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THE CHEMOTHERAPY OF AMOEBIASIS

PART II. AMINES DERIVED FORMALLY FROM EMETINE

BY

J. A. GOODSON, L. G. GOODWIN, J. H. GORVIN, M. D. GOSS, K. S. KIRBY, J. A. LOCK, R. A. NEAL, T. M. SHARP, AND W. SOLOMON

From the Wellcome Laboratories of Tropical Medicine, 183, Euston Road, N.W.1

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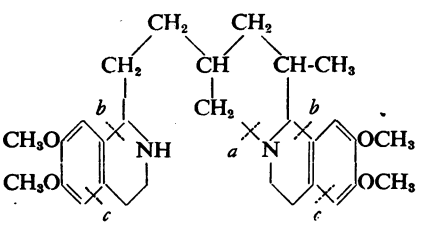
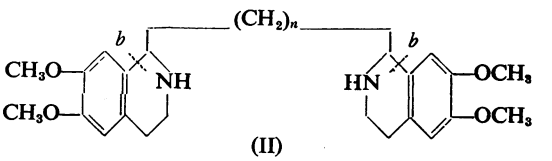
The structure of emetine according to Brindley and Pyman (1927) is probably represented by (I). If the bond shown by the dotted line at (*a*) in (I) is considered to be broken, a structure is derived consisting of two 6:7-dimethoxytetrahydro*iso*-quinoline nuclei joined at the 1 : 1′-positions by a chain of five methylene groups bearing two branches. Child and Pyman (1929) have synthesized a series of $\alpha\omega$-bis(6 : 7-dimethoxytetrahydro*iso*quinolyl) alkanes of formula (II) based on this model and found the compounds to be inactive against *Entamoeba histolytica in vitro*.



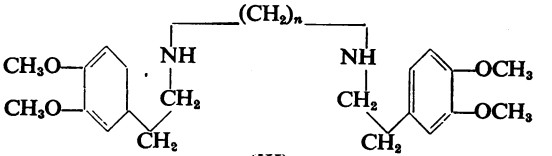
(I)

We have prepared a series of compounds (III ; $n=6$ to 10) modelled on the bis (β-3 : 4-dimethoxyphenylethylamino) alkanes resulting from the further rupture at (*b*) (*b*) of the ring system (II). The nature of the substituents in the benzene ring has been varied, and also the length of the central chain of methylene groups and of the chain between the amino group and the benzene ring.

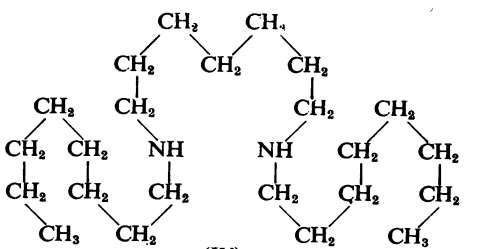
A series of bis(alkylamino)alkanes has also been prepared, the formal relationship of which to emetine is exemplified in bis(octylamino)heptane (IV). This structure is derived from that of emetine by opening out the molecule at the bonds (*a*), (*b*) (*b*) and (*c*) (*c*) in formula (I). In this series the length of the central chain of methylene groups has been varied and the chain branched, and the terminal alkyl groups have been varied in a similar manner.



(II)



(III)



(IV)

All these substances have been tested for amoebicidal activity by the methods outlined in the first paper of this series (Goodwin, Hoare and Sharp, 1948), and the results are shown in Table I. Selected members of the series have also been tested against experimental infections with trypanosomes, leishmania and malaria. The chemical syntheses and characteristics of the compounds are described in the chemical section on page 56.

As the quantities of drug available have in some cases been limited, the numbers of animals used were small. The results of the toxicity tests are very approximate, having been calculated by Kärber's method (Irwin and Cheeseman, 1939) from three or four groups of 5 mice. It will be

TABLE I

Columns 6 and 7: "+" signifies improvement, "—" no improvement.
Columns 10 and 11: "—" signifies no activity at a concentration of 10^{-4}.
Figures in parentheses denote slight activity with large doses. (e.g. "(6)" for compound No. 13 means that there was slight antimalarial activity at toxic dose levels.)

Column 12: "1" signifies no activity against *T. equiperdum*.
"2" ,, ,, ,, ,, *T. rhodesiense*.
"3" ,, ,, ,, ,, *T. congolense*.
"4" ,, ,, ,, ,, *T. cruzi*.
"5" ,, ,, ,, ,, *Leishmania donovani*.
"6" ,, ,, ,, ,, *Plasmodium gallinaceum*.

Substance	Ref. No.	Approx. LD50 (mg./kg.)		Amoebicidal tests							Other tests
				in vivo					*in vitro*		
		Oral	Sub-cut.	% diet	Caecal condition		Rats clear	%	Amoebicidal conc.	Bact.-cidal conc.	
					Wall	Conts.					
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
$\left(CH_3O\text{-}C_6H_3\text{-}(CH_2)_2NH\text{-}\right)_2(CH_2)_6$, 2HBr	1	950	250	0.2 0.1	+ —	+ —	4/7 2/8	60 25	—	—	1,3, 5,6.
,, $(CH_2)_6$, $2C_3H_6O_3$	2	..	..	0.5 0.05	— —	— —	5/6 1/6	80 15	..	..	..
,, $(CH_2)_7$, 2HBr	3	250	150	0.2 0.1	— —	— —	4/7 1/6	60 15	—	—	1,6.
,, $(CH_2)_8$, 2HBr	4	600	200	0.2 0.1 0.05	— — —	— — —	4/7 3/7 1/7	60 40 15	—	—	1,6.
,, $(CH_2)_9$, 2HBr	5	600	200	0.2 0.1 0.05	— — —	— — —	1/8 4/8 1/8	10 50 10	10^{-4}	—	6.
,, $(CH_2)_{10}$, 2HBr	6	700	550	0.2 0.1 0.05	+ + —	+ — —	3/4 2/7 1/7	75 30 15	10^{-5}	—	3,6.
$\left(CH_3O\text{-}C_6H_3\text{-}(CH_2)_2NH\text{-}\right)_2(CH_2)_6$, 2HBr	7	..	..	0.2	—	—	0/4	0	10^{-4}	—	..
,, $(CH_2)_{10}$, 2HBr	8	30	40	0.1	—	—	0/4	0	—	—	1,3.
$\left(HO\text{-}C_6H_3\text{-}(CH_2)_2NH\text{-}\right)(CH_2)_6$, 2HCl	9	..	310	0.2	—	—	0/4	0	—	—	1,3.
,, $(CH_2)_{10}$, 2HCl	10	>2000	375	0.2	—	—	0/6	0	—	—	..
$\left(HO\text{-}C_6H_3(I)\text{-}(CH_2)_2NH\text{-}\right)_2(CH_2)_6$	11	>2000	..	0.5	+	+	4/6	65	—	—	6.
,, $(CH_2)_{10}$	12	>2000	>2000	0.5	—	—	0/6	0	—	—	2,3.
$\left(Cl\text{-}C_6H_3\text{-}(CH_2)_2NH\text{-}\right)_2(CH_2)_6$, 2HBr	13	>2000	>2000	0.2 0.1 0.05	+ — —	— — —	4/6 0/5 0/7	65 0 0	10^{-4}	10^{-4}	2,3. (6)
,, $(CH_2)_8$, 2HBr	14	>2000	>2000	0.2 0.1 0.05	+ + —	— — —	9/9 8/15 4/14	100 55 30	10^{-5}	—	..

TABLE I—*continued.*

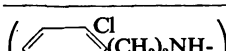
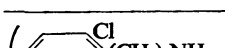
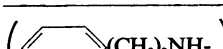
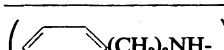
Substance	Ref. No.	Approx. LD50 (mg./kg.)		Amoebicidal tests							Other tests
				in vivo					*in vitro*		
		Oral	Sub-cut.	% diet	Caecal condition		Rats clear	%	Amoebicidal conc.	Bact.-cidal conc.	
					Wall	Conts.					
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
	15	450	>2000	0.5	Toxic				10^{-5}	—	6.
				0.2	—	—	Toxic				
				0.1	—	—	2/5	40			
,, Bismuth iodide (25.3% base)	16	..	..	0.5	+	+	5/6	80			
				0.2	+	+	3/7	40	..	..	..
	17	742	375	0.5	Toxic						
				0.2	+	+	6/6	100	10^{-6}	10^{-4}	..
				0.1	+	+	4/8	50			
,, Bismuth iodide (26% base)	18	..	..	0.5	+	+	4/6	65			
				0.2	—	+	2/8	25	..	..	..
	19	536	134	0.5	Toxic						
				0.2	+	+	3/4	75	10^{-5}	10^{-4}	6.
				0.1	—	+	1/7	15			
,, Bismuth iodide A (36.6% base)	20	..	..	0.5	+	+	5/5	100			
				0.2	—	—	1/8	10	..	..	..
,, Bismuth iodide B (22.9% base)	21	..	..	0.5	+	+	5/8	60			
				0.2	—	—	0/8	0	..	..	..
	22	120	350	0.5	—	—	Toxic		10^{-5}	—	(1),3,
				0.2	—	—	2/7	30			5.
,, ,, $2C_3H_6O_3$	23	..	..	0.2	—	—	0/3	0			
				0.1	—	—	1/6	20	..	..	1,3.
				0.05	—	—	2/6	30			
,, $(CH_2)_7$, 2HBr	24	165	400	0.5	Toxic						
				0.2	+	+	4/8	50	10^{-6}	—	(1).
				0.1	—	—	0/8	0			
				0.05	—	—	1/6	15			
,, $(CH_2)_8$, 2HBr	25	200	550	0.5	+	+	Toxic				
				0.2	+	+	9/12	75	10^{-5}	—	..
				0.1	—	—	2/7	30			
,, $(CH_2)_9$, 2HBr	26	135	68	0.5	+	+	Toxic				
				0.2	+	+	7/8	90	10^{-6}	—	
				0.1	—	—	7/8	90			..
				0.05	—	—	2/8	25			
,, $(CH_2)_{10}$, 2HBr	27	450	700	0.2	+	+	3/5	60			
				0.1	+	+	2/4	50	10^{-6}	—	1.
				0.05	—	—	3/5	60			
	28	710	410	0.5	+	+	Toxic		10^{-5}	—	..
				0.2	—	—	3/7	40			

TABLE I—*continued.*

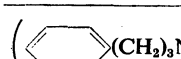
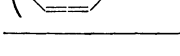
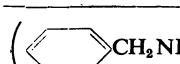
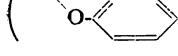
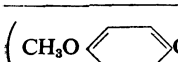
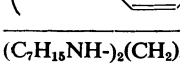
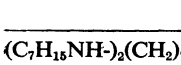
Substance	Ref. No.	Approx. LD50 (mg./kg.)		Amoebicidal tests							Other tests
				in vivo					*in vitro*		
		Oral	Sub-cut.	% diet	Caecal condition		Rats clear	%	Amoebicidal conc.	Bact.-cidal conc.	
					Wall	Conts.					
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
 $(CH_2)_{10}$, $2C_3H_6O_3$	29	1400	700	0.5 0.2	Toxic +	 +	 0/4	 0	10^{-5}	—	..
 $(CH_2)_8$, $2C_3H_6O_3$	30	308	310	0.2	—	—	1/6	15	10^{-5}	—	..
,, $(CH_2)_{10}$, $2C_3H_6O_3$	31	>2000	>2000	0.5 0.2	+ +	+ +	Toxic 4/8	 50	10^{-5}	—	..
 $(CH_2)_8$, $2C_3H_6O_3$	32	..	..	0.2	—	—	3/7	40	10^{-5}	—	..
 $(CH_2)_8$, 2HCl	33	1400	350	0.5 0.2	— —	— —	3/7 5/7	40 70	..	..	..
 $(CH_2)_8$, 2HCl	34	1400	1400	0.2 0.1	+ +	+ +	8/13 3/7	60 45	—	—	..
 $(CH_2)_8$, 2HCl	35	..	..	0.5 0.2	— —	— —	2/8 0/7	25 0	10^{-4}	—	..
 $(CH_2)_8$, 2HCl	36	..	..	0.5 0.2	— —	— —	2/7 3/6	30 50	10^{-5}		
 $(CH_2)_8$, 4HCl	37	350	175	0.2	—	—	3/8	40	10^{-4}	—	..
$(C_7H_{15}NH\text{-})_2(CH_2)_6$, 2HBr	38	450	100	0.2 0.1	+ +	+ +	4/7 4/10	60 40	10^{-5}	10^{-4}	(1),3, 5,6.
,, $2C_3H_6O_3$	39	..	154	0.5 0.2 0.1	+ + +	+ + +	5/5 1/5 2/7	100 20 30	10^{-5}	10^{-4}	(1),4, 5,6.
$(C_7H_{15}NH\text{-})_2(CH_2)_7$, 2HBr	40	350	300	0.2 0.1 0.05	+ — —	+ — —	3/6 5/15 4/9	50 33 40	10^{-5}	10^{-4}	(1).
,, $(CH_2)_8$, 2HBr	41	450	350	0.2 0.1 0.05	+ + +	+ + +	4/8 3/5 1/4	50 60 25	10^{-5}	10^{-1}	1,6.
,, ,, $2C_3H_6O_3$	42	..	..	0.2	—	—	1/2	..	..	..	..
,, $(CH_2)_9$, 2HBr	43	450	450	0.2 0.1 0.05 0.025 0.0125	Toxic + — — —	 + — — —	 12/16 3/12 5/11 0/5	 75 25 45 0	10^{-4}	—	6.

TABLE I—*continued*

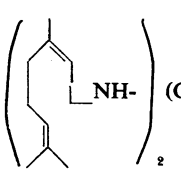
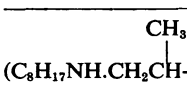
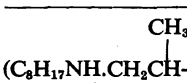
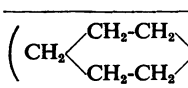
Substance	Ref. No.	Approx. LD50 (mg./kg.)		Amoebicidal tests							Other tests
				in vivo					*in vitro*		
		Oral	Sub-cut.	% diet	Caecal condition		Rats clear	%	Amoebicidal conc.	Bact.-cidal conc.	
					Wall	Conts.					
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
$(C_7H_{15}NH\text{-})_2(CH_2)_{10}$, 2HBr	44	500	350	0.2	+	+	8/9	90	10^{-5}	10^{-4}	1,3, 5,6.
				0.1	—	—	3/9	35			
				0.05	—	—	4/4	100			
				0.025	—	—	1/8	10			
				0.01	—	—	2/8	25			
$(C_6H_{13}NH\text{-})_2(CH_2)_{10}$, $2C_3H_6O_3$	45	1000	270	0.5	+	—	Toxic		10^{-4}	—	..
				0.2	—	—	Toxic				
				0.1	—	—	3/8	40			
$(C_8H_{17}NH\text{-})_2(CH_2)_8$, 2HBr	46	1800	>2000	0.2	+	+	11/14	80	10^{-5}	10^{-4}	1,3.
				0.1	—	—	1/6	15			
				0.05	—	—	7/23	35			
				0.01	—	—	6/14	40			
,, ,, $2C_3H_6O_3$	47	615	>2000	0.5	+	+	Toxic		..	..	..
				0.2	+	+	4/4	100			
				0.1	—	—	2/6	35			
$(C_9H_{19}NH\text{-})_2(CH_2)_8$, $2C_3H_6O_3$	48	700	>2000	0.2	+	+	Toxic		10^{-4}	—	..
				0.1	—	—	1/5	20			
$(C_{11}H_{23}NH)_2(CH_2)_{10}$, 2HBr	49	>2000	>2000	0.2	—	—	Toxic		—	—	
$(C_4H_9CH(C_2H_5)CH_2NH\text{-})_2(CH_2)_{10}$, 2HBr	50	>2000	>2000	0.2	—	—	0/3	0	10^{-5}	—	6.
$((CH_2{=}CH\text{-}CH_2)_3C.NH\text{-})_2(CH_2)_{10}$, 2HCl	51	1400	2000	0.5	+	+	Toxic		..	..	..
				0.2	+	+	3/6	50			
 $(CH_2)_{10}$, 2HBr	52	700	700	0.1	Toxic				10^{-5}	—	..
				0.05	+	+	5/7	70			
				0.025	—	—	1/7	15			
	53	1400	700	0.2	Toxic				10^{-5}	—	..
				0.1	+	+	3/5	60			
	54	>2000	1400	0.2	—	—	1/7	15	10^{-5}	—	..
 $(CH_2)_8$, 2HCl	55	390	200	0.5	Toxic				10^{-4}	10^{-4}	2,3.
				0.2	+	+	3/4	75			
				0.1	+	+	4/5	80			
,, $(CH_2)_{10}$, 2HCl	56	850	400	0.2	—	—	1/6	15	10^{-5}	—	2,3,6.

TABLE I—*continued.*

Substance	Ref. No.	Approx. LD50 (mg./kg.)		Amoebicidal tests							Other tests
				in vivo					*in vitro*		
		Oral	Sub-cut.	% diet	Caecal condition		Rats clear	%	Amoebicidal conc.	Bact.-cidal conc.	
					Wall	Conts.					
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
$\left(O\langle CH_2\text{-}CH_2\rangle N\text{-}\right)_2(CH_2)_{10}$, 2HCl	57	1600	180	0.5 0.2	— —	— —	2/4 2/8	50 25	—	—	..
$((C_2H_5)_2N(CH_2)_2NH\text{-})_2(CH_2)_{10}$, 4HBr	58	1200	300	0.2	—	—	1/6	15	—	—	(6).
$(C_8H_{17}NH\text{-})_2(CH_2)_5$, 2HBr	59	700	350	0.5 0.2 0.1 0.05	+ + + —	+ + + —	Toxic 5/7 1/8 0/8	 70 10 0	10^{-5}	—	..
$(C_3H_7NH\text{-})_2(CH_2)_3$, 2HBr	60	374	2000	0.5 0.2	— —	— —	1/4 1/4	25 25	— —	— —	1,3.
$(C_7H_{15}NH\text{-})_2(CH_2)_3$, 2HBr	61	10	275	0.2 0.1	— —	— —	6/11 3/6	55 50	10^{-5}	10^{-4}	6.
$(C_{13}H_{27}NH\text{-})_2(CH_2)_3$, $2C_3H_6O_3$	62	>2000	>2000	0.5 0.2 0.1	— — —	— — —	4/7 0/5 1/5	60 0 20	—	—	6.
$NH_2(CH_2)_{10}NH_2$, 2HCl	63	1500	250	0.1	—	—	1/6	15	—	—	..
$((C_4H_9)_2N\text{-})_2(CH_2)_{10}$, $2C_4H_6O_4$	64	500	950	0.5	—	—	3/6	50	10^{-4}	—	..
$((C_5H_{11})_2N\text{-})_2(CH_2)_{10}$, 2HCl	65	..	..	0.5 0.2 0.1	+ + —	+ + —	3/7 7/14 3/12	40 50 25	10^{-5}	—	..
$CH_3O\langle\rangle(CH_2)_2N\langle CH_2\text{-}CH_2\text{-}CH_2 \atop CH_2\text{-}CH_2\text{-}CH_2\rangle$, HBr	66	70	470	0.1	—	—	1/4	25	—	—	1,3.

noted that in some instances the oral toxicity of a substance is greater than the subcutaneous toxicity. This rather unusual finding is explained by the fact that most of the compounds are irritant, and whereas a localized necrosis is produced by subcutaneous injection, oral administration may result in severe and fatal damage to the walls of the alimentary tract, with secondary infection.

In the amoebicidal tests, the proportion of rats protected from infection has been expressed as a percentage, which facilitates comparison of the effects of one drug with another. As we are very conscious of the fact that percentages calculated from small numbers of animals have little meaning, the actual numbers of animals used are recorded, so that the true significance of the percentage figures may be apparent. It should be remembered that control animals may show an infection rate as low as 80 per cent, and a figure of 20 per cent protection may not indicate activity of a drug. Control animals were used in every test. The numbers of animals used were insufficient to give accurate comparisons between drugs, but were adequate to indicate whether or not a drug was likely to be of value in the treatment of amoebiasis. The effect upon the macroscopic appearance of the caecal wall and contents has been recorded here merely as a significant improvement (+) or no significant improvement (−); detailed figures are not given.

Discussion of the Results in Table I

Phenylalkylamine series

All the members of the series of bis(β-3 : 4-dimethoxyphenylethylamino)alkanes (Nos. 1 to 6) showed some activity *in vivo* but there was no significant difference between them. The improvement of the caecum produced by the compound containing 10 methylene groups suggests that it may have a slightly higher potency than the rest, and this is confirmed by the *in vitro* test.

When only one methoxy-group was present as in Nos. 7 and 8, the activity was reduced, and a similar effect was apparent in compounds 9 and 10 which contain free hydroxy-groups in the *para* positions of the benzene nuclei.

The introduction of iodine atoms into the benzene nucleus as in Nos. 11 and 12 gave rise to insoluble compounds with no increase in activity, although in this case the hexane- was more active than the decane-derivative.

The β-*p*-chlorophenylethylamino derivatives 13, 14, and 15 had some activity ; the corresponding *o*-chloro analogues (Nos. 17 and 19) were rather more active both *in vivo* and *in vitro*, but were also more toxic.

In the bis(β-phenylethylamino)alkane series (Nos. 22–27) all the compounds showed activity of a high order *in vitro*. The greatest *in vivo* activity was found in the higher members of the series. The effect of varying the length of the link between the phenyl and the amino groups is shown in Nos. 28 to 33. The optimum length seems to be a chain of two methylene groups. An increase in activity in the bis(phenylmethylamino)alkane series was found when a methylenedioxy-group was introduced into the 3 : 4- positions (No. 34), but a single *p*-methoxy or *p*-dimethylamino group was deleterious (Nos. 36 and 37).

Alkylamine series

The complete "opening out" of the emetine molecule leads to two *n*-octylamine residues connected through the N atoms by a chain of methylene groups. Owing to the ready availability of *n*-heptylamine *via* heptaldoxime we first studied the action of bis(*n*-heptylamino) alkanes. All these compounds (Nos. 38 to 44) had *in vitro* activities of the same order as the bis(β-phenylethylamino) alkane series, but in addition had bactericidal action, which probably complicated the results of the *in vitro* tests. *In vivo* these compounds were perhaps slightly more active than the phenylethylamino derivatives, but the results at low dose levels were erratic.

Alteration of the length of the alkyl chain as in Nos. 45 to 49 had little effect upon the activity, but the higher members had greater toxic effects when given in the diet than the lower members.

Branching the side-chain as in No. 50, 1 : 10-bis(2′-ethyl-*n*-hexylamino)decane and in No. 51, 1 : 10-bis(triallylcarbinamino) decane, where the chain is both branched and unsaturated, did not increase the *in vivo* activity, but the longer, branched, unsaturated compound, bis-geranylamino)decane (No. 52) again showed a high *in vivo* activity, accompanied however by an increased toxicity.

The introduction of methyl groups into the methylene chain connecting the two basic radicals (Nos. 53 and 54) had little effect.

When the alkyl chain was replaced by a *cyclo*hexyl radical (Nos. 55 and 56) the activity was not appreciably affected, but replacement of the alkylamino residues by tertiary basic groups as in 1 : 10-NN′-dimorpholyldecane (No. 57) resulted in complete loss of activity both *in vitro* and *in vivo*. The introduction of a basic side chain as in 1 : 10-bis(β-diethylaminoethylamino)decane (No. 58) had a similar effect.

Reduction in the number of methylene groups connecting the two secondary amino groups to five or three, even when the molecular weight was increased by the introduction of longer alkyl groups, caused almost complete loss of activity (Nos. 59 to 62).

The primary diamine, 1 : 10-diaminodecane (No. 63), was completely inactive and the ditertiary bases, 1 : 10-bis(dibutylamino)- and 1 : 10-bis(diamylamino)decane (Pyman, 1937 ; Nos. 64 and 65), were considerably less active than the disecondary bases of about the same molecular weight (*cf.* Nos. 44 and 47).

The cyclic tertiary amine No. 66, obtained as a by-product, was inactive.

The effect of solubility

The activities of the sparingly soluble hydrobromides and the readily soluble lactates were not significantly different (Nos. 1, 2 ; 22, 23 ; 38, 39 ; 41, 42 ; 46, 47). Nos. 15,17, and 19 have been converted into insoluble bismuth iodides of variable composition, Nos. 16, 18, 20 and 21 ; these were less toxic, but the activities were no greater than those of equivalent amounts of the parent compounds, except No. 16, which was slightly more active than No. 15.

None of the compounds is comparable with emetine in amoebicidal activity. Emetine protects most of the rats at a concentration in the diet of

0.001 per cent, whereas the best of the synthetic compounds are practically useless at concentrations lower than 0.1 per cent.

Although many members of the series have acute toxicities which are less than that of emetine, they are very irritant substances and it is unlikely that any would be suitable for clinical trial.

Chemical Section

Two general methods were used for the preparation of the secondary diamines; (a) an α,ω-alkylene dihalide was treated with a primary amine, or (b) an α,ω-alkylene diamine with an alkyl halide. The reactions were carried out in a variety of solvents—alcohol, amyl alcohol, ether, acetone, benzene, toluene or xylene—or without solvent, and for varying lengths of time. The choice of method was usually determined by the availability of the starting materials. In general the first method gave better yields, but, using alkylene dihalides containing 5 or 6 carbon atoms, there was a tendency for ring closure to take place with formation of N-alkyl(aralkyl)-piperidines or -hexamethyleneimines. The bis(phenylmethylamino) alkanes were most conveniently prepared *via* the anils.

1 : 6-*Bis*(β-3′ : 4′-*dimethoxyphenylethylamino*)*hexane* (No. 1). β-3 : 4-Dimethoxyphenylethylamine (7.24 g.), 1 : 6-dibromohexane (4.88 g.) and xylene (20 cc.) were allowed to stand for 24 hours and then heated to 115° for 30 mins. A crystalline solid separated on cooling; after recrystallization from alcohol glistening platelets of 1 : 6-*bis*(β-3′ : 4′-*dimethoxyphenylethylamino*)*hexane dihydrobromide*, m.p. 260–262°, were obtained in 29% yield. (Found: C, 51.5; H, 7.0; N, 4.6; Br, 26.6 $C_{26}H_{40}O_4N_2,2HBr$ requires C, 51.5; H, 7.0; N, 4.6; Br, 26.4%.) The dilactate (No. 2) forms plates from acetone, m.p. 120°. (Found: C, 61.4; H, 8.4. $C_{26}H_{40}O_4N_2,2C_3H_6O_3$ requires C, 61.5; H, 8.4%.)

1 : 7-*Bis*(β-3′ : 4′-*dimethoxyphenylethylamino*)*heptane* (No. 3) was obtained similarly in 24% yield as *dihydrobromide* from 1 : 7-dibromoheptane and β-3 : 4-dimethoxyphenylethylamine. It forms leaflets from alcohol, m.p. 240°. (Found: N, 4.7; Br, 25.8. $C_{27}H_{42}O_4N_2$, 2HBr requires N, 4.5; Br, 25.8%.) The *dihydrochloride* forms needles from alcohol, m.p. 247°. (Found: C, 60.7; H, 8.2. $C_{27}H_{42}O_4N_2,2HCl$ requires C, 61.0; H, 8.3%.)

1 : 8-*Bis*(β-3′ : 4′-*dimethoxyphenylethylamino*)*octane* (No. 4). The *dihydrobromide*, m.p. 251°, was obtained similarly from 1 : 8-dibromo-octane and the amine in 40% yield. (Found: N, 4.8; Br, 25.5. $C_{28}H_{44}O_4N_2,2HBr$ requires N, 4.4; Br, 25.2%.) The *dihydrochloride* forms needles from alcohol, m.p. 245–247°. (Found: C, 61.8; H, 8.6; N, 5.3; Cl, 12.4. $C_{28}H_{44}O_4N_2,2HCl$ requires C, 61.6; H, 8.5; N, 5.1; Cl, 13.0%.)

1 : 9 *Bis*(β-3′ : 4′-*dimethoxyphenylethylamino*)*nonane* (No. 5). The *dihydrobromide*, obtained similarly from 1 : 9-dibromononane in 32% yield, forms leaflets from alcohol, m.p. 248°. (Found: N, 4.6; Br, 24.7. $C_{29}H_{46}O_4N_2,2HBr$ requires N, 4.3; Br, 24.65%.) The *dihydrochloride* forms needles from alcohol, m.p. 251°. (Found: Cl, 12.8. $C_{29}H_{46}O_4N_2,2HCl$ requires Cl, 12.7%.)

1 : 10-*Bis*(β-3′ : 4′-*dimethoxyphenylethylamino*)*decane* (No. 6). The *dihydrobromide*, leaflets from alcohol, m.p. 251°, was obtained similarly in 45% yield from 1 : 10-dibromodecane and homoveratrylamine. (Found: N, 4.5; Br, 24.2. $C_{30}H_{48}O_4N_2,2HBr$ requires N, 4.2; Br, 24.1%.) The *dihydrochloride* forms needles from alcohol, m.p. 244–245°. (Found: C, 62.9; H, 8.9. $C_{30}H_{48}O_4N_2,2HCl$ requires C, 62.8; H, 8.8%.)

1 : 6-*Bis*(β-p-*methoxyphenylethylamino*)*hexane* (No. 7). β-*p*-Methoxyphenylethylamine (15.1 g.), alcohol (25 cc.) and 1 : 6-dibromohexane (6.1 g.) were heated under reflux for 24 hours and 2*N*-alcoholic HBr (25 cc.) added. The crystalline precipitate was filtered off and boiled with alcohol to remove *p*-methoxyphenylethylamine hydrobromide. The residue, recrystallized from a large volume of alcohol, deposited 1 : 6-*bis*(β-p-*methoxyphenylethylamino*)*hexane dihydrobromide* in crystals m.p. 308°. (Found: C, 52.8; H, 7.4; N, 5.1; Br, 29.1. $C_{34}H_{36}O_2N_2$, 2HBr requires C, 52.75; H, 7.0; N, 5.1; Br, 29.25%.) The *dipicrate* forms yellow crystals from alcohol, m.p. 198°. (Found: C, 51.3; H, 5.1; N, 13.5. $C_{34}H_{36}O_2N_2$, $2C_6H_3O_7N_3$ requires C, 51.3; H, 5.0; N, 13.3%.) The bases regenerated from the original mother-liquors were dissolved in alcohol and on addition of a hot alcoholic solution of picric acid deposited an oil; the clear decanted liquor on standing deposited orange crystals of β-*p*-methoxyphenylethylamine picrate mixed with yellow crystals of *N*-β-p-*methoxyphenylethylhexamethyleneimine picrate*. These were readily separated by hot benzene in which the former is insoluble. The latter formed yellow crystals from benzene, m.p. 151°, yield 37%. (Found: C, 54.7; H, 6.0; N, 12.2. $C_{15}H_{23}ON,C_6H_2O_7N_3$ requires C, 54.5; H, 5.7; N, 12.1%.) The *hydrobromide* (No. 66), colourless crystals from alcohol, melts at 196°. (Found: C, 57.3; H, 7.9; N, 4.4; Br, 25.6. $C_{15}H_{23}ON$, HBr requires C, 57.3; H, 7.9; N, 4.5; Br, 25.4%.) The ring structure was confirmed by failure of the base to yield an acetyl derivative and by the formation of a *methiodide*, m.p. 132°. (Found: C, 51.1; H, 7.1; N, 3.9; OMe, 8.3; NMe, 7.5. $C_{15}H_{23}ON,CH_3I$ requires C, 51.2; H, 7.0; N, 3.7; OMe, 8.3; NMe, 7.7%.)

1 : 10-*Bis*(β-p-*methoxyphenylethylamino*)*decane* (No. 8). The *dihydrobromide* was obtained in 53% yield in a similar manner to that just described but omitting the treatment with picric acid. It separates from a large volume of alcohol in crystals, m.p. 304° (decomp.). (Found: N, 4.9; Br, 26.7. $C_{28}H_{44}O_2N_2,2HBr$ requires N, 4.65; Br, 26.5%.)

1 : 6-*Bis*(β-p-*hydroxyphenylethylamino*)*hexane* (No. 9). This was prepared by heating the methoxy-derivative (No. 7) with 8 times its weight of hydrochloric acid (*d*, 1.2) in a sealed tube at 170° for 6 hours. The *dihydrochloride* separated from water in silky needles, m.p. 255–257°. (Found: C, 61.2; H, 7.9; N, 6.3; Cl, 16.8. $C_{22}H_{32}O_2N_2,2HCl$ requires C, 61.5; H, 8.0; N, 6.5; Cl, 16.5%.)

1 : 10-*Bis*(β-p-*hydroxyphenylethylamino*)*decane* (No. 10). The corresponding methoxy-compound (No. 8) heated in a sealed tube with hydrochloric acid (*d*, 1.2) furnished 1 : 10-*bis*(β-p-*hydroxyphenylethylamino*)*decane dihydrochloride* in needles from water. m.p. 238° (decomp.).

(Found: C, 64.8; H, 8.7; N, 5.4; Cl, 14.7. $C_{26}H_{40}O_2N_2$, 2HCl requires C, 64.3; H, 8.7; N, 5.8; Cl, 14.6%.)

1 : 6-*Bis*(β-3′-*iodo*-4′-*hydroxyphenylethylamino*)*hexane* (No. 11). To a stirred solution of the hydroxy-compound (No. 9) (2.0 g.) in methyl alcohol (120 cc.) 10% aqueous ammonia (4 cc.) was added followed by iodine (2.4 g.) in 50% potassium iodide solution (9.6 g.). The precipitate was collected, washed in turn with methanol, water and methanol. The base formed an almost white powder, m.p. 175°, yield 94%. (Found: I, 42.4. $C_{22}H_{30}O_2N_2I_2$ requires I, 41.7%.) The iodine atoms are assumed to be in the 3′-positions.

1 : 10-*Bis*(β-3′-*iodo*-4′-*hydroxyphenylethylamino*)*decane* (No. 12). This was prepared in 93% yield from No. 10 in a similar way. The base melted at 169° (decomp.). (Found: C, 46.9; H, 6.2; N, 4.5; I, 40.3. $C_{26}H_{38}O_2N_2I_2$ requires C, 47.0; H, 5.8; N, 4.2; I, 38.2%.) The iodine atoms are assumed to be in the 3′-positions.

β-p-*Chlorophenylethylamine*. Dry ammonia was passed for 3–4 hours through fused *p*-chlorophenylpropionic acid at 180°. The powdered product was freed from a little unchanged acid by extraction with aqueous ammonia and the insoluble p-*chlorophenylpropionamide* recrystallized from benzene. It formed tetragonal plates, m.p. 133°, yield 82%. (Found: C, 59.3; H, 5.8; N, 7.9; Cl, 19.3. $C_9H_{10}ONCl$ requires C, 58.9; H, 5.5; N, 7.6; Cl, 19.3%.) It was converted into *p*-chlorophenylethylamine, b.p. 129–135/24 mm., by the method of McRae and Vining (1932). The *picrate* forms light orange-coloured prisms from alcohol, m.p. 212°. (Found: N, 14.8; Cl, 9.3. $C_8H_{10}NCl,C_6H_3O_7N_3$ requires N, 14.6; Cl, 9.2%.) The *hydrobromide* separates from alcohol in colourless crystals, m.p. 237°. (Found: C, 40.6; H, 5.0; N, 5.7. $C_8H_{10}NCl,HBr$ requires C, 40.6; H, 4.7; N, 5.9%.)

β-o-*Chlorophenylethylamine*. This base was prepared in 67% yield from β-*o*-chloropropionamide in a similar manner. It is a colourless liquid, b.p. 128°/23–26 mm. The *picrate* forms yellow crystals from alcohol, m.p. 187°. (Found: C, 43.7; H, 3.9; Cl, 9.2. $C_8H_{10}NCl,C_6H_3O_7N_3$ requires C, 43.7; H, 3.4; Cl, 9.2%.) The *hydrobromide*, which is very soluble in alcohol, separates from a concentrated solution as a *dihydrate*, m.p. 92° with previous sintering. (Found: loss at 50° in a vacuum 12.2. $C_8H_{10}NCl,2H_2O$ requires loss 13.2%.) The anhydrous salt has m.p. 190°. (Found: C, 40.9; H, 4.9; N, 6.1; Cl, 14.7; Br, 33.2. $C_8H_{10}NCl,HBr$ requires C, 40.6; H, 4.7; N, 5.9; Cl, 15.0; Br, 33.8%.)

1 : 6-*Bis*(β-p-*chlorophenylethylamino*)*hexane* (No. 13). β-p-Chlorophenylethylamine (4 mols.) in alcohol was heated under reflux for 24 hours with 1 : 6-dibromohexane (1 mol.). The product was neutralized with 2*N*-alcoholic hydrobromic acid and after standing the crystalline deposit was filtered off and recrystallized to give 1 : 6-*bis*(β-p-*chlorophenylethylamino*)*hexane dihydrobromide* in colourless crystals, m.p. 301° (decomp.), yield 29%. (Found: N, 5.2; Cl, 12.5; Br, 28.1. $C_{22}H_{30}N_2Cl_2,2HBr$ requires N, 5.1; Cl, 12.8; Br, 28.8%.) The *dipicrate* separated from alcohol in yellow crystals, m.p. 219°. (Found: C, 48.5; H, 4.8; N, 12.9; Cl, 8.0. $C_{22}H_{30}N_2Cl_2,2C_6H_3O_7N_3$ requires C, 48.0; H, 4.3; N, 13.2; Cl, 8.3%.) The bases liberated from the mother-liquors from the above hydrobromide were converted to picrates from which *N*-β-p-*chlorophenylethylhexamethylene*imine *picrate* was obtained by extraction with benzene. It separated from this solvent in yellow needles, m.p. 181° in a yield of 32%. (Found: C, 51.8; H, 5.4; N, 12.1; Cl, 7.5. $C_{14}H_{20}NCl,C_6H_3O_7N_3$ requires C, 51.45; H, 5.0; N, 12.0; Cl, 7.6%.) The *hydrobromide* forms plates from alcohol, m.p. 263° (decomp.). (Found: C, 52.8; H, 6.7; N, 4.6; Cl, 11.1; Br, 25.1. $C_{14}H_{20}NCl,HBr$ requires C, 52.75; H, 6.6; Cl, 11.1; Br, 25.1%.)

1 : 8-*Bis*(β-p-*chlorophenylethylamino*)*octane* (No. 14). The *dihydrobromide* was obtained in 44% yield by the above process using 1 : 8-dibromo-octane and *p*-chlorophenylethylamine. It is very sparingly soluble in alcohol from which it is deposited in crystals, m.p. 291° (decomp.). (Found: C, 49.4; H, 6.5; N, 4.9; Cl, 11.7; Br, 26.4. $C_{24}H_{34}N_2Cl_2,2HBr$ requires C, 49.4; H, 6.2; N, 4.8; Cl, 12.2; Br, 27.4%.) The *dipicrate* forms yellow crystals from alcohol, m.p. 183°. (Found : C, 49.3; H, 4.6; N, 12.6. $C_{24}H_{34}N_2Cl_2,2C_6H_3O_7N_3$ requires C, 49.2; H, 4.6; N, 12.7%.)

1 : 10-*Bis*(β-p-*chlorophenylethylamino*)*decane* (No. 15). The *dihydrobromide* was obtained in 53% yield from 1 : 10-dibromodecane and the appropriate amine in crystals from alcohol, m.p. 290° (decomp.). (Found: C, 51.3; H, 6.6; N, 4.6. $C_{26}H_{38}N_2Cl_2,2HBr$ requires C, 51.1; H, 6.6; N, 4.6%.) The *dipicrate* forms yellow needles from alcohol, m.p. 170°. (Found: C, 50.3; H, 5.0; N, 12.0. $C_{26}H_{38}N_2Cl_2,2C_6H_3O_7N_3$ requires C, 50.3; H, 4.9; N, 12.35%.) The *dilactate* separates from alcohol in crystals, m.p. 160°. (Found: N, 4.6; Cl, 11.9. $C_{26}H_{38}N_2Cl_2,2C_3H_6O_3$ requires N, 4.45; Cl, 11.3%.) The bismuth iodide (No. 16), formed by addition of excess of potassium bismuth iodide to a solution of the lactate in water forms an insoluble red powder approximating in composition to $B,2HI,BiI_3$. (Found: base 25.3. $B,2HI,BiI_3$ requires base, 23.8%.)

1 : 8-*Bis*(β-o-*chlorophenylethylamino*)*octane* (No. 17). The *dihydrobromide* was obtained in 38% yield by heating β-*o*-chlorophenylethylamine and 1 : 8-dibromo-octane in alcoholic solution. It is very sparingly soluble in alcohol from which it separates in crystals, m.p. 266° (decomp.). (Found: C, 49.8; H, 6.4; N, 4.7. $C_{24}H_{34}N_2Cl_2,2HBr$ requires C, 49.4; H, 6.2; N, 4.8%.) The *dipicrate* forms yellow crystals from alcohol, m.p. 154°. (Found: C, 49.3; H, 4.7; N, 13.1. $C_{24}H_{34}N_2Cl_2,2C_6H_3O_7N_3$ requires C, 49.2; H, 4.6; N, 12.7%.) The *dilactate* is very soluble in alcohol and crystallizes on addition of acetone, m.p. 171°. (Found: N, 4.6; Cl, 11.8. $C_{24}H_{34}N_2Cl_2,2C_3H_6O_3$ requires N, 4.65; Cl, 11.8%.) The bismuth iodide (No. 18) prepared in the usual manner from the lactate formed an insoluble red powder containing 26% of base.

1 : 10-*Bis*(β-o-*chlorophenylethylamino*)*decane* (No. 19). The *dihydrobromide* was obtained in 45% yield from 1 : 10-dibromodecane and the appropriate amine; it separates from much alcohol in crystals, m.p. 262° (decomp.). (Found: C, 51.4; H, 6.9; N, 4.3; Cl, 11.7; Br, 26.4. $C_{26}H_{38}N_2Cl_2,2HBr$ requires C, 51.1; H, 6.6;

N, 4.6; Cl, 11.6; Br, 24.15%.) The *dipicrate* forms yellow crystals from alcohol, m.p. 121°. (Found: N, 12.4; Cl, 7.5; $C_{26}H_{38}N_2Cl_2,2C_6H_3O_7N_3$ requires N, 12.35; Cl, 7.8%.) The *dilactate* (No. 19) is deposited from hot alcohol in crystals, m.p. 131°. (Found: C, 61.1; H, 8.1; N, 4.7. $C_{26}H_{38}N_2Cl_2,2C_3H_6O_3$ requires C, 61.0; H, 8.0; N, 4.45%.) Two different bismuth iodides were obtained by the addition of varying amounts of potassium bismuth iodide to an aqueous solution of the lactate. Preparation A (No. 20) contained 36.6% of base and B (No. 21) 22.9% of base. These correspond approximately to compounds of the composition $B,2HI,BiI_3$ and $B,2HI,2BiI_3$ which require 34.65% and 23.8% of base respectively.

1 : 6-*Bis*(β-*phenylethylamino*)*hexane* (No. 22). β-Phenylethylamine (10 g.) and 1 : 6-dibromohexane (10.16 g.) in benzene (30 cc.) were heated under reflux for 2 hours. After cooling 1 : 6-*bis*(β-*phenylethylamino*)-*hexane dihydrobromide* was collected and recrystallized from alcohol. It forms plates, m.p. 314–317°, yield 12.5%. (Found: C, 54.7; H, 7.2; N. 6.1; Br, 32.55. $C_{22}H_{32}N_2,2HBr$ requires C, 54.3; H, 7.05; N, 5.8; Br, 32.9%.) The *dilactate* (No. 23) separates from alcohol-acetone in prisms, m.p. 155–157°. (Found: C, 66.6; H, 8.95. $C_{22}H_{32}N_2,2C_3H_6O_3$ requires C, 66.7; H, 8.8%.)

1 : 7-*Bis*(β-*phenylethylamino*)*heptane* (No. 24). The *dihydrobromide* was obtained in 24% yield from 1 : 7-dibromoheptane and β-phenylethylamine by the above method. It forms plates from alcohol, m.p. 313°. (Found: C, 55.2; H, 7.4. $C_{23}H_{34}N_2,2HBr$ requires C, 55.2; H, 7.2%.) The *dilactate* separates from acetone in crystals, m.p. 150–152°. (Found: C, 67.3; H, 9.1. $C_{23}H_{34}N_2,2C_3H_6O_3$ requires C, 67.2; H, 8.9%.)

1 : 8-*Bis*(β-*phenylethylamino*)*octane* (No. 25). 1 : 8-Diamino-octane (4.32 g.), obtained by the action of hydrazoic acid on sebacic acid, was heated on a water bath for 15 mins. with β-phenylethyl bromide (11.1 g.) and benzene (10 cc.). The solid which separated was collected and crystallized from alcohol. The *hydrobromide* was thus obtained in leaflets, m.p. 312°, yield 27%. (Found: C, 56.4; H, 7.6. $C_{24}H_{36}N_2,2HBr$ requires C, 56.0; H, 7.45%.) The *dilactate* forms needles, m.p. 150–151°. (Found: C, 67.8; H, 9.1. $C_{24}H_{36}N_2,2C_3H_6O_3$ requires C, 67.6; H, 9.1%.)

1 : 9-*Bis*(β-*phenylethylamino*)*nonane* (No. 26). β-Phenylethylamine (12.1 g.) and 1 : 9-dibromononane (14.3 g.) dissolved in benzene (25 cc.) were left to stand at room temperature for 48 hours. The crystalline solid which separated was recrystallized from alcohol to give the *dihydrobromide*, m.p. 300–302°, in 21.6% yield. (Found: C, 56.8; H, 8.05. $C_{25}H_{38}N_2,2HBr$ requires C, 56.8; H, 7.7%.) The *dilactate* forms clusters of needles from alcohol-acetone, m.p. 134–136°. (Found: C, 68.3; H, 9.4. $C_{25}H_{38}N_2,2C_3H_6O_3$ requires C, 68.1; H, 9.2%.)

1 : 10-*Bis*(β-*phenylethylamino*)*decane* (No. 27). β-Phenylethylamine and 1 : 10-dibromodecane heated for 2 hours under reflux in benzene solution furnished the *dihydrobromide* in 13.5% yield after crystallization from alcohol, m.p. 302°–304°. (Found: C, 57.7; H, 7.9. $C_{26}H_{40}N_2,2HBr$ requires C, 57.6; H, 7.8%.) The *dilactate* forms needles from alcohol-acetone, m.p. 146°. (Found: C, 68.7; H, 9.1. $C_{26}H_{40}N_2,2C_3H_6O_3$ requires C, 68.5; H, 9.35%.)

1 : 8-*Bis*(γ-*phenylpropylamino*)*octane* (No. 28). The *dihydrobromide* was obtained in 37% yield by heating γ-phenylpropylamine (4 mols.) with 1 : 8-dibromo-octane (1 mol.) in alcoholic solution for 24 hours. It forms crystals sparingly soluble in alcohol, m.p. 284° (decomp.). (Found: C, 57.5; H, 8.2; N, 5.1; Br, 29.9. $C_{26}H_{40}N_2,2HBr$ requires C, 57.6; H, 7.8; N, 5.2; Br, 29.5%.) The *dipicrate* gave yellow crystals from alcohol, m.p. 153°. (Found: C, 54.3; H, 5.75; N, 13.7. $C_{26}H_{40}N_2,2C_6H_3O_7N_3$ requires C, 54.2; H, 5.5; N, 13.4%.) The *dilactate* crystallizes from alcohol-acetone, m.p. 147°. (Found: C, 68.5; H, 9.4; N, 5.5. $C_{26}H_{40}N_2,2C_3H_6O_3$ requires C, 68.5; H, 9.35; N, 5.0%.)

1 : 10-*Bis*(γ-*phenylpropylamino*)*decane* (No. 29). The *dihydrobromide*, obtained in a similar manner in 50% yield from 1 : 10-dibromodecane and the amine, is sparingly soluble in alcohol and forms crystals, m.p. 283°. (Found: C, 59.1; H, 8.2; N, 4.3; Br, 28.4. $C_{28}H_{44}N_2$, 2HBr requires C, 58.9; H, 8.1; N, 4.9; Br, 28.0%.) The *dilactate* separates from alcohol-acetone in crystals, m.p. 119°. (Found: N, 4.8. $C_{28}H_{44}N_2,2C_3H_6O_3$ requires N, 4.8%.)

1 : 8-*Bis*(δ-*phenylbutylamino*)*octane* (No. 30). The *dihydrobromide* was obtained similarly in 32% yield from δ-phenylbutylamine and 1 : 8-dibromo-octane. It crystallizes from alcohol in needles, m.p. 281° (decomp.). (Found: C, 58.3; H, 8.0; N, 5.3; Br, 28.9. $C_{28}H_{44}N_2$, 2HBr requires C, 58.9; H, 8.1; N, 4.9; Br, 28.0%.) The *dilactate* crystallizes on addition of acetone to a concentrated alcoholic solution, m.p. 149°. (Found: C, 69.5; H, 9.4; N, 5.0. $C_{28}H_{44}N_2,2C_3H_6O_3$ requires C, 69.35; H, 9.6; N, 4.8%.)

1 : 10-*Bis*(δ-*phenylbutylamino*)*decane* (No. 31). The *dihydrobromide* was obtained in 43% yield from δ-phenylbutylamine and 1 : 10-dibromodecane. It is sparingly soluble in alcohol, m.p. 282° (decomp.). (Found: C, 60.4; H, 8.2; N, 4.8; Br, 26.9. $C_{30}H_{48}N_2,2HBr$ requires C, 60.2; H, 8.4; N, 4.7; Br, 26.7%.) The *dilactate* crystallized from alcohol, m.p. 125°. (Found: C, 69.8; H, 9.4; N, 4.8. $C_{30}H_{48}N_2,2C_3H_6O_3$ requires C, 70.1; H, 9.8; N, 4.5%.)

1 : 8-*Bis*(ε-*phenylamylamino*)*octane* (No. 32). The *dihydrobromide* was obtained in 73% yield from ε-phenylamylamine and 1 : 8-dibromo-octane. It is fairly soluble in hot alcohol and separates in crystals, m.p. 258°. (Found: C, 60.5; H, 8.0; N, 4.5. $C_{30}H_{48}N_2,2HBr$ requires C, 60.2; H, 8.4; N, 4.7%.) The *dilactate* forms six-sided plates from alcohol-acetone, m.p. 117°. (Found: C, 70.0; H, 9.8; N, 4.7. $C_{30}H_{48}N_2,2C_3H_6O_3$ requires C, 70.1; H, 9.8; N, 4.5%.)

1 : 8-*Bis*(*phenylmethylamino*)*octane* (No. 33). 1 : 8-Diamino-octane (2.9 g.) was heated under reflux with benzaldehyde (4.5 g.) for 1 hour to yield 1 : 8-*bis*-(*benzylideneamino*)*octane* which after distillation at 220–230/0.1 mm. crystallized on cooling, m.p. 30–31°. (Found : C, 82.8; H, 8.8. $C_{22}H_{28}N_2$ requires C, 82.5; H, 8.8%.) The anil was reduced with hydrogen (PtO_2

catalyst) in alcoholic solution. On addition of hydrochloric acid (*d* 1.2) to the filtered solution 1:8-*bis*-(*phenylmethylamino*)*octane dihydrochloride* was obtained m.p. 276-280° after crystallization from alcohol. (Found: C,66.4; H, 8.5; Cl, 17.9. $C_{22}H_{32}N_2,2HCl$ requires C, 66.5; H, 8.6; Cl, 17.9%.) The *base* formed crystals, m.p. 37–38.5°. (Found: C, 81.1; H, 9.8; N, 8.5. $C_{22}H_{32}N_2$ requires C, 81.4; H, 9.9; N, 8.6%.)

1 : 8-*Bis*(3′ : 4′-*methylenedioxyphenylmethylamino*)-*octane* (No. 34). By a similar procedure, piperonal was converted to 1:8-*bis*(3′:4′-*methylenedioxybenzylideneamino*)*octane*, m.p. 111–112° from alcohol. (Found: C, 70.8; H, 7.2. $C_{24}H_{28}O_4N_2$ requires C, 70.6; H, 6.9%.) Catalytic reduction gave the *base*, leaflets from alcohol, m.p. 69–70°. (Found: C, 69.7; H, 8.1; N, 6.6. $C_{24}H_{32}O_4N_2$ requires C, 69.9; H, 7.8; N, 6.8%.) The *dihydrochloride* melted at *ca.* 274°. (Found: C, 59.2; H, 6.9. $C_{24}H_{32}O_4N_2,2HCl$ requires C, 59.4; H, 7.1%.)

1 : 8-*Bis*(3′ : 4′-*dimethoxyphenylmethylamino*)*octane* (No. 35). Veratric aldehyde was converted similarly into 1:8-*bis*(3′:4′-*dimethoxybenzylideneamino*)*octane*, leaflets from alcohol, m.p. 108.5–109.5°. (Found: C, 71.2; H, 8.5. $C_{26}H_{36}O_4N_2$ requires C, 70.9; H, 8.2%.)

The *base*, obtained by catalytic reduction of the anil, formed leaflets from alcohol, m.p. 83°. (Found: C, 69.9; H, 9.0. $C_{26}H_{40}O_4N_2$ requires C, 70.2; H, 9.1%.) The *dihydrochloride* crystallized from alcohol, m.p. 231–232° (decomp.). (Found: C, 60.5; H, 8.1; Cl, 14.0. $C_{26}H_{40}O_4N_2,2HCl$ requires C, 60.4; H, 8.2; Cl, 13.7%.)

1 : 8-*Bis*(p-*methoxyphenylmethylamino*)*octane* (No. 36). *p*-Methoxybenzaldehyde with 1 : 8-diamino-octane yielded 1:8-*bis*(p-*methoxybenzylideneamino*)*octane*, leaflets from alcohol, m.p. 64–65°. (Found: C, 74.7; H, 8.3; N, 7.4. $C_{24}H_{32}O_2N_2$ requires C, 75.7; H, 8.5; N, 7.4%.) Reduction of the anil gave the *base*, m.p. 60.5–61.5°, after crystallization from light petroleum. (Found: C, 74.7; H, 9.4; N, 7.1. $C_{24}H_{36}O_2N_2$ requires C, 75.0; H, 9.4; N, 7.3%.) The *dihydrochloride* melted at 275–276°. (Found: C, 62.8; H, 8.3. $C_{24}H_{36}O_2N_2,2HCl$ requires C, 63.0; H, 8.4%.)

1 : 8-*Bis*(p-*dimethylaminophenylmethylamino*)*octane* (No. 37). *p*-Dimethylaminobenzaldehyde and 1:8-diamino-octane treated in the usual manner gave 1:8-*bis*(p-*dimethylaminobenzylideneamino*)*octane* which crystallized from alcohol in yellow leaflets, m.p. 105–106°. (Found: C, 75.8; H, 9.3. $C_{26}H_{38}N_4$ requires C, 76.8; H, 9.4%.) Catalytic reduction furnished the *base*, long, fibrous needles from light petroleum, m.p. 65–66°. (Found: C, 75.7; H, 10.2; N, 13.2. $C_{26}H_{42}N_4$ requires C, 76.1; H, 10.3; N, 13.65%.) The *tetrahydrochloride* formed a felted crystalline mass from alcohol, m.p. *ca.* 214° (decomp.). (Found: N, 9.3; Cl, 23.8. $C_{26}H_{42}N_4$, 4HCl requires N, 9.5; Cl, 23.9%.)

1:6-*Bis*(n-*heptylamino*)*hexane* (No. 38). *n*-Heptylamine (6.9 g.) was mixed with 1:6-dibromohexane (7.3 g.) and xylene (50 cc.). After standing overnight the mixture was heated under reflux for ½ hour. On cooling, the *dihydrobromide* separated; it forms plates from alcohol, m.p. 329°, yield 34%. (Found: C, 50.6; H, 9 8. $C_{20}H_{44}N_2,2HBr$ requires C, 50.6; H, 9.8%.) The *dihydrochloride* crystallizes in shining plates from alcohol-acetone, m.p. 340°. (Found: C, 62.8; H, 11.95; N, 7.35; Cl, 18.5. $C_{20}H_{44}N_2,2HCl$ requires C, 62.3; H, 12.0; N, 7.3; Cl, 18.4%.) The *dilactate* (No. 39) forms colourless needles from acetone, m.p. 105°. (Found: C, 63.0; H, 11.2. $C_{20}H_{44}N_2,2C_3H_6O_3$ requires C, 63.4; H, 11.45%.)

1:7-*Bis*(n-*heptylamino*)*heptane* (No. 40). The *dihydrobromide* was obtained in a similar manner from heptylamine and 1:7-dibromoheptane. It forms plates from alcohol, m.p. 318°. (Found: N, 5.8; Br, 32.8. $C_{21}H_{46}N_2,2HBr$ requires N, 6.0; Br, 33.1%.) The *dilactate* crystallizes from alcohol-acetone, m.p. 143–146°. (Found: C, 64.5; H, 11.3. $C_{21}H_{26}N_2,2C_3H_6O_3$ requires C, 64.0; H, 11.2%.)

1:8-*Bis*(n-*heptylamino*)*octane* (No. 41). *n*-Heptylamine (4.8 g.) and 1:8-dibromo-octane (5.72 g.) were heated under reflux with acetone (30 cc.) until solid separated. After cooling, the *dihydrobromide* was collected. It forms leaflets from alcohol, m.p. 308°, yield 25%. (Found: N, 5.8; Br, 32.3. $C_{22}H_{48}N_2,2HBr$ requires N, 5.45; Br, 31.8%.) The *dilactate* (No. 42) crystallizes from acetone in needles, m.p. 103–104°. (Found: C, 64.8; H, 11.5. $C_{22}H_{48}N_2,2C_3H_6O_3$ requires C, 64.6; H, 11.6%.)

1:9-*Bis*(n-*heptylamino*)*nonane* (No. 43). The *dihydrobromide* was obtained from *n*-heptylamine and 1:9-dibromononane in 25% yield by heating in xylene for 7 hours. It separates from alcohol in leaflets m.p. 305°. (Found: N, 5.6; Br, 31.4. $C_{23}H_{50}N_2,2HBr$ requires N, 5.4; Br, 30.9%.) The *dilactate* forms needles from acetone, m.p. 132–134°. (Found: C, 65.15; H, 12.1. $C_{23}H_{50}N_2,2C_3H_6O_3$ requires C, 65.1; H, 11.7%.)

1:10-*Bis*(n-*heptylamino*)*decane*, (No. 44). The *dihydrobromide* prepared similarly in 24% yield from *n*-heptylamine and 1:10-dibromodecane forms leaflets from alcohol, m.p. 320–322°. (Found: C, 54.55; H, 10.2; N, 5.5; Br, 30.2. $C_{24}H_{52}N_2,2HBr$ requires C, 54.3; H, 10.3; N, 5.3; Br, 30.1%.) The *dilactate*, needles from dry alcohol-acetone, melts at 138–139°. (Found: C, 65.6; H, 11.8. $C_{24}H_{52}N_2,2C_3H_6O_3$ requires C, 65.7; H, 11.8%.)

1:10-*Bis*(n-*hexylamino*)*decane* (No. 45). The *dihydrobromide* was obtained in 45% yield from 1:10-dibromodecane and *n*-hexylamine (4 mols.) by heating for 16 hours in dry alcohol. It forms colourless needles, m.p. 315–317°. (Found: C, 53.0; H, 9.8; N, 6.0; Br, 31.9. $C_{22}H_{48}N_2,2HBr$ requires C, 52.6; H, 10.0; N, 5.6; Br, 31.8%.) The *dilactate* separates from alcohol in feathery needles, m.p. 141–143°. (Found: C, 64.6; H, 11.6; N, 5.1. $C_{22}H_{48}N_2,2C_3H_6O_3$ requires C, 64.55; H, 11.6; N, 5.4%.)

1:8-*Bis*(n-*octylamino*)*octane* (No. 46). The *dihydrobromide*, obtained in 42% yield from 1:8-dibromo-octane and *n*-octylamine (4 mols.) in boiling alcohol (20 hours), forms plates, m.p. 314°. (Found: C, 54.2; H, 9.2; N, 5.5. $C_{24}H_{52}N_2,2HBr$ requires C, 54.3; H, 10.3; N, 5.3%.) The *dilactate* (No. 47) separates in plates from alcohol, m.p. 105–106°. (Found: C, 65.4; H, 11.5; N, 4.7. $C_{24}H_{52}N_2,2C_3H_6O_3$ requires C, 65.7; H, 11.8; N, 5.1%.)

1 : 8-*Bis*(n-*nonylamino*)*octane* (No. 48). The *dihydrobromide* was obtained similarly from *n*-nonylamine and 1 : 8-dibromo-octane in platelets, m.p. 310–312°. (Found: C, 56.4; H, 9.3; N, 4.95; Br, 28.8. $C_{26}H_{56}N_2,2HBr$ requires C, 55.9; H, 10.5; N, 5.0; Br, 28.6%.) The *dilactate* (No. 48) forms short thin needles from dry alcohol-acetone, m.p. 109–111°. (Found: C, 66.4; H, 11.95; N, 4.5. $C_{26}H_{56}N_2,2C_3H_6O_3$ requires C, 66.6; H, 11.9; N, 4.9%.)

1 : 10-*Bis*(n-*undecylamino*)*decane* (No. 49). 1 : 10-Diaminodecane (4.3 g.) in amyl alcohol (26 cc.) was boiled under reflux and *n*-undecylbromide (11.8 g.) added gradually during 6 hours. Heating was continued for a further 18 hours. On cooling the *dihydrobromide* separated as a mass of crystals which after recrystallization from *iso*propylalcohol and from alcohol formed feathery needles, m.p. 302–305°, yield 20%. (Found: C, 59.85; H, 11.05; N, 4.6; Br, 25.2. $C_{32}H_{68}N_2,2HBr$ requires C, 59.7; H, 11.0; N, 4.4; Br, 24.9%.)

1 : 10-*Bis*(2′-*ethyl*-n-*hexylamino*)*decane* (No. 50). 1-Bromo-2-ethyl-*n*-hexane (19.3 g.) and 1 : 10-diaminodecane (8.6 g.) were heated under reflux in benzene (50 cc.) for 15 hours. After removing the benzene, the residue was heated for 15 minutes with 2% alcoholic sodium hydroxide, the alcohol distilled off and the bases extracted with ether. The residue from the ether was extracted with hot ligroin (b.p. 90–120°), cooled, filtered from diaminodecane and then treated with dry HCl. The *dihydrochloride* which separated formed fine needles from water, m.p. 128–132°, yield 10%. (Found: C, 66.3; H, 12.1; N, 6.0; Cl, 15.4. $C_{26}H_{56}N_2,2HCl$, requires C, 66.5; H, 12.4; N, 6.0; Cl, 15.1%.) The *dihydrobromide* crystallizes from alcohol in fine needles, m.p. 169–172°. (Found: C, 56.3; H, 10.5; N, 5.3; Br, 28.6. $C_{26}H_{56}N_2,2HBr$ requires C, 55.9; H, 10.5; N, 5.0; Br, 28.6%.)

1 : 10-*Bis*(*triallylcarbinamino*)*decane* (No. 51). 1 : 10-Dibromodecane was heated in alcoholic solution with 7 mols. of triallylcarbinamine (Henze, Allen and Leslie, 1943) for 24 hours. The solvent was removed and the crystalline residue shaken with ether and sodium hydroxide. The ether on evaporation left an oil from which excess of triallylcarbinamine was removed by distillation under reduced pressure at an oil bath temperature of 140°. The residue was converted to *dihydrochloride*, colourless crystals from water, m.p. 246–251° (decomp.). (Found: C, 70.0; H, 10.5; N, 5.5; Cl, 13.5. $C_{30}H_{52}N_2,2HCl$ requires C, 70.15; H, 10.6; N, 5.5; Cl, 13.8%.) The *dinitrate* forms clusters of crystals from water, m.p. 190° (decomp.). (Found: C, 63.8; H, 9.85; N, 10.0. $C_{30}H_{52}N_2,2HNO_3$ requires C, 63.6; H, 9.6; N, 9.9%.)

1 : 10-*Bis*(*geranylamino*)*decane* (No. 52). 1 : 10-Dibromodecane was heated under reflux for 24 hours with 4 parts by weight of geranylamine. Addition of ether precipitated a mixture of hydrobromides which on recrystallization from *iso*propylalcohol gave silky platelets of *bis*(*geranylamino*)*decane dihydrobromide*, m.p. 218°. (Found: C, 59.3; H, 9.4; N, 4.6; Br, 26.7. $C_{30}H_{56}N_2$, 2HBr requires C, 59.4; H, 9.6; N, 4.6; Br, 26.35%.)

1 : 9-*Bis*(n-*octylamino*)-2 : 8-*dimethylnonane* (No. 53). 2 : 8-Dimethyl-1 : 9-dibromononane (5.4 g.) and *n*-octylamine (17.78 g.) in dry alcohol (30 cc.) were heated under reflux for 16 hours, the solvent removed and the residue shaken with ether and alkali. After removing the ether, excess of octylamine was distilled off under reduced pressure (12.0 g. b.p. 96–98°/45 mm.) and the residue converted to *dihydrobromide*. After recrystallization from *iso*propyl alcohol the salt was obtained in 60% yield, m.p. 248–251° with previous sintering. (Found: C, 56.5; H, 10.35; N, 4.7. $C_{27}H_{58}N_2,2HBr$ requires C, 56.6; H, 10.6; N, 4.9%.)

1 : 10-*Bis*(n-*octylamino*)-2 : 9-*dimethyldecane* (No. 54). The *dihydrobromide* was obtained in a similar manner from 2 : 9-dimethyl-1 : 10-dibromodecane, in 50% yield. It forms fine needles from *iso*propyl alcohol, m.p. 242–244°, with previous sintering. (Found: C, 57.65; H, 10.7; N, 5.05. $C_{28}H_{60}N_2,2HBr$ requires C, 57.3; H, 10.7; N, 4.8%.)

1 : 8-*Bis*(cyclo*hexylamino*)*octane* (No. 55) was obtained from 1 : 8-dibromo-octane and *cyclo*hexylamine. After removal of excess *cyclo*hexylamine the *base* was distilled at about 200°/0.2 mm. (yield 84%). After a second distillation the base crystallized on cooling, m.p. 27–28°. (Found: N, 8.9. $C_{20}H_{40}N_2$ requires N, 9.1%.) The *dihydrochloride* forms colourless crystals from hot alcohol in which it is sparingly soluble, m.p. 284–285°. (Found: C, 63.0; H, 11.1; Cl, 18.6. $C_{20}H_{40}N_2,2HCl$ requires C, 63.0; H, 11.1; Cl, 18.6%.)

1 : 10-*Bis*(cyclo*hexylamino*)*decane* (No. 56) was obtained in a similar manner from 1 : 10-dibromodecane in 95% yield. The *base* boils at *ca.* 205°/0.2 mm. and crystallizes on cooling, m.p. 35–36.5°. (Found: C, 78.3; H, 13.1. $C_{22}H_{44}N_2$ requires C, 78.5; H, 13.2%.) The *dihydrochloride* forms colourless crystals from alcohol, m.p. 322° (decomp.). (Found: C, 64.7; H, 11.3; Cl, 17.45. $C_{22}H_{44}N_2,2HCl$ requires C, 64.5; H, 11.3; Cl, 17.3%.)

1 : 10-*N*: *N*′-*Dimorpholyldecane* (No. 57). 1 : 10-Dibromodecane (4.5 g.) was heated under reflux for 12 hours with morpholine (5.22 g.) and dry alcohol (15 cc.). Some morpholine hydrochloride separated. The mixture was made alkaline with NaOH and steam distilled to remove morpholine and alcohol. The residue was extracted with ether and the base converted to *dihydrochloride* which separates from dry alcohol in needles, m.p. 240–242° (decomp.) yield 84%. (Found: C, 56.15; H, 10.3; N, 7.4; Cl, 18.25. $C_{18}H_{36}O_2N_2,2HCl$ requires C, 56.1; H, 9.9; N, 7.3; Cl, 18.4%.)

1 : 10-*Bis*(β-*diethylaminoethylamino*)*decane* (No. 58). 1 : 10-Diaminodecane (8.2 g.) in benzene (50 cc.) was mixed with freshly prepared β-diethylaminoethyl chloride and left overnight. Potassium carbonate (7.9 g.) was added and the mixture heated under reflux for 20 hours. After removing the benzene the residue was shaken with ether and sodium hydroxide solution. The ether was dried and evaporated, and the residue distilled. A fraction b.p. 200–240°/6 mm. was collected and converted to *tetrahydrobromide*. It forms microscopic needles from amyl alcohol, m.p. 190–192° (3.5 g.). (Found: C, 37.9;

H, 8.0; N, 8.9; Br, 45.6. $C_{20}H_{50}N_4$,4HBr requires C, 38.0; H, 7.8; N, 8.1; Br, 46.0%.)

1 : 5-*Bis*(n-*octylamino*)*pentane* (No. 59). Cadaverine (1.0 g.) in absolute alcohol (5 cc.) was heated under reflux for 7.5 hours with *n*-octyl bromide (3.8 g.). The *dihydrobromide* separated from alcohol in flat needles, m.p. 329–332° (decomp.), yield 15%. (Found: Br, 33.6. $C_{21}H_{46}N_2$,2HBr requires Br, 32.7%.) By heating 1 : 5-dibromopentane with *n*-octylamine only *N*-octylpiperidine, b.p. 136–8/18 mm. was obtained. The hydrochloride had m.p. 189–191°. (c.f. v. Braun and Buchmann, 1931.)

1 : 3-*Bis*(n-*propylamino*)*propane* (No. 60). The *dihydrobromide* was obtained by adding 1 : 3-dibromopropane (20.2 g.) slowly during 2.5 hours to a boiling solution of *n*-propylamine (11.8 g.) in benzene (20 cc.). The mixture was heated for a further 4 hours, the hydrobromide filtered off and recrystallized from alcohol. It forms plates, m.p. 304° (7.0 g.). (Found: N, 8.75; Br, 49.7. $C_9H_{22}N_2$,2HBr requires N, 8.75; Br, 50.0%.)

1 : 3-*Bis*(n-*heptylamino*)*propane* (No. 61). *n*-Heptylamine (11.5 g.) was mixed with 1 : 3-dibromopropane (10.1 g.) in benzene (10 cc.). The mixture developed heat; it was left to stand for several days, the mush of crystals filtered off and washed with water to remove heptylamine hydrochloride. The residue of 1 : 3-*bis*(n-*heptylamino*)*propane dihydrobromide* furnished platelets from alcohol, m.p. 320–322°. (Found: C, 47.25; H, 8.9; N, 6.75; Br, 37.25. $C_{17}H_{38}N_2$,2HBr requires C, 47.2; H, 9.3; N, 6.5; Br, 37.0%.)

1 : 3-*Bis*(n-*tridecylamino*)*propane* (No. 62). The *dihydrobromide* was obtained in 65% yield by heating 1 : 3-dibromopropane and *n*-tridecylamine in dry alcohol for 18 hours. After two crystallizations from alcohol it formed platelets, m.p. 304–307°. (Found: N, 4.8. $C_{29}H_{62}N_2$,2HBr requires N, 4.7%.) The *dilactate* separates from alcohol in rosettes of stout needles, m.p. 148–150°, very sparingly soluble in water. (Found: C, 68.0; H, 12.0; N, 4.8. $C_{29}H_{62}N_2$,$2C_3H_6O_3$ requires C, 67.9; H, 12.05; N, 4.5%.)

1 : 10-*Bis*(*di*-n-*butylamino*)*decane* (No. 64). This was obtained by the method of B.P. 433,086. The *acid succinate* separates from ethyl acetate in oily drops which slowly crystallize. After washing with acetone the salt had m.p. 81–86°. (Found: C, 64.5; H, 10.3. $C_{26}H_{56}N_2$,$2C_4H_6O_4$ requires C, 64.5; H, 10.8%.)

Summary

1. Several series of secondary diamines formally related to emetine have been prepared and tested against *Entamoeba histolytica* both *in vitro* and *in vivo*.

2. Selected members of the series have also been tested against experimental infections with trypanosomes, leishmania and malaria.

3. Bis (β - 3 : 4 - dimethoxyphenylethylamino) - alkanes in which the hydrocarbon chain contained 6 to 10 carbon atoms were active. The corresponding 4-monomethoxy compounds were less active.

4. Bis (β - phenylethylamino) alkanes also showed activity which was increased by the introduction of chlorine into the *ortho-* or *para-* positions of the benzene ring. The *ortho-* compound was most active but also more toxic. Bis(phenylalkylamino)alkanes with either a greater number or fewer carbon atoms between the nucleus and the amino group were less effective.

5. Bis(alkylamino)alkanes containing 7 or 8 carbon atoms in the alkyl groups and 6 to 10 carbon atoms in the connecting chain also showed activity. This was slightly higher *in vivo* than that of the bis(β-phenylethylamino)alkane series, but results at low dose-levels were erratic.

We are indebted to Dr. H. King for a gift of 1 : 10-bis(*n*-amylamino)decane dihydrochloride (No. 65). Our thanks are also due to Messrs. P. Amsden, P. Hankin, J. M. Judd, R. Nicholson, R. Penfound, F. J. Peters, K. Pratley, A. G. Turner, C. F. Varney and the Misses S. Pluthero and R. Shipman for much assistance in the experimental work.

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THE CHEMOTHERAPY OF AMOEBIASIS

PART III. VARIANTS OF BIS(DIAMYLAMINO)DECANE

BY

J. A. GOODSON, L. G. GOODWIN, J. H. GORVIN, M. D. GOSS, K. S. KIRBY, J. A. LOCK, R. A. NEAL, T. M. SHARP, AND W. SOLOMON

From the Wellcome Laboratories of Tropical Medicine, 183, Euston Road, London, N.W.1

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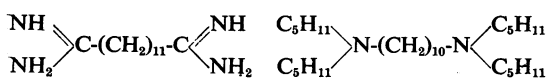
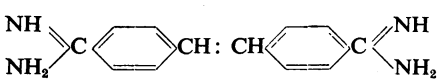
1 : 11-Diamidinoundecane (I) and 1 : 10-bis(di-*n*-amylamino)decane (II) are similarly constituted in that both contain two terminal basic radicals separated by a long chain of methylene groups. The former was shown by King, Lourie, and Yorke (1937) to be an active trypanocide in high dilution and the latter by Pyman (1937) to be an active amoebicide. Later Ashley, Barber, Ewins, Newbery, and Self (1942) modified the structure

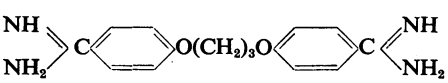


I

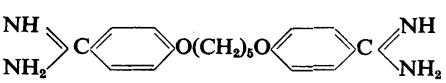
II



III



IV



V

of (I) by interrupting the chain with phenyl and phenylether groups, and obtained such compounds as 4 : 4′-diamidinostilbene (" stilbamidine ") (III), 4 : 4′-diamidinodiphenoxy-propane (" propamidine ") (IV) and -pentane (" pentamidine ") (V) which were shown by Lourie and Yorke (1939) to have greatly enhanced trypanocidal activity.

We have now studied the effect on amoebicidal activity of similar changes in the structure of 1 : 10-bis(di-*n*-amylamino)decane, and of the corresponding secondary bases. A few derived quaternary ammonium salts have also been included. The methods of testing were those described in Part I by Goodwin, Hoare, and Sharp (1948), and the results are given in Table I.

Discussion of Results in Table I

The results with the standard substances 1 : 10-bis(di-*n*-butylamino)decane (No. 64) and 1 : 10-bis-(di-*n*-amylamino)decane (No. 65, II) showed the compounds to be much less active *in vitro* than Pyman's results indicated. This may be due to the fact that the cultures used by Pyman contained a mixed bactericidal flora, whereas our tests were made upon a culture of amoebae with a single strain of *Bact. coli*. These compounds had no significant activity *in vivo*.

The tertiary aromatic amines (Nos. 67–73) were found to be completely inactive, both *in vitro* at a concentration of 10^{-4} and *in vivo* in high doses, and a similar inactivity was found in the series of tertiary aromatic amines containing ether groupings (Nos. 74–81). These are weak bases, but the more strongly basic tertiary araliphatic compounds (Nos. 82–84) also showed no significant activity.

Since all the active compounds recorded in Part II were secondary amines a number of secondary aromatic amines were prepared (Nos. 85–92); here a slight *in vitro* activity became apparent when the alkyl group was amyl (No. 92) or heptyl (No. 89), but the compounds had practically no action *in vivo*. Nos. 86, 87, and 90, which, in addition to the two secondary amino-groups, carry two tertiary amino-groups, again had but slight activity. The length of the chain connecting the benzene rings seems to have little or no influence in these series.

In the group of secondary araliphatic amines (Nos. 93 to 106), the majority of the compounds had a moderate degree of *in vitro* activity, two showed a slight *in vivo* activity at high dose-levels (Nos. 103 and 104), and in two cases (Nos. 100 and 105) there was a high *in vitro* activity but no action *in vivo*. This group shows clearly that the *in vitro* test taken alone is inadequate as a means of assessing the value of a new drug. In the above instance activity is shown by a group of compounds therapeutically useless; in Part I it

TABLE I

Columns 6 and 7: "+" signifies improvement, "−" no improvement.
Columns 10 and 11: "−" signifies no activity at a concentration of 10^{-4}.

Column 12: "1" signifies no activity against *T. equiperdum*.
"2" ,, ,, ,, ,, *T. rhodesiense*.
"3" ,, ,, ,, ,, *T. congolense*.
"4" ,, ,, ,, ,, *T. cruzi*.
"5" ,, ,, ,, ,, *Leishmania donovani*.
"6" ,, ,, ,, ,, *Plasmodium gallinaceum*.

Substance	Ref. No.	Approx. LD50 (mg./kg.)		Amoebicidal tests							Other tests
				in vivo					*in vitro*		
		Oral	Sub-cut.	% diet	Caecal condition		Rats clear	%	Amoebicidal conc.	Bact.-cidal conc.	
					Walls	Conts.					
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
$(C_4H_9)_2N(CH_2)_{10}N(C_4H_9)_2$, $2C_4H_6O_4$	64	500	930	0.5	−	−	3/6	50	10^{-4}	−	..
$(C_5H_{11})_2N(CH_2)_{10}N(C_5H_{11})_2$, 2HCl	65	..	..	0.5 0.2 0.1	+ + −	+ + −	3/7 7/14 3/12	40 50 25	10^{-5}	−	..
Tertiary aromatic amines											
$\left((C_4H_9)_2N\langle\bigcirc\rangle-\right)_2$, 2HCl	67	180	>2000	0.5 0.2 0.1	− − −	− − −	0/3 0/4 0/7	0 0 0	−	−	1,3,4, 5,6.
$\left((C_5H_{11})_2N\langle\bigcirc\rangle-\right)_2$, 2HCl	68	2000	2000	0.5	−	−	8/11	75	−	−	..
$\left((C_4H_9)_2N\langle\bigcirc\rangle-\right)_2CH_2$, 2HCl	69	950	>2000	0.5 0.2 0.1	Toxic − −	 − −	 2/8 0/7	 25 0	−	−	1,4,6.
$\left((C_5H_{11})_2N\langle\bigcirc\rangle-\right)_2CH_2$, 2HCl	70	..	..	0.5	−	−	6/13	45	−	−	5.
$\left((C_4H_9)_2N\langle\bigcirc\rangle-\right)_2(CH_2)_2$, 2HCl	71	350	>2000	0.1	−	−	3/10	30	−	−	1,6.
$\left(C_5H_{11})_2N\langle\bigcirc\rangle-\right)_2(CH_2)_2$, 2HCl	72	>2000	>2000	0.5	−	−	1/5	20	−	−	1,3.
$\left((C_4H_9)_2N\langle\bigcirc\rangle CH=\right)_2$,2HCl	73	350	>2000	0.2	−	−	0/6	0	−	−	1,5,6.
Tertiary amino phenyl ethers											
$\left((C_4H_9)_2N\langle\bigcirc\rangle-\right)_2O$, 2HCl	74	230	>2000	0.5 0.2	− −	− −	0/6 1/5	0 20	−	−	..
$\left((C_5H_{11})_2N\langle\bigcirc\rangle-\right)_2O$, 2HCl	75	165	>2000	0.5	−	−	0/6	0	−	−	1,3.
$\left((C_4H_9)_2N\langle\bigcirc\rangle O-\right)_2CH_2$, 2HCl	76	2000	>2000	0.5	−	−	0/4	0	−	−	1,3.

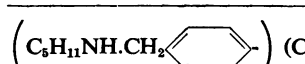
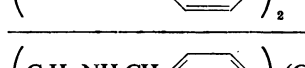
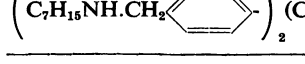
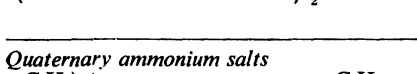
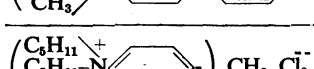
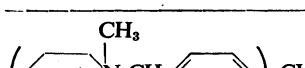
TABLE I—*continued*

Substance	Ref. No.	Approx. LD50 (mg./kg.)		Amoebicidal tests							Other tests
				in vivo					*in vitro*		
		Oral	Sub-cut.	% diet	Caecal condition		Rats clear	%	Amoebicidal conc.	Bact.-cidal conc.	
					Walls	Conts.					
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
$\left((C_5H_{11})_2N\text{-}C_6H_3\text{-}O\text{-}\right)_2CH_2$, 2HCl	77	470	350	0.5 0.2	— —	— —	4/7 3/5	55 60	—	—	..
$\left((C_4H_9)_2N\text{-}C_6H_3\text{-}O\text{-}\right)_2(CH_2)_2$, 2HCl	78	600	>2000	0.2 0.1	— —	— —	2/8 0/8	25 0	—	—	4,5.
$\left((C_5H_{11})_2N\text{-}C_6H_3\text{-}O\text{-}\right)_2(CH_2)_2$, 2HCl	79	800	>2000	0.5 0.2 0.1	— + —	— + —	1/3 0/4 3/7	35 0 40	—	—	1,3, 5,6.
$\left((C_4H_9)_2N\text{-}C_6H_3\text{-}O\text{-}\right)_2(CH_2)_3$, 2HCl	80	2000	>2000	0.5	—	—	2/4	50	—	—	..
$\left((C_5H_{11})_2N\text{-}C_6H_3\text{-}O\text{-}\right)_2(CH_2)_3$, 2HCl	81	950	>2000	0.5	—	—	2/8	25	—	—	..
$\left((C_2H_5)_2N(CH_2)_2O\text{-}C_6H_4\text{-}\right)_2$, 2HCl	82	70	270	0.2	—	—	0/6	0	—	—	1,3,5.
Tertiary araliphatic amines											
$\left((C_4H_9)_2N.CH_2\text{-}C_6H_4\text{-}\right)_2$, 2HBr	83	350	>1000	0.5 0.2	Toxic —	—	1/8	10	—	—	4,6.
$\left(C_5H_{10}N.CH_2\text{-}C_6H_4\text{-}\right)_2CH_2$, 2HCl	84	..	..	0.5 0.2	+ —	+ —	Toxic 3/3 0/8	100 0	10^{-4}	—	..
Secondary aromatic amines											
$\left(C_4H_9NH\text{-}C_6H_4\text{-}\right)_2$, 2HCl	85	250	>2000	0.2	—	—	0/6	0	—	—	1,5,6.
$\left((C_2H_5)_2N(CH_2)_2NH\text{-}C_6H_4\text{-}\right)_2$, 3HCl	86	570	330	0.5 0.2	— —	— —	1/5 1/5	20 20	10^{-4}	—	2,3.
$\left((C_2H_5)_2N(CH_2)_3NH\text{-}C_6H_4\text{-}\right)_2$, 4HBr	87	..	..	0.5 0.2	+ —	+ —	3/8 2/7	40 30	10^{-4}	—	(6).
$\left(C_4H_9NH\text{-}C_6H_4\text{-}\right)_2CH_2$, 2HCl	88	300	>2000	0.2 0.1	— —	— —	0/3 1/9	0 10	—	—	1,6.
$\left(C_7H_{15}NH\text{-}C_6H_4\text{-}\right)_2CH_2$, 2HCl	89	>2000	>2000	0.5 0.2 0.1	+ — —	+ — —	Toxic 2/8 0/6	 25 0	—	—	..

TABLE I—*continued*

Substance	Ref. No.	Approx. LD50 (mg./kg.)		Amoebicidal tests							Other tests
				in vivo					*in vitro*		
		Oral	Sub-cut.	% diet	Caecal condition		Rats clear	%	Amoe-bicidal conc.	Bact. -cidal conc.	
					Walls	Conts.					
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
$\left((C_2H_5)_2N(CH_2)_2NH\text{-}C_6H_4\right)_2CH_2$, 4HCl	90	..	1400	0.5	—	—	0/6	0	10^{-4}	—	5,6.
$\left(C_4H_9NH\text{-}C_6H_4\right)_2(CH_2)_2$, 2HCl	91	..	..	..	..	..	..	..	—	—	6.
$\left(C_5H_{11}NH\text{-}C_6H_4\right)_2(CH_2)_2$, 2HCl	92	>2000	>2000	0.5 0.2	+ —	+ —	1/4 4/5	25 80	10^{-4}	—	1,3,6.
Secondary araliphatic amines											
$C_3H_7NH.CH_2C_6H_4CH_2NH.C_3H_7$, 2HCl	93	550	450	0.15	—	—	0/6	0	—	—	6.
$C_4H_9NH.CH_2C_6H_4CH_2NH.C_4H_9$, 2HCl	94	350	310	0.5 0.2	— —	— —	2/6 1/5	35 20	—	—	2,3,6.
$C_5H_{11}NH.CH_2C_6H_4CH_2NH.C_5H_{11}$, 2HCl	95	230	175	0.5	—	—	0/4	0	—	—	2,3.
$\left(C_4H_9NH.CH_2\text{-}C_6H_4\right)_2$, 2HCl	96	1500	1500	0.2	—	—	1/3	35	10^{-4}	—	2,3,6.
$\left(C_6H_5NH.CH_2\text{-}C_6H_4\right)_2$, 2HCl	97	930	810	0.5 0.2 0.1	— — —	— — —	Toxic 2/5 3/7	 40 40	10^{-4}	—	..
$\left(C_4H_9NH.CH_2\text{-}C_6H_4\right)_2CH_2$, 2HCl	98	..	..	0.5 0.2	— —	— —	0/3 2/4	0 50	10^{-4}	—	1,3.
$\left(C_5H_{11}NH.CH_2\text{-}C_6H_4\right)_2CH_2$, 2HCl	99	933	574	0.2	—	—	0/4	0	10^{-4}	—	6.
$\left(C_6H_5NH.CH_2\text{-}C_6H_4\right)_2CH_2$, 2HCl	100	..	..	0.5	—	—	2/4	50	—	—	5,6.
$\left(C_6H_5CH_2NH.CH_2\text{-}C_6H_4\right)_2CH_2$,2HCl	101	>2000	>2000	0.5	—	—	0/4	0	10^{-4}	—	..
$\left(C_3H_7NH.CH_2\text{-}C_6H_4\right)_2(CH_2)_2$, 2HCl	102	>2000	270	0.2	—	—	2/13	15	—	—	2,3.
$\left(C_4H_9NH.CH_2\text{-}C_6H_4\right)_2(CH_2)_2$, 2HCl	103	80	120	0.5 0.2	— —	— —	5/8 0/4	60 0	10^{-4}	—	..

TABLE I—*continued*

Substance	Ref. No.	Approx. LD50 (mg./kg.)		Amoebicidal tests							Other tests
				in vivo					*in vitro*		
		Oral	Sub-cut.	% diet	Caecal condition		Rats clear	%	Amoebicidal conc.	Bact.-cidal conc.	
					Walls	Conts.					
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
	104	..	250	0.5 0.2	+ —	+ —	3/4 1/8	75 10	10^{-5}	—	..
	105	>2000	>2000	0.2	—	—	0/1 T	oxic	10^{-5}	—	6.
	106	470	1000	0.5 0.2 0.1	Toxic + +	 + +	 2/5 4/7	 40 55	10^{-5}	—	..
Quaternary ammonium salts 	107	>2000	550	0.5 0.2	Toxic —	 —	 4/5	 80	10^{-4}	—	3.
	108	440	100	0.2 0.1 0.05	+ — —	— — —	6/6 0/4 0/2	100 0 0	10^{-4}	—	2,3.
,, $(CH_2)_2.\ddot{I}_2^-$	109	20	..	0.5	—	—	1/10	10	10^{-4}	—	1,3,6.
	110	..	..	0.5	—	—	4/8	50	..	..	..

was shown that diodoquin, although active *in vivo*, had no appreciable *in vitro* activity.

The quarternary ammonium salts (Nos. 107–110) were slightly more active than the corresponding tertiary bases (Nos. 67, 70, 72, and 84).

Chemical Section

Aromatic amines

NNN'N'-Tetra-n-*butylbenzidine* (No. 67). Benzidine (1.84 g., anhydrous) was refluxed in *n*-butanol with a 33% excess of *n*-butylbromide (7.3 g.) and potassium carbonate (3.7 g.) for 16 hours. The filtered solution was evaporated and the residue shaken with ether and aqueous sodium hydroxide to isolate the crude product, which was then dissolved in light petroleum (b.p. 40–60°) and passed through a column of activated alumina. The *base* (3.2 g., 78%), which exhibited a blue fluorescence in organic solvents, was obtained on evaporation of the petrol solution; it crystallized from alcohol in flakes m.p. 58.5°. (Found: C, 82.2; H, 10.8. $C_{28}H_{44}N_2$ requires C, 82.3; H, 10.9%). The *dipicrate*, which crystallized in yellow flakes from alcohol, had m.p. 203–204° (decomp.). (Found: C, 55.4; H, 5.9; N, 12.9. $C_{28}H_{44}N_2, 2C_6H_3O_7N_3$ requires C, 55.4; H, 5.8; N, 12.9%). The *dihydrochloride*, m.p. 240–250° (decomp.), was readily soluble in alcohol but suffered partial hydrolysis in aqueous solution. (Found: N, 6.1; Cl, 14.9. $C_{28}H_{44}N_2$, 2HCl requires N, 5.8; Cl, 14.8%). The base reacted with methyl iodide in benzene to form a *monomethiodide* (No. 107) which crystallized from ethanol, m.p. 146–147° (after drying at 100° *in vacuo*). (Found: C, 63.3; H, 8.5; I, 24.3. $C_{28}H_{44}N_2,CH_3I$ requires C, 63.3; H, 8.6; I, 23.1%).

An alternative method of obtaining tetra-*n*-butylbenzidine utilized the oxidative procedure of Ullmann and Dieterle (1904) and of Fröhlich (1911): Di-*n*-butylaniline (4.1 g.), concentrated sulphuric acid (20 g.), and turpentine (0.1 g.) were heated together at 190–200° for 4½ hours. The mixture was made alkaline and, after removal of unchanged dibutylaniline by steam-distillation, the residual mass was dried, powdered and extracted with

benzene (Soxhlet). The dark extract was evaporated and the residue, decolorized by filtration of its solution in light petroleum through alumina, consisted of NNN'N'-tetra-*n*-butylbenzidine (2.6 g., 64%).

NN'-Di-n-*butylbenzidine* (No. 85). When benzidine was butylated with only half the above quantity of *n*-butyl bromide the resulting mixture of bases was only partially soluble in light petroleum (b.p. 40–60°). When the undissolved substance was dissolved in benzene and passed through a column of alumina some unchanged benzidine remained in the column, while the benzene carried through *NN'-di*-n-*butylbenzidine*, which crystallized from alcohol in laminae m.p. 72°. (Found: C, 81.0; H, 9.8. $C_{20}H_{28}N_2$ requires C, 81.0; H, 9.5%.) The *dihydrochloride* crystallized from ethanol in fine needles m.p. *ca.* 280° (decomp.). (Found: C, 64.4; H, 8.4. $C_{20}H_{28}N_2$,2HCl requires C, 65.0; H, 8.2%.)

The base was also obtained in small yield by the oxidation of *n*-butylaniline with sulphuric acid in the manner previously described.

NNN'N'-Tetra-n-*amylbenzidine* (No. 68). The amylation of benzidine was carried out in a similar manner to the butylation, using a 33% excess of *n*-amylbromide in *n*-butanol. The *base* obtained on removal of the petroleum was distilled at *ca.* 270°/0.5 mm., and was obtained as an oil. (Found: C, 83.0; H, 11.5; N, 6.3. $C_{32}H_{52}N_2$ requires C, 82.7; H, 11.3; N, 6.0%.) The *dipicrate* crystallized from ethanol in small yellow prisms m.p. 186–187°. (Found: C, 57.4; H, 6.3; N, 12.5. $C_{32}H_{52}N_2$, $2C_6H_3O_7N_3$ requires C, 57.3; H, 6.3; N, 12.1%.) The *dihydrochloride*, m.p. 230–235° (decomp.), crystallized from ethanol on addition of ether. (Found: C, 70.9; H, 10.0. $C_{32}H_{52}N_2$,2HCl requires C, 71.5; H, 10.1%.)

Bis(p-*NN-di*-n-*butylaminophenyl*)*methane* (No. 69) This was prepared according to Reid and Lynch (1936) and, in 75% yield, by the butylation of bis(*p*-aminophenyl)methane. The base was obtained as an oil, b.p. 280–320°/20 mm. (Found: C, 82.7; H, 11.4. Calc.: C, 82.4; H, 11.0%.) The dipicrate, golden flakes from ethanol, had m.p. 183–184° (Reid and Lynch, 1936, recorded m.p. 156°). (Found: C, 55.8; H, 5.9; N, 12.8. Calc.: C, 55.9; H, 6.0; N, 12.7%.) The *dihydrochloride* m.p. *ca.* 220° (decomp.) was very soluble in ethanol and in water. (Found: Cl, 14.6. $C_{29}H_{46}N_2$,2HCl requires Cl, 14.3%.)

Bis(p-*NN-di*-n-*amylaminophenyl*)*methane* (No. 70). The *base*, obtained by amylation of bis(*p*-aminophenyl)-methane with a 33% excess of *n*-amylbromide in the manner previously described, formed a viscous oil. (Found: C, 83.1; H, 11.2. $C_{33}H_{54}N_2$ requires C, 82.8; H, 11.4%.) The *dihydrochloride* crystallized from ethanol, m.p. 203° (decomp.). (Found: Cl, 13.0. $C_{33}H_{54}N_2$,2HCl requires Cl, 12.9%.) The *dimethiodide*, flat jagged needles from ethanol, had m.p. *ca.* 140° in a sealed tube (softening at 70–75°). (Found: N, 3.8; I, 33.4. $C_{33}H_{54}N_2$,$2CH_3I$ requires N, 3.7; I, 33.3%.) The dimethochloride (No. 108) was prepared from this by the usual procedure.

Butylation of α: β-*bis*(p-*aminophenyl*)*ethane*. Butylation carried out by the standard method previously described gave an oil which distilled at *ca.* 230°/0.01 mm. The distillate, α: β-*bis*(p-*NN-di*-n-*butylaminophenyl*)*ethane* (No. 71), crystallized from ethanol in laminae m.p. 34.5–35.5°. (Found: C, 82.5; H, 11.1; N, 6.7. $C_{30}H_{48}N_2$ requires C, 82.5; H, 11.1; N, 6.4%.) The base and its solutions in ether or alcohol exhibited a strong violet fluorescence. The *dipicrate* crystallized from ethanol in golden needles or laminae m.p. 173.5–174.5° (slow heating); with rapid heating dimorphic change occurred at 174–175° and the m.p. was 188–189°. (Found: C, 56.7; H, 6.3; N, 12.6. $C_{30}H_{48}N_2$,$2C_6H_3O_7N_3$ requires C, 56.4; H, 6.1; N, 12.5%.) The *dihydrochloride*, soluble in ethanol and in water, had m.p. *ca.* 231° (decomp.). (Found: Cl, 13.9. $C_{30}H_{48}N_2$,2HCl requires Cl, 13.1%.)

When α: β-bis(*p*-aminophenyl)ethane (11.5 g.) was heated with *n*-butylbromide (35 g., 16% excess) in an autoclave at 200° for 40 hours the resulting mixture of bases reacted readily with acetic anhydride to give an oily product which was treated several times with warm light petroleum (b.p. 40–60°). Solid material crystallized from the petrol on standing and, on evaporation, the filtered solution gave an oil which was mainly α: β-bis(*p*-NN-di-*n*-butylaminophenyl)ethane. The solid material (12.8 g.) was crystallized from benzene/light petroleum to give α: β-*bis*(p-*N*-n-*butylacetamidophenyl*)-*ethane* in needles m.p. 85–86°. (Found: C, 76.2; H, 9.0; N, 6.8. $C_{26}H_{36}O_2N_2$ requires C, 76.4; H, 8.9; N, 6.9%.) On deacetylation with alcoholic hydrochloric acid this derivative gave α: β-*bis*(p-*N*-n-*butylaminophenyl*)*ethane* (No. 91) which formed crystals m.p. 86–87° from aqueous ethanol. (Found: C, 81.3; H, 9.6; N, 8.6. $C_{22}H_{32}N_2$ requires C, 81.5; H, 9.9; N, 8.6%.) The dihydrochloride had m.p. *ca.* 235° (decomp.). (Found: Cl, 18.3. $C_{22}H_{32}N_2$,2HCl requires Cl, 17.8%.)

Amylation of α: β-*bis*(p-*aminophenyl*)*ethane*. The standard amylation procedure did not in this case bring about complete reaction; a further treatment with *n*-amyl bromide was found to be necessary. α: β-*Bis*(p-*NN-di*-n-*amylaminophenyl*)*ethane* (No. 72) crystallized from 80% alcohol in jagged needles m.p. 40° showing a strong violet fluorescence. (Found: C, 83.0; H, 11.6. $C_{34}H_{56}N_2$ requires C, 83.0; H, 11.5%.) The *dipicrate*, yellow needles from ethanol, had m.p. 207–208°. (Found: C, 58.0; H, 6.7; N, 12.1. $C_{34}H_{56}N_2$,$2C_6H_3O_7N_3$ requires C, 58.1; H, 6.6; N, 11.8%), and was used in separating the pure base from the incompletely amylated reaction product. The *dihydrochloride* had m.p. 214–215°. (Found: Cl, 12.4. $C_{34}H_{56}N_2$,2HCl requires Cl, 12.5%.) The *dimethiodide* (No. 109) separated as a crystalline powder m.p. 158–160° (decomp.) on addition of benzene to its alcoholic solution. (Found: C, 55.2; H, 8.0; I, 32.3. $C_{34}H_{56}N_2$,$2CH_3I$ requires C, 55.7; H, 8.1; I, 32.7%.)

When the products of the incomplete reaction in light petroleum (b.p. 40–60°) were passed through a column of alumina, α: β-*bis*(p-*N*-n-*amylaminophenyl*)*ethane* (No. 92) was adsorbed. The base was recovered by elution with ether/light petroleum and crystallized from ethanol in laminae m.p. 86°. (Found: C, 81.8; H, 10.2; N, 8.2. $C_{24}H_{36}N_2$ requires C, 81.8; H, 10.3; N, 8.0%.) The *dihydrochloride* had m.p. *ca.* 240° (decomp.). (Found:

N, 7.0; Cl, 17.0. $C_{24}H_{36}N_2,2HCl$ requires N, 6.6; Cl, 16.7%.)

Trans-4:4′-*bis*(*di*-n-*butylamino*)*stilbene* (No. 73). This was obtained on applying the standard butylation procedure to *trans*-4:4′-diaminostilbene. The *base*, which exhibited a strong violet fluorescence in organic solvents, crystallized from ethanol in opaque laminae m.p. 70–71°. (Found: C, 82.8; H, 10.7; N, 6.6. $C_{30}H_{46}N_2$ requires C, 82.9; H, 10.7; N, 6.5%.) The *dipicrate*, small golden needles from much ethanol, had m.p. *ca.* 213° (decomp.). (Found: C, 56.6; H, 6.0; N, 12.4. $C_{30}H_{46}N_2,2C_6H_3O_7N_3$ requires C, 56.5; H, 5.9; N, 12.6%.) The *dihydrochloride* had m.p. 240–242°. (Found: N, 5.7; Cl, 13.9. $C_{30}H_{46}N_2,2HCl$ requires N, 5.5; Cl, 14.0%.)

Tertiary aromatic amines derived from phenyl ethers

Bis(p-*aminophenoxy*)*alkanes*. The bis(*p*-aminophenoxy)alkanes used were prepared by the method described by Kinzel (1898) for the preparation of α:β-bis(*p*-aminophenoxy)ethane. α*γ*-*Bis*(p-*nitrophenoxy*)*propane* from sodium *p*-nitrophenate and 1:3-dibromopropane forms anhydrous crystals from alcohol, m.p. 132°. (Found: C, 56.6; H, 4.8; N, 8.8. $C_{15}H_{14}O_6N_2$ requires C, 56.6; H, 4.4; N, 8.8%.) α*γ*-Bis(*p*-acetamidophenyl)propane, m.p. 183°, was obtained in 87% yield by reduction of the above nitro compound with powdered iron and acetic acid (99%). On hydrolysis with hydrochloric acid it yielded α*γ*-*bis*(p-*aminophenyl*)*propane dihydrochloride*, m.p. 268° after recrystallization from water, yield 75%. (Found: C, 54.6; H, 6.2; N, 8.2; Cl, 21.4. $C_{15}H_{18}O_2N_2,2HCl$ requires C, 54.4; H, 6.1; N, 8.5; Cl, 21.4%.)

Bis(*dialkylaminophenyl*)*ethers* (Nos. 74–81). The general method for the preparation of these compounds is illustrated by the following example. To a boiling solution of 4:4′-diaminodiphenylether (4 g.) and *n*-butylbromide (22 g.) in alcohol (25 cc.), a solution of sodium (2.5 g.) in alcohol (80 cc.) was added at such a rate as to maintain a slightly alkaline reaction. After 12 hours the alcohol was removed and the residue diluted with water and extracted with ether. After distilling off the solvent the base was dissolved in light petroleum (b.p. 40–60°), passed through a column of alumina and purified as picrate. The picrate was then converted to hydrochloride in the usual manner. The properties of the compounds are given in Table II.

4:4′-*Bis*(β-*diethylaminoethoxy*)*diphenyl* (No. 82). 4:4′-Dihydroxydiphenyl (6.2 g.) was treated with sodium (1.6 g.) in ethanolic solution. The solution was refluxed overnight with β-diethylaminoethyl chloride (from 14.3 g. of the hydrochloride). The concentrated solution was made alkaline and extracted with ether; the resulting oil (3.5 g.). dissolved in light petroleum (b.p. 40–60°) was passed through a column of alumina. The *base* (2.9 g., 23%) obtained on removal of the solvent gave crystals, m.p. 45.5°, from aqueous alcohol. (Found: C, 75.0; H, 9.4; N, 7.4. $C_{24}H_{36}O_2N_2$ requires C, 75.0; H, 9.4; N, 7.3%.) The *dihydrochloride* had m.p. 244–245° (decomp.). (Found: C, 63.4; H, 8.6; Cl, 15.7. $C_{24}H_{36}O_2N_2,2HCl$ requires C, 63.0; H, 8.4; Cl, 15.5%.)

Tertiary araliphatic amines

4:4′-*Bis*(*di*-n-*butylaminomethyl*)*diphenyl* (No. 83). 4:4′-Bis(bromomethyl)diphenyl (3.4 g.) and dibutylamine (2.75 g.) in toluene (50 cc.) were heated under reflux for 10 hours. The somewhat oily solid was filtered off, washed with hot toluene and recrystallized from acetone. The *dihydrobromide* separated in long shining rods, m.p. 227°. (Found: C, 60.45; H, 9.0; Br, 26.3. $C_{30}H_{48}N_2,2HBr$ requires C, 60.2; H, 8.4; Br, 26.7%.)

4:4′-*Bis*(*N-piperidinomethyl*)*diphenylmethane* (No. 84). A solution of 4:4′-bis(bromomethyl)diphenylmethane (7.1 g.) and piperidine (3.4 g.) in ethanol (35 cc.) was refluxed for 7 hours, concentrated, and shaken with 10% sodium hydroxide and benzene. The benzene solution

TABLE II

Compound	No.	m.p.	Found % C	H	N	Cl	Formula	Requires C	H	N
Bis(p-*di*-n-*butylaminophenyl*)*ether*,2*HCl*	74		65.5	9.3		13.9	$C_{28}H_{44}ON_2,2HCl, H_2O$	65.2	9.4	
do. *dipicrate*		182°	54.4	5.7	13.3		$C_{28}H_{44}ON_2,2C_6H_3O_7N_3$	54.4	5.7	12
Bis(p-*di*-n-*amylaminophenyl*)*ether dipicrate*	75	148°	56.2	6.2	12.3		$C_{32}H_{52}ON_2,2C_6H_3O_7N_3$	56.3	6.2	11
Bis(p-*di*-n-*butylaminophenoxy*)*methane* 2*HCl*	76	88°[1]	62.3	9.4	5.15	12.7	$C_{29}H_{4}O_2N_2,2HCl,2H_2O$	62.0	9.0	5
do. *dipicrate*		168°	53.95	5.65	12.4		$C_{29}H_{46}O_2N_2,2C_6H_3O_7N_3$	53.95	5.7	12
Bis(p-*di*-n-*amylaminopheroxy*)*methane* 2*HCl*	77	84°[2]	63.95	9.5	4.7	11.5	$C_{33}H_{54}O_2N_2,2HCl,2H_2O$	63.95	9.8	4
do. *dipicrate*		140°	55.5	6.2	12.1		$C_{33}H_{54}O_2N_2,2C_6H_3O_7N_3$	55.9	6.2	11
αβ-*Bis*(p-*di*-n-*butylaminophenoxy*)*ethane* 2*HCl*	78	205°[3]			5.2	13.1	$C_{30}H_{48}O_2N_2$, 2HCl			5
do. *dipicrate*		156°	54.4	5.9	11.9		$C_{30}H_{48}O_2N_2,2C_6H_3O_7N_3$	54.4	5.9	12
αβ-*Bis*(p-*di*-n-*amylaminophenoxy*)*ethane* 2*HCl*	79	181°	68.0	9.65	5.0	11.4	$C_{34}H_{56}O_2N_2$, 2HCl	68.3	9.8	4
do. *dipicrate*		170°	56.3	6.7	11.6		$C_{34}H_{56}O_2N_2,2C_6H_3O_7N_3$	56.2	6.4	11
α*γ*-*Bis*(p-*di*-n-*butylaminophenoxy*)*propane* 2*HCl*	80	169°[4]	66.8	9.3	5.0	12.6	$C_{31}H_{50}O_2N_2$,2HCl	67.0	9.4	5
do. *dipicrate*		202°	54.9	5.9	12.3		$C_{31}H_{50}O_2N_2,2C_6H_3O_7N_3$	54.9	6.0	11
α*γ*-*Bis*(p-*di*-n-*amylaminophenoxy*)*propane* 2*HCl*	81	94°			4.8	11.5	$C_{35}H_{58}O_2N_2$,2HCl			4
do. *dipicrate*		198°	56.95	6.7	11.25		$C_{35}H_{58}O_2N_2,2C_6H_3O_7N_3$	56.6	6.5	11

[1]The anhydrous salt melts at 130°. [2]The anhydrous salt melts at 180°. [3]The dihydrate melts at 112°. [4]The dihydrate mel

gave an oil (3.1 g.) which was dissolved in light petroleum (b.p. 40–60°) and filtered through alumina. The resulting *base*, after distillation at 230°/0.5 mm., formed crystals m.p. 63–65° from aqueous ethanol. (Found: C, 82.0; H, 8.9; N, 7.5. $C_{25}H_{34}N_2$ requires C, 82.8; H, 9.5; N, 7.7%.) The *dipicrate*, orange-yellow needles from much ethanol, had m.p. 181–182° (after drying at 100° *in vacuo*). (Found: N, 13.8. $C_{25}H_{34}N_2,2C_6H_3O_7N_3$ requires N, 13.7%.) The *dihydrochloride* crystallized from alcohol-ether, m.p. *ca.* 300° (decomp.). (Found: C, 68.8; H, 7.8; Cl, 16.0. $C_{25}H_{34}N_2,2HCl$ requires C, 68.9; H, 8.3; Cl, 16.3%.) The *dimethiodide* separated from alcohol-benzene in yellowish crystals, m.p. 175° (decomp.). (Found: C, 50.6; H, 6.2. $C_{25}H_{34}N_2,2CH_3I$ requires C, 50.2; H, 6.2%.)

Secondary aromatic amines

NN'-Bis(β-diethylaminoethyl)benzidine (No. 86). Benzidine (4.4 g.) was refluxed overnight with β-diethylaminoethyl chloride (from 12 g. of the hydrochloride) and potassium carbonate (5 g.) in xylene. The solvent was removed by steam-distillation and a basic oil (11 g.) recovered by extraction with ether from alkaline solution. Partial purification was effected by passing the oil dissolved in light petroleum (b.p. 40–60°) through a column of alumina. The product (9.4 g.) was treated in ethanol with picric acid (11.5 g.) and the oily picrate which separated was extracted several times with acetone/ethanol. The extracts, on evaporation and basification, gave an oil from which an ether-insoluble hydrochloride (3.8 g.) was obtained. The *base* was obtained from this by treatment with ammonia; it crystallized in soft flakes m.p. 70° from aqueous ethanol. (Found: C, 75.3; H, 9.7; N, 14.6. $C_{24}H_{38}N_4$ requires C, 75.3; H, 10.0; N, 14.7%.) The *trihydrochloride*, soluble in ethanol, had m.p. *ca.* 235°. (Found: N, 21.8; Cl, 11.5. $C_{24}H_{38}N_4,3HCl$ requires N, 21.6; Cl, 11.4%.)

NN'-Bis(γ-diethylaminopropyl)benzidine (No. 87). Benzidine (4.5 g.) was refluxed with γ-diethylaminopropyl chloride and potassium carbonate in *n*-butanol, the method of procedure being that of the previous experiment. The oil (6.0 g.) obtained from the petrol solution gave a picrate (3.4 g.) when treated with picric acid (4.3 g.) in ethanol. The *base* (1.5 g.) obtained from the picrate was distilled at *ca.* 320°/0.4 mm. (Found: C, 76.4; H, 11.4; N, 13.3. $C_{26}H_{42}N_4$ requires C, 76.1; H, 10.3; N, 13.6%.) It formed a tetrahydrobromide as reported by Work (1940) and a *tripicrate* which separated as golden-yellow crystals m.p. 125° (decomp.) from acetone. (Found: C, 46.4; H, 4.8; N, 15.8. $C_{26}H_{42}N_4$, $3C_6H_3O_7N_3,2H_2O$ requires C, 46.6; H, 4.7; N, 16.1%.)

Bis(p-*N*-n-*butylaminophenyl)methane* (No. 88). This compound was obtained from *n*-butylaniline and formaldehyde as a crystalline solid m.p. 44–45°. (Wagner, 1934, gave m.p. 41–42°; Reid and Lynch, 1936, recorded m.p. 45°.) The *dihydrochloride* had m.p. 160–162°. (Found: C, 65.4; H, 8.5. $C_{21}H_{30}N_2,2HCl$ requires C, 65.7; H, 8.4%.)

Bis(p-*N*-n-*heptylaminophenyl)methane* (No. 89). Bis(*p*-aminophenyl)methane (2.47 g.) was boiled with sodamide (1 g.) in dry xylene for 4 hours; *n*-heptylbromide (4.5 g.) was added, and the mixture refluxed overnight. The solvent was removed by steam-distillation and the reaction product extracted with ether from alkaline solution. The resulting dark-coloured oil was dissolved in light petroleum (b.p. 40–60°) and the solution passed twice through a column of alumina. The colourless oil (4.0 g.) obtained on removal of solvent was distilled at 0.2 mm., collecting material distilling up to 280°. This crude base was treated in ethanol with a little 10% hydrochloric acid, causing the separation of an oily hydrochloride which on standing at 0° formed a semi-solid mass. This was pressed on a porous tile and crystallized from ethanol/ether to give bis(p-*N*-n-*heptylaminophenyl)methane dihydrochloride* (0.9 g., 15%) m.p. 195–196°. (Found: C, 69.1; H, 9.5. $C_{27}H_{42}N_2$, 2HCl requires C, 69.4; H, 9.5%), which readily became blue in moist air. The *base* was purified by alumina (in light petroleum/benzene) and formed crystals m.p. 48° from aqueous ethanol. (Found: C, 81.7; H, 10.7; N, 6.9. $C_{27}H_{42}N_2$ requires C, 82.2; H, 10.7; N, 7.1%.)

Bis(p-β-*diethylaminoethylaminophenyl)methane* (No. 90). Bis(*p*-aminophenyl)methane (9.9 g.) was refluxed overnight with β-diethylaminoethyl chloride (from 18.1 g. of the hydrochloride) and potassium carbonate (7.2 g.) in ethanol. The resulting basic oil (17 g.), purified by alumina (light petroleum solution) was distilled at 0.2 mm., collecting material (7.3 g.) distilling above 240°. This product was purified by recrystallization of the tetrahydrochloride, m.p. *ca.* 167–169° from ethanol. The salt was too deliquescent for satisfactory analyses to be obtained. The *base* was an oil b.p. *ca.* 280°/0.2 mm. (Found: C, 75.8; H, 10.2; N, 13.7. $C_{25}H_{40}N_4$ requires C, 75.7; H, 10.2; N, 14.1%.)

Secondary araliphatic amines

Preparation of aromatic bromomethyl compounds. A modification of the chloromethylation procedure of Cambron (1939) was adopted for the bromomethylation of benzyl bromide, diphenyl, diphenylmethane and α: β-diphenylethane. The general method is illustrated by the following example: Diphenylmethane (39 g.) was added to a mixture of paraformaldehyde (30 g.), hydrobromic acid (77 cc., *d* 1.7), phosphoric acid (57 cc., *d* 1.75) and glacial acetic acid (95 g.). The solution was maintained at 95–110° for 5 hours while dry hydrogen bromide (20–30 g.) was passed in, left overnight and heated for a further 8 hours. The mixture was poured into water (1,000 c.c.), and the pasty precipitate filtered off and crystallized from benzene. 4: 4'-*Bisbromomethyldiphenylmethane* (33 g., 40%) separated from benzene in long prisms m.p. 153.5°. (Found: C, 50.9; H, 4.0; Br, 45.1. $C_{15}H_{14}Br_2$ requires C, 51.0; H, 4.0; Br, 45.1%.)

In a similar manner were prepared p-xylylene dibromide (34% yield), 4: 4'-bisbromomethyldiphenyl (35%) (*cf.* v. Braun, 1937) and 4: 4'-*bisbromomethyl*-α: β-*diphenylethane* (34%) which crystallized from acetone in laminae m.p. 117–120°. (Found: C, 52.1; H, 4.5; Br, 43.1. $C_{16}H_{16}Br_2$ requires C, 52.2; H, 4.4; Br, 43.4%.)

Preparation of aromatic alkylaminomethyl derivatives (Nos. 93–106). Condensation of the bromomethyl compounds with alkylamines proceeded readily in such

solvents as alcohol, benzene or xylene, with or without the addition of sodium iodide. In all cases, however, the required product was accompanied by a considerable amount of amorphous substance of high molecular weight, apparently formed by condensation of the -NH groups in the product with further molecules of bromomethyl compound (*cf.* v. Braun, 1937); these rendered the purification of the product somewhat difficult. The formation of compounds of high molecular weight was reduced by refluxing the bromomethyl compound with an excess (10 mols.) of the alkylamine for 3–5 hours without other solvents. The excess of alkylamine was removed at 100° under reduced pressure and the residue shaken with 10% sodium hydroxide and ether. The oil obtained on evaporation of the ether was then treated with light petroleum (b.p. 40–60°) in which all the bases, with the exception of the 4 : 4′-bis(*cyclo*hexylaminomethyl) derivatives of diphenyl and α : β-diphenylethane, were very soluble, but in which the amorphous material was almost insoluble. The petroleum solution was clarified by filtration through alumina, and evaporated. The resulting base was dissolved in ethanol and the solution, filtered through kieselguhr to remove further traces of amorphous material, was treated with hydrochloric acid (*d* 1.2) to precipitate the *dihydrochloride*. This procedure was used in the preparation of all the compounds in Table III with the exception of two prepared in presence of a solvent. The *bases* were redistilled or, in some cases, crystallized from aqueous ethanol from which they separated in laminae. The dihydrochlorides were insoluble in ethanol but dissolved fairly readily in warm water to a neutral solution.

TABLE III

Compound	No.	b.p. or m.p.	Found %				Formula	Requires %			
			C	H	N	Cl		C	H	N	C
1 : 4-*Bis*(n-*propylaminomethyl*)*benzene*	93	b.p. *ca.*310°	76.5	10.9			$C_{14}H_{24}N_2$	76.3	11.0		
do. *dihydrochloride*		subl.>320°	57.8	8.9		24.2	$C_{14}H_{24}N_2,2HCl$	57.3	8.9		24
1 : 4-*Bis*(n-*butylaminomethyl*)*benzene*	94	Oil					$C_{16}H_{28}N_2$				
do. *dihydrochloride*		subl.>320°	60.2	9.1	8.4		$C_{16}H_{28}N_2,2HCl$	59.8	9.4	8.7	
1 : 4-*Bis*(n-*amylaminomethyl*)*benzene*	95	b.p.150°/0.2mm.	78.2	11.6	10.1		$C_{18}H_{32}N_2$	78.2	11.7	10.1	
do. *dihydrochloride*		decomp.>320°	62.3	10.0		20.4	$C_{18}H_{32}N_2,2HCl$	61.9	9.8		20
4 : 4′-*Bis*(n-*butylaminomethyl*)*diphenyl*	96	m.p.43.5–45°	81.6	10.0			$C_{22}H_{32}N_2$	81.4	9.9		
do. *dihydrochloride*		decomp.>360°	66.6	8.5		17.7	$C_{22}H_{32}N_2,2HCl$	66.5	8.6		17
4 : 4′-*Bis*(cyclo*hexylaminomethyl*)*diphenyl*	97	m.p.94.5–95.5°	83.8	9.8			$C_{26}H_{36}N_2$	82.9	9.6		
do. *dihydrochloride*		decomp.>360°	69.3	8.8		15.6	$C_{26}H_{36}N_2,2HCl$	69.5	8.5		15
4 : 4′-*Bis*(n-*butylaminomethyl*)*diphenyl-methane*	98	m.p.9–10°	80.9	10.4	8.2		$C_{23}H_{34}N_2$	81.6	10.1	8.3	
do. *dihydrochloride*		decomp.>320°	67.4	8.8	6.6	17.0	$C_{23}H_{34}N_2,2HCl$	67.2	8.8	6.8	17
4 : 4′-*Bis*(n-*amylaminomethyl*)*diphenyl-methane*	99	b.p.238°/1.0mm.	81.4	10.6	7.6		$C_{25}H_{38}N_2$	81.9	10.5	7.6	
do. *dihydrochloride*		decomp.*ca.*327°	68.8	9.1			$C_{25}H_{38}N_2,2HCl$	68.3	9.2		
4 : 4′-*Bis*(cyclo*hexylaminomethyl*)*diphenyl-methane*	100	m.p.37–38.5°	83.8	9.8			$C_{27}H_{38}N_2$	83.0	9.8		
do. *dihydrochlortde*		decomp.>320°	70.2	8.9		15.1	$C_{27}H_{38}N_2,2HCl$	70.0	8.7		15
4 : 4′-*Bis*(*benzylaminomethyl*)*diphenylmethane*	101	Oil	85.3	7.7	7.1		$C_{29}H_{30}N_2$	85.7	7.4	6.9	
do. *dihydrochloride*		decomp.>350°	72.0	6.7		14.4	$C_{29}H_{30}N_2,2HCl$	72.6	6.7		14
4 : 4′-*Bis*(n-*propylaminomethyl*)-α : β-*diphenylethane*	102	m.p.53–54.5°	81.8	10.1			$C_{22}H_{32}N_2$	81.4	9.9		
do. *dihydrochloride*		m.p.*ca.*345°	66.5	8.4		18.0	$C_{22}H_{32}N_2,2HCl$	66.5	8.6		17
4 : 4′*Bis*(n-*butylaminomethyl*)-α : β-*diphenylethane*	103	m.p.46–47°	81.8	10.4	7.9		$C_{24}H_{36}N_2$	81.8	10.3	8.0	
do. *dihydrochloride*		decomp.>320°	67.9	9.1		16.7	$C_{24}H_{36}N_2,2HCl$	67.8	9.0		16
4 : 4′-*Bis*(n-*amylaminomethyl*)-α : β-*diphenylethane*	104	m.p.7–8°	82.3	10.6	7.4		$C_{26}H_{40}N_2$	82.1	10.6	7.4	
do. *dihydrochloride*		decomp.333°	68.9	9.0		15.6	$C_{26}H_{40}N_2,2HCl$	68.9	9.3		15
4 : 4′-*Bis*(n-*heptylaminomethyl*)-α : β-*diphenylethane*	105	m.p.35–36°	81.3	11.3			$C_{30}H_{48}N_2$	82.5	11.1		
do. *dihydrochloride*		decomp.341°	70.7	10.5		13.9	$C_{30}H_{48}N_2,2HCl$	70.7	9.9		13
4 : 4′-*Bis*(cyclo*hexylaminomethyl*)-α : β-*diphenylethane*	106	m.p.115–116°	83.1	10.2			$C_{28}H_{40}N_2$	83.1	10.0		
do. *dihydrochloride*		decomp.>360°	69,7	9.4		14.7	$C_{28}H_{40}N_2,2HCl$	70.4	8.9		14

*By refluxing 4 : 4′-bischloromethyldiphenylmethane (7.7 g.) with *n*-butylamine (7.0 g.) and sodium bromide in xylene.
†By refluxing 4 : 4′-bisbromomethyldiphenylmethane (9.7 g.) with benzylamine (7.0 g.) and sodium iodide in xylene.

SUMMARY

1. A series of tertiary aromatic diamines in which two aromatic rings are connected by alkylene chains or chains interrupted by ether groupings have been shown to have no significant amoebicidal activity either *in vitro* or *in vivo*.

2. Some of the similarly constituted secondary diamines showed a slight activity *in vitro*.

3. Most of the secondary araliphatic diamines tested showed some activity *in vitro*, but no activity *in vivo* except at toxic dose-levels.

4. Quaternary ammonium salts were slightly more active than the corresponding tertiary bases.

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