus oxychloride (15 ml.) added to the residue. The solution was gently heated for 5—8 hr., then the solvent was removed *in vacuo*. Treatment with concentrated hydrochloric acid on the water-bath for 3 hr. was followed by addition, with cooling, of concentrated aqueous sodium acetate and concentrated aqueous ammonia until the pH was *ca.* 6·5. The aqueous solution was extracted with benzene, and the benzene extract dried (Na_2SO_4) and concentrated *in vacuo*.

After addition of pentane (5—10 vol.) and cooling, crystals were formed. They were sensitive to sunlight but appeared quite stable in the dark (Table 4). The C_2 compound has been described by Everett.[10] Hydrolysis was measured by Ross's method.[19]

We thank Professor A. Haddow, F.R.S., for the biological results and Dr. H. J. Barber of May and Baker Laboratories for kindly supplying the 1,12-di-*o*-methoxyphenoxydodec-6-ene. This investigation was supported by grants to this Institute from the British Empire Cancer Campaign, the Jane Coffin Childs Memorial Fund for Medical Research, the Anna Fuller Fund, and the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service.

CHESTER BEATTY RESEARCH INSTITUTE,
INSTITUTE OF CANCER RESEARCH: ROYAL CANCER HOSPITAL,
FULHAM ROAD, LONDON, S.W.3. [*Received, April 4th,* 1959.]

[19] Ross, *J.*, 1949, 183.