[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF INDIANA UNIVERSITY]

PREPARATION OF POLYAMINO SUBSTITUTED DIPHENYLMETHANES[1]

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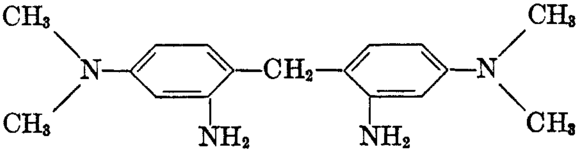
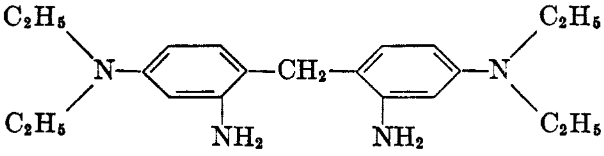
It has been known for a long time that acridine compounds possess antimalarial activity. The outstanding example of this type of compound is Atabrine which has sufficient activity to make it a good substitute for quinine. However, Atabrine like all other acridine derivatives is appreciably toxic. It is therefore important to continue the search for other quinine substitutes having fewer undesirable physiological side reactions. One approach to this problem is the synthesis of compounds closely related to Atabrine but not having the acridine nucleus.

It was found by Small (1) that 2,2′-diamino-4,4′-bisdimethylaminodiphenylmethane (I) and 2,2′-diamino-4,4′-bisdiethylaminodiphenylmethane (II) possess antimalarial activity in avian malaria.



I



II

These compounds may be thought of as precursors to the acridines and thus be related to Atabrine since it has been shown by Biehringer (2) that compounds of this type may be deaminated to produce dihydroacridines which are readily oxidized by oxygen or ferric chloride to acridines.

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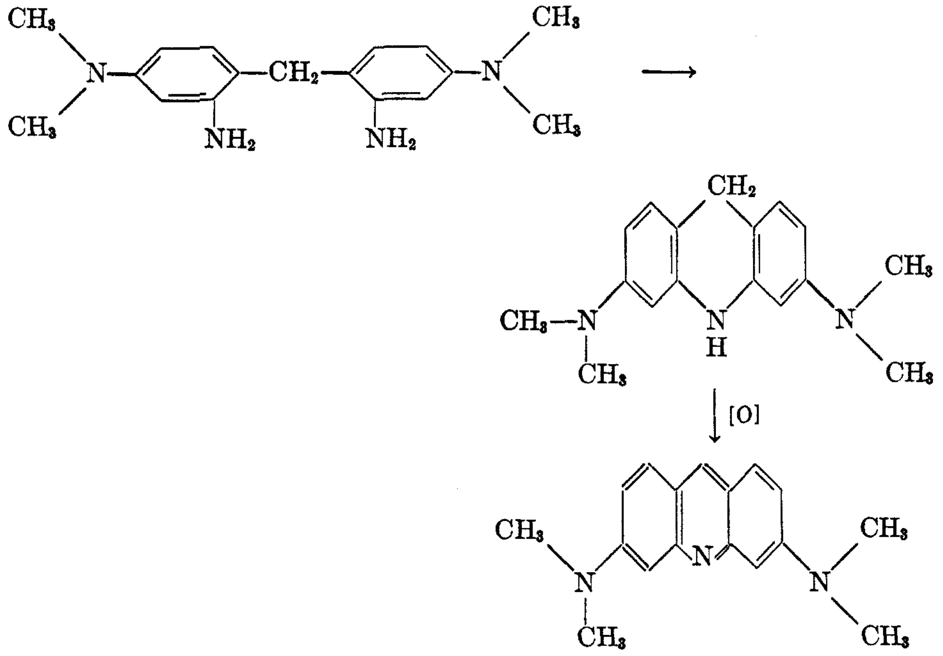
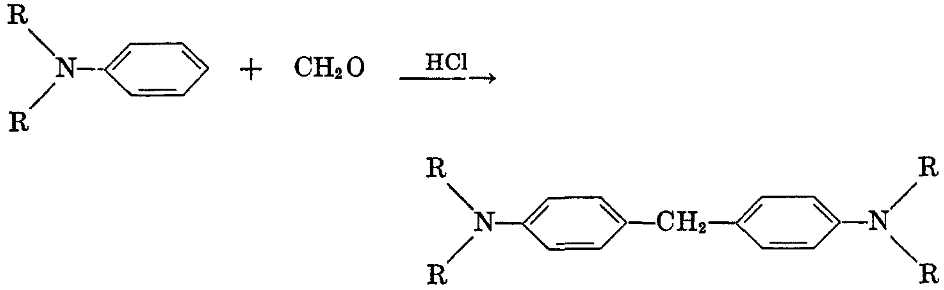
[1] This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Indiana University at Bloomington, Indiana.

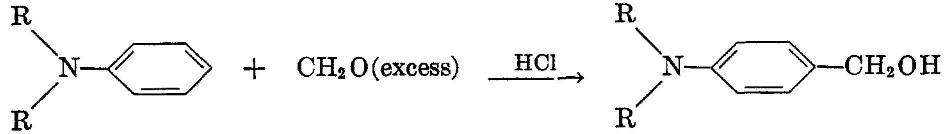


In view of these facts it was decided to prepare a number of chloro-, alkoxyl,- and alkyl-substituted polyaminodiphenylmethanes in order to see whether or not they would be more active and less toxic than the acridines.

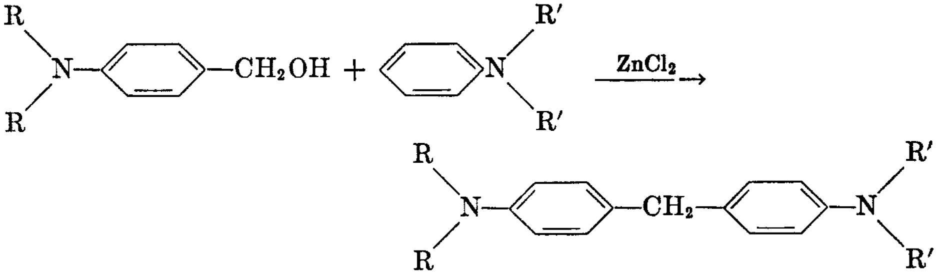
To prepare the symmetrically substituted diaminodiphenylmethanes the appropriate aniline derivatives were allowed to react with the calculated amount of formaldehyde.



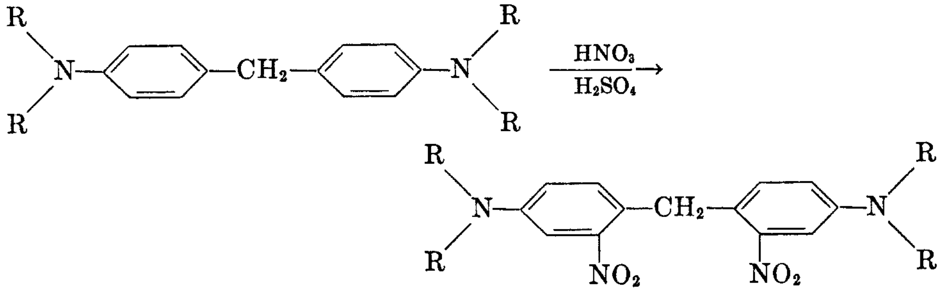
In the case of the unsymmetrically substituted diaminodiphenylmethanes it was necessary first to treat one of the substituted anilines with an excess of formaldehyde to obtain a benzyl alcohol.



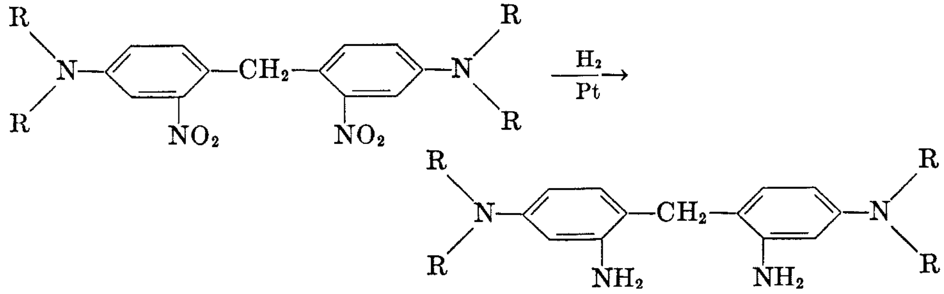
The benzyl alcohols thus formed were then allowed to react with another substituted aniline to produec the desired unsymmertical diaminodiphenylmethane derivative.



The tetraaminodiphenylmethanes were prepared by first nitrating the corresponding diaminodiphenylmethane with a sulfuric acid-nitric acid mixture to the dinitro derivative. According to previous workers these nitro groups enter the 2,2′ positions (2, 3). When half the calculated amount of nitric acid was used a mononitro derivative was formed.



The reduction of the dinitro compounds by the usual chemical methods was in general unsatisfactory for the yields were low or the nitro groups failed to reduce. Catalytic hydrogenation worked very well even with the compounds containing halogen atoms, provided that absolute ethyl alcohol was used as the solvent. It was found that water considerably reduced the rate of reduction of the dinitro compounds. This is in agreement with some observations made by Adams and co-workers (4) on the reduction of some simple mononitro compounds except that the effect of the presence of water on the reduction of the dinitro compounds was much more pronounced. Even a small percentage of water would add hours rather than minutes to the reduction time.



The compounds prepared are shown in Tables I, II, and III of the Experimental.

TABLE I

DIAMINODIPHENYLMETHANES

	M.P. OR B.P., °C., UNCORR.	CALC'D	FOUND
2,2'-Dichloro-4,4'-bis-(diethylamino)-diphenylmethane	68–69	N 7.38	7.37
3-Chloro-4,5'-bis-(dimethylamino)-2'-methoxydiphenylmethane*	104 (dec.)	N 3.96	4.00
3'-Chloro-4-dimethylamino-5'-diethylamino-2-methoxydiphenymethane	95	N 3.81	4.14
3,3'-Dichloro-4,4'-bis-(dimethylamino)-diphenylmethane$\cdot 2HCl$	70–73	Cl^- 17.92	17.87
3-Chloro-4-dimethylamine-4'-diethylamino-diphenylmethane*	115	N 3.97	4.30
3-Chloro-4-dimethylamino-4'-di-*n*-propylaminodiphenylmethane*	220 (dec.)	N 3.81	3.41
3-Chloro-4-dimethylamino-4'-di-*n*-butylaminodiphenylmethane*	220 (dec.)	N 3.68	3.71
3-Chloro-4-dimethylamino-5'-amino-2'-methoxydiphenylmethane$\cdot 2HCl \cdot 4H_2O$	172–174	Cl^- 16.3	16.2
3-Chloro-4-dimethylamino-2'-methyl-5'-aminodiphenylmethane$\cdot 2HCl \cdot 3H_2O$	174–176 (dec.)	Cl^- 17.6	17.4
4,4'-Bis-(methyl-*n*-propylamino)diphenylmethane	291–296/40 mm.		
2,4'-Bis-(dimethylamino)-5-methyldiphenylmethane	85–86		
2,2'-Dichloro-4,4'-bis-(dimethylamino)-diphenylmethane	98–99	[b]	
2,2'-Bis-(dimethylamino)-5,5'-dimethyl-diphenylmethane		[a]	
3-Chloro-4,4'-bis-(dimethylamino)-diphenylmethane		[b]	
4,4'-Bis-(methylethylamino)diphenylmethane	253–255/18 mm.	[c]	
3,3'-Dichloro-6,6'-bis-(dimethylamino)-diphenylmethane		[b]	
2,4'-Bis-(dimethylamino)-5-chlorodiphenylmethane	159–160	N 9.70	9.69

* Prepared as a salt of 1,1'methylene-bis-(2-hydroxy-3-naphthoic acid). The melting points are for the salts.

[a] Previously prepared by Braun and Kruber, *Ber.*, **45**, 2977 (1912).

[b] Previously prepaed by Braun and Kruber, *Ber.*, **46**, 3460 (1913).

[c] Previously prepared by Frohlich, *Ber.*, **44**, 1062 (1911).

Acknowledgment: We wish to thank Dr. Lyndon Small of The National Institute of Health, Bethesda, Maryland, for suggesting this problem.

EXPERIMENTAL

N,N-Dialkylanilines. These compounds were synthesized by treating the desired aniline with a trialkyl orthophosphate similar to the procedure previously described (5).

3-Chloro-4-dimethylaminobenzyl alcohol. 3-Chloro-4-dimethylaminobenzyl alcohol was prepared by the procedure of Braun and Kruber (6). A yield of 71.9 g. of the benzyl alcohol was obtained from 146.6 g. of *o*-chlorodiethylaniline. The other benzyl alcohols used in this work were prepared by a similar procedure.

TABLE II

NITRO-DIAMINODIPHENYLMETHANES

	M.P., °C. (UNCORR.)	CALC'D	FOUND
2,2'-Dinitro-4,4'-bis-(diethylamino)-diphenylmethane	119–120	[a]	
2,2'-Dinitro-4,4'-bis-(methyl-*n*-propylamino)diphenylmethane	83		
2,4'-Dinitro-2',4-bis-(diethylamino)-5-methyldiphenylmethane		11.94	11.90
2,2'-Dinitro-4,4'-bis-(diethylamino)-6,6'-dimethyldiphenylmethane	118–119	N 13.07	12.76
2,2'-Dinitro-6,6'-dichloro-4,4'-bis-(dimethylamino)diphenylmethane	157–157.5	Cl 17.19	17.24
2,2'-Bis-(dimethylamino)-4,4'-dinitro-5,5'-dimethyldiphenylmethane	107–108	[b]	
3-Chloro-4,4'-bis-(dimethylamino)-6,6'-dinitrodiphenylmethane	183		
2,2'-Dinitro-4,4'-bis-(methylethylamino)-diphenylmethane	101–102	N 15.05	14.74
3-Chloro-4-dimethylamino-2'-methyl-5'-nitrodiphenylmethane	86–87		
2,2'-Dinitro-4,4'-bis-(dimethylamino)-diphenylmethane		[c]	
2,2'-Dinitro-6,6'-dichloro-4,4'-bis-(diethylamino)diphenylmethane	77	N 11.94	11.90
4,4'-Dinitro-5,5'-dichloro-2,2'-bis-(dimethylamino)diphenylmethane	120–122	Cl 17.19	17.68
2-Nitro-6,6'-dichloro-4,4'-bis-(dimethylamino)diphenylmethane	95–98	Cl 19.29	19.62

[a] Previously prepared by Epstein, *Chem. Zentr.*, **74**, I, 798 (1903).

[b] Previously prepared by Braun, Kruber and Aust, *Ber.*, **46**, 3056 (1913).

[c] Previously prepared by Pinnow, *Ber.*, **27**, 3162 (1894).

Diaminodiphenylmethanes. Method A. The symmetrically substituted diaminodiphenylmethanes were synthesized by allowing two moles of the desired N,N-dialkylaniline to react with approximately nine-tenths of a mole of formaldehyde. A typical example of this method is illustrated by the preparation of 2,2'-dichloro-4,4'-bis-diethylaminodiphenylmethane.

Method B. The unsymmetrically substituted diaminodiphenylmethanes were prepared by allowing an aminobenzyl alcohol to react with an N,N-dialkylaniline. The preparation of 3-chloro-4-dimethylamino-4'-di-*n*-butylaminodiphenylmethane serves to illustrate the procedure used.

2,2'-Dichloro-4,4'-bis-diethylaminodiphenylmethane. To 100 g. (0.545 mole) of *m*-chlorodiethylaniline in a 500-cc. round-bottomed flask was added 68 g. of concentrated hydrochloric acid with stirring and cooling. To this solution was added 17.1 g. of 40% formaldehyde (8.8 g. or 83% of the theoretical amount) and it was allowed to stand for twelve hours. The solution was refluxed for five hours, allowed to stand for forty hours at room temperature, then poured upon 300 g. of ice and made basic with cold sodium hydroxide solution (60 g. of sodium hydroxide in 300 cc. of water). The product separated as an oil. The basic mixture was steam-distilled to remove the unchanged *m*-chlorodiethylaniline and then extracted with benzene. The benzene was removed by distillation and the residue was distilled under diminished pressure. The first fraction, which weighed 9 g., distilled at 95–100° (1.5–2 mm.). The main fraction of 61.8 g., which distilled at 240–250° (1.5–2 mm.), was 2,2'-dichloro-4,4'-bis-diethylaminodiphenylmethane. Crystals were obtained from alcohol which melted at 68–69°. Twenty-five and three-tenths grams of unchanged *m*-chlorodiethylaniline was recovered. The yield, based on the amount of *m*-chlorodiethylaniline which reacted, was 80.3%.

TABLE III

TETRA-AMINODIPHENYLMETHANES

	M.P., °C. (UNCORR.)	CALC'D	FOUND
2,2'-Diamino-4,4'-bis-(methyl-*n*-propylamino)diphenylmethane tetrahydrochloride		N 11.52	11.49
2,2'-Diamino-4,4'-bis-(diethylamino)-6,6'-dimethyldiphenylmethane trihydrochloride	180 (dec.)	Cl 22.30	22.30
2,2'-Diamino-4,4'-bis-(dimethylamino)-6,6'-dichlorodiphenylmethane dihydrochloride	(dec.)	Cl 33.29	33.21
2,2'-Bis-(dimethylamino)-4,4'-diamino-5,5'-dimethyldiphenylmethane trihydrochloride	[a]	Cl 25.22	25.12
3-Chloro-4,4'-bis-(dimethylamino)-6,6'-diaminodiphenylmethane	134	N 17.57	17.59
2,2'-Diamino-4,4'-bis-(methylethylamino)-diphenylmethane, salt with 1,1'-methylene-bis-(2-hydroxy-3-naphthoic acid)	210 (dec.)	N 5.14	4.76
2,2'-Dichloro-4,4'-bis-(diethylamino)-6,6'-diaminodiphenylmethane trihydrochloride tetrahydrate	193–195 (dec.)	Cl$^-$ 18.00	17.99
2,4'-Bis-(dimethylamino)-4,2'-diamino-5-methyldiphenylmethane		[b]	
2,2',4,4'-Tetra(diethylamino)diphenylmethane tetrahydrochloride	180–193	Cl 23.75	23.60
2,2'-Bis-(acetylamino)-4,4'-bis-(dimethylamino)diphenylmethane	231	N 15.21	15.00
2,2'-Diamino-4,4'-bis-(dimethylamino)-diphenylmethane		[c]	

[a] Previously prepared as the free base by Braun, Kruber and Aust., *Ber.*, **46**, 3056 (1913).

[b] Previously prepared by Braun, Kruber, and Aust, *Ber.*, **46**, 3056 (1913).

[c] Previously prepared by Biehringer, *J. prakt. Chem.*, [2], **54**, 242 (1899).

Anal. Calc'd for $C_{21}H_{28}Cl_2N_2$: N, 7.38. Found: N, 7.37.

2,2'-Dichloro-4,4'-bis-diethylamino-6,6'-dinitrodiphenylmethane. To 120 g. of concentrated sulfuric acid was added slowly 21.0 g. (0.055 mole) of 2,2'-dichloro-4,4'-bis-diethylaminodiphenylmethane. To this solution in a flask surrounded by a water-bath at room temperature was added with vigorous stirring a mixture of 11.4 g. (0.128 mole) of concentrated nitric acid and 11.4 g. of concentrated sulfuric acid. The addition required about an hour and during this time the water-bath became somewhat warmer. The orange solution was allowed to stand at room temperature for twenty-four hours, poured upon cracked ice and neutralized with a saturated sodium carbonate solution. The gummy material which separated was collected on a filter and washed thoroughly with water to remove the inorganic salts. The residue was recrystallized twice from hot alcohol; after the second recrystallization, 8.3 g. (32%) of the pure, orange 2,2'-dichloro-4,4'-bis-diethylamino-6,6'-dinitrodiphenylmethane was obtained which melted at 77°.

Anal. Calc'd for $C_{21}H_{26}Cl_2N_4O_4$: N, 11.94. Found: N, 11.90.

A similar procedure was used for the preparation of all of the dinitro compounds with the exception that some of the reactions were carried out at 0° instead of room temperature.

2,2'-Dichloro-4,4'-bis-diethylamino-6,6'-diaminodiphenylmethane trihydrochloride tetrahydrate. Three grams (0.064 mole) of 2,2'-dichloro-4,4'-bis-diethylamino-6,6'-dinitrodiphenylmethane was dissolved in 100 cc. of absolute alcohol and 0.057 g. of platimum oxide catalyst was added. Reduction was carried out at 25° and with an initial pressure of hydrogen of about forty pounds. The theoretical amount of hydrogen was used in about four hours. The solution was filtered by gravity into a warm flask containing low-boiling petroleum ether. The vapors of petroleum ether displaced the oxygen in the flask and thus prevented darkening of the amine. Most of the alcohol and petroleum ether were removed under reduced pressure. Low-boiling petroleum ether was added to the concentrated alcoholic solution and the solution cooled, but the amine oiled out of solution and could not be obtained crystalline.

After all the alcohol and petroleum ether had been removed, 100 cc. of dry benzene was added and dry hydrogen chloride passed into the solution for one or two minutes. A pink hydrochloride precipitated and was removed by filtration. Traces of solvent were removed under reduced pressure in a vacuum desiccator. A yield of 2.8 g. (79.8%) of 2,2'-dichloro-4,4'-bis-diethylamino-6,6'-diaminodiphenylmethane trihydrochloride trihydrate was obtained which melted with decomposition at 193–195°.

Anal. Calc'd for $C_{21}H_{41}Cl_5N_4O_4$: Cl (ionizable), 18.00. Found: Cl, 17.99.

3-Chloro-4-dimethylamino-4'-di-n-butylaminodiphenylmethane. To 25.0 g. (0.135 mole) of 3-chloro-4-dimethylaminobenzyl alcohol was added 52.0 g. (0.254 mole) of di-*n*-butylaniline and 40 g. of fused zinc chloride. After heating and stirring the mixture at 180° for nine and one-half hours, the viscous mass was poured into cold water. Excess sodium hydroxide was added to the solution and the mixture heated to boiling to dissolve the zinc hydroxide which precipitated when the complex was decomposed with base. The oily layer containing the product and unreacted starting material was removed from the water layer by extraction with benzene. The benzene solution was dried and distilled under reduced pressure. Twenty-one grams of di-*n*-butylaniline was recovered. The yield of 3-chloro-4-dimethylamino-4'-di-*n*-butylaminodiphenylmethane which distilled at 235–242°/3 mm., was 34.8 g. or 69.2% on the basis or the benzyl alcohol used.

To 10.325 g. (0.0277 mole) of this diamine was added about 10 cc. of concentrated hydrochloric acid. The solution was diluted and heated to boiling at which time a dilute ammonium hydroxide solution was added dropwise until a drop produced a point of lasting turbidity.

To 10.758 g. (0.0277 mole) of 1,1'-methylene-bis-(2-hydroxy-3-naphthoic acid) was added an excess of dilute ammonium hydroxide. The solution was made neutral by boiling until all of the excess ammonia was expelled.

When the above solutions were cool, and each had been diluted to about 400 cc. with distilled water, they were mixed with vigorous stirring. The precipitate which formed was filtered off and washed well with water. After drying the precipitate over phosphorus pentoxide the product weighed 20.1 g. This is a 95% yield of the 1,1′-methylene-bis(2-hydroxy-3-naphthoic acid) salt of 3-chloro-4-dimethylamino-4′-di-*n*-butylaminodiphenylmethane.

Anal. Calc'd for $C_{43}H_{49}ClN_4O_6$: N, 3.68. Found: N, 3.71.

SUMMARY

A series of 31 new di-, tri-, and tetra-amino substituted diphenylmethanes have been prepared. All of the tetra-amino diphenylmethanes and some of the diaminodiphenylmethanes were submitted for testing of their antimalarial activity.

BLOOMINGTON, IND.

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