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N,N′-Polymethylene-*bis*-anilines and Related Compounds

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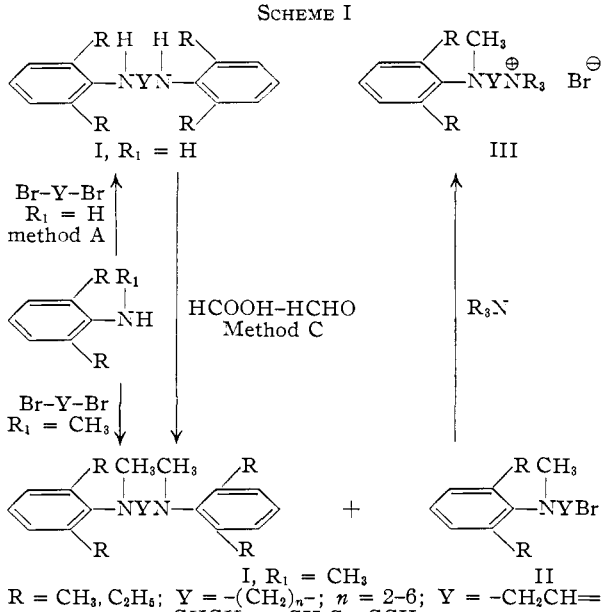
Series of N,N′-polymethylene-(2,6-dialkylanilines) and N-methyl-ω-2,6-dialkylanilinoalkylene halides have been synthesized for pharmacologic evaluation. Significant effects have been noted upon examination as anesthetics, central nervous system depressants and hypotensive agents.

It is generally accepted that steric factors associated with N,N-disubstituted-2,6-dialkylanilines result in loss of planarity with inhibition of resonance and hindrance to solvation[1] in these systems.

The pharmacologic response to such hindered functions would be anticipated to differ from that of typical aryl or alkylamines and could contribute distinctive therapeutic properties. In this paper the synthesis of a series of N,N′-polymethylene-bis-(2,6-dialkylanilines) was undertaken to examine the effects of such structures on pharmacologic activity.

The most convenient synthesis of the required compounds was by treatment of the selected polymethylene dihalide with an excess of the 2,6-dialkylaniline,[2] and the scope of reactions studied has been detailed in Scheme I.

SCHEME I



R = CH_3, C_2H_5; Y = $-(CH_2)_n-$; n = 2–6; Y = $-CH_2CH{=}CHCH_2-$; $-CH_2C{\equiv}CCH_2-$

This method proved to be serviceable for most of the variants of Y but did not yield the desired structure I, R_1 = H, Y = $-(CH_2)_4-$, probably as a result of pyrrolidine formation.[3] The corresponding structure I, R_1 = CH_3, Y = $(CH_2)_4-$, was obtained readily. The compounds of the type I, R_1 = H, could be converted to I, R_1 = CH_3, by N-methylation. The structures of the type I have been compiled in Table I.

The compounds of the type I, R_1 = CH_3, did not yield crystalline quaternary compounds with methyl iodide or methyl sulfate, which is attributable to steric hindrance.[1,4] The di-acid salts of the polymethyl-bis-anilines of the type I, R_1 = H, formed readily (see Table I, compounds 4, 6, 7, 9, 10, 21 and 23).

The reaction of the N-methyl-2,6-dialkylaniline with an excess of the α,ω-polymethylene dibromide or dichloride provided a convenient synthesis of the N-methyl-ω-2,6-dialkylanilinoalkyl halides (II). These compounds darkened rapidly on standing, and even upon storage at 10° became contaminated by a crystalline precipitate.[5] On reaction with tertiary amines, the freshly distilled aminoalkyl halide II yielded compounds (III) containing a quaternary nitrogen function and the hindered tertiary amine function. The compounds II and III have been described in Table II.

An alternative synthetic approach to structures of the type I was *via* the bis-anilides IV which were readily obtainable by the reaction of the dibasic acid chloride and the appropriately substituted aniline. The anilides so prepared have been described in Table III.

Inspection of the physical data shown in Table III indicates an interesting melting point pattern. The structures IV, R_1 = H, have high melting points, with IV, R = ethyl, melting lower than IV, R = methyl, in each instance. The melting points approach one another as "*n*" is increased (compounds 1 *vs.* 6, 2 *vs.* 7, 3 *vs.* 8, 4 *vs.* 9). Compound 4, wherein R_1 = methyl, melts 158° lower than its congener, compound 3, wherein R_1 = hydrogen. The melting point peak is reached when n = 2 (compounds 3 and 8). These factors, coupled with the poor solubility of the compounds in organic solvents, and the high steric strain of structures as formally shown would indicate that the bis-2,6-dialkylanilides described in Table III (with the exception of compound 4) exist largely in the form V.[6]

The existence of the bis-anilides in the form V would foretell difficulties with the projected use of

(1) (a) B. M. Wepster, *Rec. trav. chim.*, **76**, 357 (1957); (b) G. Thomson, *J. Chem. Soc.*, 1113 (1946); (c) R. N. Beale, *ibid.*, 4494 (1954); (d) M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 174; (e) H. C. Brown, *J. Chem. Soc.*, 1248 (1956); (f) W. G. Brown and S. Fried, THIS JOURNAL, **65**, 1841 (1943).

(2) A. H. Sommers and S. E. Aaland, *ibid.*, **75**, 5280 (1953).

(3) A. H. Sommers, *ibid.*, **78**, 2439 (1956).

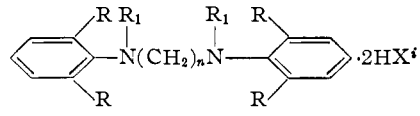
(4) Sommers and Aaland (ref. 2) found that N,N′-bis-(2,6-dimethoxyphenyl)-pentamethylenediamine gave only an oily hydrochloride salt, and the picrate derivative reflected a mixture of mono- and dipicrates.

(5) The nature of the precipitate was not established, but it is unlikely that steric factors would permit intramolecular quaternization and it is believed that dehydrohalogenation occurs with formation of the hydrochloride salt of the parent compound or of the dehydrohalogenated amine.

(6) A somewhat similar rationalization of melting point data was advanced by W. M. Pearlman and C. K. Banks, THIS JOURNAL, **70**, 3726 (1948), in a study of chlorodiamino-*sym*-triazines.

TABLE I

POLYMETHYLENE-BIS-(2,6-DIALKYLANILINES) AND SALTS

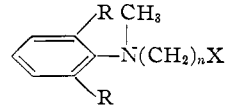


No.	n	HX	B.p., °C.	Mm.	M.p.,[a,b] °C.	Yield, %	Method	Formula	Analyses,[d] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
R = CH₃, R₁ = H														
1	2		168	0.2	37–40[c]	6	A	$C_{18}H_{24}N_2$	80.6	81.1	9.0	9.0	10.4	9.8
2	3		172–174	.2	71–73[c]	50	A	$C_{19}H_{26}N_2$	80.8	81.1	9.3	8.9	9.0	10.0
3	4		172–184	.11	61–63[c]	25	B	$C_{20}H_{28}N_2$	81.0	81.1	9.5	9.4	9.5	9.7
4	4	HPic.[g]			193–196[b1]			$C_{32}H_{34}N_8O_{14}$	50.9	51.3	4.5	4.6	14.8	14.8
5[f]	5		190–194	0.1	40–42[c]	17	A							
6[f]	5	HCl			249–250[b2]			$C_{21}H_{32}Cl_2N_2$					7.3	7.2[e1]
7	5	HPic.[g]			116–118[b1]			$C_{33}H_{36}N_8O_{14}$					14.6	14.8
8	6		200–210	0.1		40	A	$C_{22}H_{32}N_2$	81.4	81.5	9.9	9.9	8.6	8.8
9	6	HCl			198–205[b2]			$C_{22}H_{34}Cl_2N_2$					7.1	7.2[e2]
10	[h]	HCl			226–227[b2]	17	A	$C_{20}H_{26}Cl_2N_2$	65.7	66.1	7.1	7.3	7.7	7.8
R = CH₃, R₁ = CH₃														
12	2		148–152	0.2	48–51[c]	15	A	$C_{20}H_{28}N_2$	81.0	81.1	9.5	9.5	9.4	9.2
13	3		158–163	.05		43	C	$C_{21}H_{30}N_2$	81.2	81.2	9.7	10.0	9.0	9.0
14	4		150–154	.06		13	A	$C_{22}H_{32}N_2$	81.4	81.1	9.9	9.7	8.6	8.7
15	5		156–164	.03		28	C	$C_{23}H_{34}N_2$	81.6	81.5	10.1	10.1		
16	6		184	.04		52	C	$C_{24}H_{36}N_2$	81.8	81.6	10.3	10.4	8.0	8.0
17	[h]		158–162	.08		18	A	$C_{22}H_{28}N_2$	82.4	81.9	8.8	8.9	8.7	8.7
R = C₂H₅, R₁ = H														
18	2		178–184	0.08		33	A	$C_{22}H_{32}N_2$	81.4	81.7	9.9	9.6	8.6	8.7
19	3		243–258	.16		6	A	$C_{23}H_{34}N_2$	81.6	81.9	10.1	10.0		
20	5		186–194	.07		19	A	$C_{25}H_{38}N_2$	81.9	82.0	10.4	9.8		
21	5	HCl			188–195[b2]			$C_{25}H_{40}Cl_2N_2$	68.2	68.0	9.2	8.7	6.4	6.4
22	6		220–240	.3		18	A	$C_{26}H_{40}N_2$	82.0	81.8	10.6	10.4	7.4	7.3
23	6	HCl			179–185[b2]			$C_{26}H_{42}Cl_2N_2$	68.8	68.5	9.3	9.2	6.2	6.1[e3]
R = C₂H₅, R₁ = CH₃														
24	2		168–173	0.12		22	C	$C_{24}H_{36}N_2$	81.8	81.8	10.3	10.3	7.9	7.6
25	3		166–176	.18		9	C	$C_{25}H_{38}N_2$	81.9	81.4	7.6	8.4	10.5	10.5
26	5		174–184	.15		47	C	$C_{27}H_{22}N_2$	82.2	82.1	10.7	10.9	7.1	6.9

[a] Melting points were determined on a Fisher–Johns melting point block. [b] Recrystallizing solvent: [b1] water, [b2] methanol–ethyl acetate. [c] Melting points represent unrecrystallized material. The compounds were characterized as the liquids, and these on prolonged standing crystallized to yield solids melting as indicated. [d] Analyses by Weiler and Strauss, Oxford, England. [e] Halogen, % calcd., % found: [e1] 18.5, 18.5; [e2] 17.9, 18.3; [e3] 15.6, 15.7. [f] Reported b.p. 175–180° (0.1 mm.), m.p. 41–42°; the dihydrochloride, reported m.p. 247–248° in ref. 2. [g] HPic. = picric acid. [h] $-(CH_2)_n-$ is $CH_2C{=}CCH_2-$. [i] Compound not characterized under the HX column are free bases.

TABLE II

N-(2,6-DIALKYLPHENYL), N-METHYLAMINOALKYL HALIDES AND DERIVED QUATERNARY AMMONIUM SALTS

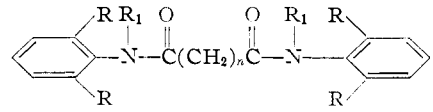


No.	n	X	B.p., °C.	Mm.	M.p.,[c] °C.	Yield, %	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
R = CH₃									
1	3	Br	90–94	0.2		29	$C_{12}H_{18}BrN$	5.5	5.6[a]
2	3	Br[d]			142–144	52	$C_{19}H_{33}BrN_2$	7.8	7.7
3	3	Br[e]			185–187	38	$C_{18}H_{31}BrN_2$	7.9	7.9
4	4	Cl	94–98	.07		7	$C_{13}H_{20}ClN$	6.2	6.2
5	4	Br	98–102	.18		21	$C_{13}H_{20}BrN$	4.8	5.2
6	4	Br[d]			150–152	75	$C_{19}H_{35}BrN_2$	7.6	7.6
7	5	Br	124–128	.4		22	$C_{14}H_{22}BrN$	4.9	5.3
8	6	Br	146–154	.5		35	$C_{15}H_{24}BrN$	4.7	4.6
9	6	Br[e]			133–134	31	$C_{21}H_{37}BrN_2$	7.1	7.0
10	[b]	Cl	92–96	.08		29	$C_{13}H_{18}Cl$	6.3	6.4
R = C₂H₅									
11	3	Br	108–112	.1		26	$C_{14}H_{22}BrN$	4.9	5.1
12	[b]	Cl	104–106	.26		26	$C_{15}H_{22}ClN$	5.6	5.7

[a] Bromine, calcd.: 30.8. Found: 30.7. [b] $-(CH_2)-$ in generic formula is replaced by $-CH_2CH{=}CHCH_2-$. [c] Compounds for which melting points are shown were recrystallized from ethyl acetate–acetonitrile. [d] Quaternary ammonium salt with triethylamine. [e] Quaternary ammonium salt with N-methylpiperidine.

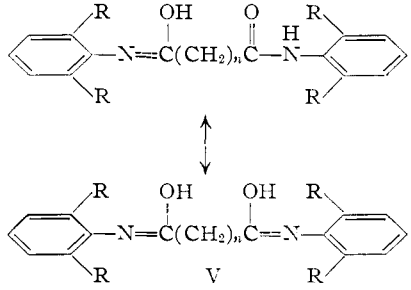
TABLE III

BIS-2,6-DIALKYLANILIDES



No.	R	n	M.p.,[b] °C.	Yield,[c] %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	CH_3	0[e]	264–265	65	$C_{18}N_{20}N_2O_2$	72.9	73.0	6.8	7.0	9.4	9.2
2	CH_3	1	266–267	71	$C_{19}H_{22}N_2O_2$	73.5	73.1	7.1	7.3	9.0	8.9
3	CH_3	2	322–323	83	$C_{20}H_{24}N_2O_2$	74.0	73.8	7.5	6.9	8.6	8.6
4[a]	CH_3	2	165	41[d]	$C_{22}H_{28}N_2O_2$	75.0	75.0	8.0	8.4	8.0	7.7
5	CH_3	4	290–292	72	$C_{22}H_{28}N_2O_2$	75.0	75.1	8.0	8.2	7.9	8.2
6	C_2H_5	0[e]	224–225	60	$C_{22}H_{28}N_2O_2$	75.0	75.3	8.0	8.0	8.0	7.8
7	C_2H_5	1	237–242	64	$C_{23}H_{30}N_2O_2$	75.4	75.1	8.2	7.8	7.6	8.2
8	C_2H_5	2	300–302	44	$C_{24}H_{32}N_2O_2$	75.7	75.4	8.5	8.3	7.4	6.9
9	C_2H_5	4	284–285	58	$C_{26}H_{36}N_2O_2$	76.4	76.7	8.9	9.0	6.9	7.1

[a] R_1 = hydrogen in all instances except compound 4 where $R_1 = CH_3$. [b] Melting points are not corrected. [c] The recrystallizing solvent was methyl Cellosolve unless otherwise indicated. [d] Solvent, methanol. [e] Compounds where $n = 0$ represent bis-oxanilides.

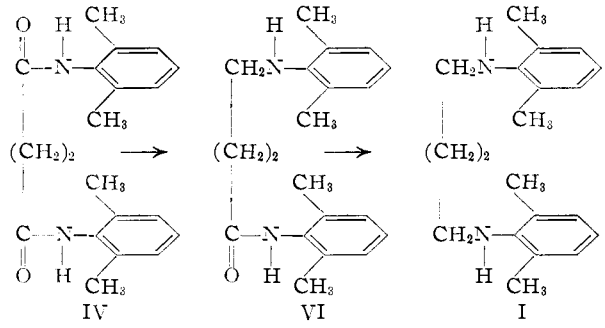


these compounds as reactants for the preparation of I by lithium aluminum hydride reduction. Such compounds would be expected to form unreactive complexes of the type —N=C(OAlH$_3$)—[7] leading to very slow reductions.

This proved to be the case and, accordingly, only one system was studied in detail, involving the preparation of N,N′-tetramethylene-bis-(2,6-dimethylaniline) which was not obtained by method A.

The attempted synthesis of I, $R_1 = CH_3$, $R_1 = H$, Y = $-(CH_2)_4-$, from the diamide IV *via* lithium aluminum hydride resulted in but partial reduction to the mono-anilide VI[3,8] as shown in Scheme II.

SCHEME II (METHOD B)



Isolation of the compound VI and further treatment with lithium aluminum hydride yielded the required N,N′-tetramethylene-bis-(2,6-dimethylaniline). Apparently, in its formation, the mono-anilide VI forms an insoluble complex with the lithium aluminum hydride which hinders further reduction, but which does not reconstitute when compound VI is isolated and again treated with lithium aluminum hydride.

Pharmacology.—The compounds in this study were examined for their properties[9] as anesthetics, central nervous system depressants, hypotensive agents and adrenergic blocking agents.

Significant pharmacologic findings with 2,6-dialkyl substituted anilines are confined largely to the excellent local anesthetic effect obtained with xylocaine.[10]

Examination for anesthetic potency[11] in the polymethylene-bis-anilines described in Table I indicates that good anesthetic response is obtained with selected structures. Thus, the following data, Table I compound no., ED_{50} mg./ml., $LD_{min.}$ mg./kg. (mice), were obtained: 2, 0.44, > 1000; 5, 0.34, > 1000; 8, 5.2. > 1000; 15, 12, > 1000. The following compounds, evaluated by this procedure, did not show any response: 10, 13, 14, 16, 18, 19, 22, 24 and 26. Also negative was the response of N-methyl-N-(β-phenethyl)-2,6-dimethylaniline which had been prepared to assess the need for two anilino groups in structures of this type; comparable data noted for xylocaine: ED_{50} 6.8 mg./ml., $LD_{min.}$ 225 mg./kg.

Selected structures show good local anesthetic response when compared to xylocaine. The best activity appears to be confined to structures I, $R_1 = H$, Y = $-(CH_2)_n-$, $n = 3, 5$. Compound 15, the congener of compound 5, having $R_1 = CH_3$, was the only structure showing activity in the group I, $R_1 = CH_3$. Substitution (as in I, R = ethyl) depressed the anesthetic effect (see compounds 19 *vs.* 2, 22 *vs.* 8, 26 *vs.* 15).

(7) R. L. Hinman, THIS JOURNAL, **78**, 2463 (1956).

(8) F. J. Marshall, *ibid.*, **78**, 3696 (1956), in a study of diones such as hydantoins, barbiturates and thiouracils noted only partial reduction even in the presence of excess of lithium aluminum hydride.

(9) The factor of solvation as an important determinant of physiologic properties has been observed recently by A. Nisonoff and D. Pressman, THIS JOURNAL, **79**, 5565 (1957). In that paper, in a study of the annular nitrogen of pyridine as a determinant of immunologic specificity, it has been assumed that the antibody forms against pyridine with its ring nitrogen in the hydrated state.

(10) L. S. Goodman and A. Gilman, "The Pharmacological Basis of Therapeutics," 2nd ed., The Macmillan Co., New York, N. Y., 1955, p. 369.

(11) M. R. A. Chance and H. Lobstein, *J. Pharmacol.*, **82**, 203 (1944). In our work the anesthetic response has been reported as ED_{50} in mg./ml. This is the concentration of test solution which reduces the number of blinks to 50%.

Of particular interest in this study was the evaluation of the compounds of the type I, $R_1 = CH_3$, as central nervous system depressants. In view of steric factors[1d] it would appear that the configuration at each nitrogen would be for the methyl polymethylene amino group to be nearly planar and in turn, in a plane perpendicular to the plane of the benzene ring. This is in contrast to the coplanar configuration characterizing the aryl nitrogen and the rings in the phenothiazine-derived tranquilizing agents. Compound 14, (N,N′-tetramethylene-bis-N-methyl-2,6-dimethylaniline), with an $LD_{min.}$ of over 1000 mg./kg. showed outstanding effects when evaluated for its capacity to reduce the motor activity of rats.[12] At a level of 20 mg./kg. subcutaneous it caused a reduction of 73% in motor activity. Significant responses in this category were confined largely to I, $R_1 = CH_3$, and were noted with Table I compounds 13, 14, 15, 16 and 18.

In the halides of Table II, intramolecular quaternization is inhibited due to steric factors. Although the distance between the nitrogen and X is more than the two-carbon chain considered requisite[13] for the β-haloethylamine adrenergic blocking agents, we evaluated these structures for this response. Compound 4, Table II, showed slight adrenergic inhibition at 5 mg./kg. ($LD_{min.}$ > 1000 mg./kg.), while 10 and 11 were negative.

The remaining pharmacologic objective of this work was to assess the quaternary compounds of the type III reported in Table II. These compounds have certain features of the familiar hexamethionium structure with the exception that one of the nitrogens is present as a tertiary amine group, while the nitrogen at the other terminus of the alkylene chain is a quaternary nitrogen. It was hoped that such structures would improve upon the noted poor oral absorption characteristic of the methionium antihypertensives.[14] Compound 6 ($L-D_{min.}$ 100 mg./kg.) and compound 9 ($LD_{min.}$ 250 mg./kg.) showed moderate and sustained hypotensive effects when evaluated in dogs.[12]

Interestingly, the compounds in Table I were generally without noted effect on the blood pressure with the exception of compound 18 which caused marked, lasting hypotension.

Experimental[15]

N-Methyl-2,6-dimethylaniline.—A mixture of 140 g. (1.14 moles) of 2,6-dimethylaniline and 140 g. (0.98 mole) of methyl iodide was heated on the steam-bath for 0.25 hr. The crystalline mass which formed, 217 g., was separated, rinsed with ether, dried and dissolved in 300 ml. of water. After addition of excess 6 *N* sodium hydroxide, the product was extracted with three 200-ml. portions of ether. The combined ether extracts were dried (magnesium sulfate), and filtered, the ether removed and the residue distilled. The product, 96.7 g. (69%), was collected at 206°.[16] Similar runs gave 77, 75 and 67%.

N-Methyl-2,6-diethylaniline.—In a manner similar to that described above using 2,6-diethylaniline[17] the product was obtained in 81% yield, boiling at 229–231°.

Anal. Calcd. for $C_{11}H_{17}N$: C, 80.9; H, 10.5; N, 8.6. Found: C, 80.8; H, 10.7; N, 8.6.

Method A. N,N′-Ethylene-bis-(N-methyl-2,6-dimethylaniline) (Table I, Compound 12).—A mixture of 27 g. (0.2 mole) of N-methyl-2,6-dimethylaniline, 9.4 g. (0.05 mole) of ethylene dibromide and 50 mg. of potassium iodide was heated in an oil-bath at 140° for 1 hr. After addition of 100 ml. of water and 100 ml. of 6 *N* sodium hydroxide, the product was extracted with three 100-ml. portions of ether. The combined ether extracts were dried (magnesium sulfate), filtered, the ether removed and the residue distilled. The product, 2.25 g. (15%), boiled at 148–152° (0.2 mm.).

N,N′-Hexamethylene-bis-(2,6-diethylaniline) Dihydrochloride (Table I, Compound 23).—Upon addition of 9.0 g. of hexamethylene-bis-2,6-diethylaniline to 30 ml. of concentrated hydrochloric acid, and standing, there was obtained 9.2 g. (86%) of product, m.p. 178–194°.

N,N′-Bis-(2,6-diethylphenyl)-adipamide (Table III, Compound 9).—A solution of 4.88 g. (0.0267 mole) of adipyl chloride in 30 ml. of dry ether was added gradually with stirring to a solution of 15.95 g. (0.107 mole) of 2,6-diethylaniline in 100 ml. of ether. After the addition, stirring was continued for 1 hr. and the mixture of product and 2,6-diethylaniline hydrochloride was separated and washed with ether and then with water. The product was separated and recrystallized from methyl Cellosolve. There was obtained 6.5 g. (58%).

Method B. (γ-[2,6-Dimethylanilino]-butyr)-2,6-dimethylanilide. (Scheme II, Compound VI).—A mixture of 4.56 g. (0.12 mole) of lithium aluminum hydride in 300 ml. of ether was stirred under reflux and 13 g. (0.04 mole) of N,N′-bis-(2,6-dimethylphenyl)-succinamide (Table III, compound 3) in 200 ml. of dioxane added. The reaction was maintained under reflux for 60 hr. After cautious addition of 2 ml. of water, 4.5 ml. of 40% sodium hydroxide was added with continued stirring for 3 hr. Ether (400 ml.) was added and the residue separated and rinsed with two 300-ml. portions of ether. The combined filtrates were concentrated to about 25 ml. and on standing at 10°, 5.9 g. (47.5%) of the product separated, m.p. 145–148°, recrystallized (heptane) m.p. 149–150°.

Anal. Calcd. for $C_{20}H_{26}N_2O$: C, 77.4; H, 8.4. Found: C, 77.5; H, 8.0.

N,N′-Tetramethylene-bis-(2,6-dimethylaniline) (Table I, Compound 3).—A mixture of 1.52 g. (0.04 mole) of lithium aluminum hydride in 300 ml. of ether was treated with a slurry of 4.65 g. (0.015 mole) of (γ-[2,6-dimethylanilino]-butyr)-2,6-dimethylanilide in 300 ml. of ether. After stirring under reflux for 30 hr. and standing for an additional 90 hr., 1 ml. of water followed by 1 ml. of saturated sodium chloride and 2.25 ml. of 40% sodium hydroxide solution was added. The formed granular precipitate was separated, rinsed with ether and the combined ether filtrates concentrated. Unreacted anilide (2.4 g.) precipitated and was separated. The filtrate was evaporated to yield a residue which was distilled. There was obtained 1.11 g. (25%) of product boiling at 172–182° (0.11 mm.). On standing at room temperature the product crystallized, m.p. 61–63°, recrystallized (pentane) m.p. 72–73°.

Anal. Calcd. for $C_{28}H_{28}N_2$: C, 81.0; H, 9.5; N, 9.5. Found: C, 81.1; H, 9.4; N, 9.7.

Method C. N,N′-Trimethylene-bis-(N-methyl-2,6-dimethylaniline (Table I, Compound 13).—To a solution of 12.4 g. (0.044 mole) of N,N′-trimethylene-bis-(2,6-dimethylaniline) (Table I, compound 2) in 25 ml. (0.56 mole) of 87% formic acid, there was added 14 ml. (0.17 mole) of 37% aqueous formaldehyde and the mixture heated on a steam-bath for 10 hr. After addition of 60 ml. of *N* hydrochloric acid, the reaction mixture was concentrated *in vacuo* and the residue was dissolved in 100 ml. of water and treated with 40 ml. of 6 *N* sodium hydroxide. The product was extracted with three 100-ml. portions of ether, the combined ether extracts dried (magnesium sulfate), filtered, the ether removed and the residue distilled. The product obtained, 5.9 g. (43%), boiled at 158–163° (0.05 mm.).

N-(6-Bromohexyl)-N-methyl-2,6-dimethylaniline (Table

(12) S. L. Shapiro, H. Soloway and L. Freedman, *J. Am. Pharm. Assoc., Sci. Ed.*, **46**, 333 (1957), detail the method used and control drug responses. This paper also describes procedures for evaluation of the hypotensive response.

(13) (a) G. E. Ullyot and J. F. Kerwin, "Medicinal Chemistry," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 234; (b) J. D. P. Graham, *Brit. J. Pharmacol.*, **12**, 489 (1957).

(14) Reference 10, p. 636.

(15) Descriptive data shown in the tables are not reproduced in the Experimental section.

(16) Beilstein, "Organische Chemie," XII, p. 1108, reports b.p. 206–207°.

(17) The authors are grateful to the Ethyl Corporation for generous samples of this material.

II, Compound 8).—A mixture of 9.25 g. (0.0685 mole) of N-methyl-2,6-dimethylaniline, 33.4 g. (0.137 mole) of 1,6-dibromohexane and 50 mg. of potassium iodide was heated in an oil-bath at 140° for 25 minutes. After addition of 100 ml. of water, the cooled mixture was made alkaline with 6 *N* sodium hydroxide and promptly extracted with three 100-ml. portions of ether. The combined ether extracts were dried (magnesium sulfate), filtered, the ether removed and the residue distilled. The product, 7.1 g. (35%), boiled at 146–154° (0.5 mm.).

N-Methyl-(3-[N-methyl-2,6-dimethylanilino]-propyl)-piperidinium Bromide (Table II, Compound 3).—A mixture of 1.79 g. (0.007 mole) of N-(3-bromopropyl)-N-methyl-2,6-dimethylaniline (Table II, compound 1) and 0.73 g. (0.0074 mole) of N-methylpiperidine in 5 ml. of acetonitrile was heated under reflux for 1 hr. When cool, 0.95 g. (38%) of colorless crystals was filtered off, washed with ethyl acetate and dried *in vacuo*, m.p. 185–187.5°.

Anal. Calcd. for $C_{18}H_{31}BrN_2$: C, 60.8; H, 8.7; N, 7.9; Br, 22.5. Found: C, 60.9; H, 8.8; N, 7.9; Br, 22.6.

N-Methyl-N-β-phenethyl-2,6-dimethylaniline.—A mixture of 13.6 g. (0.1 mole) of N-methyl-2,6-dimethylaniline and 37 g. (0.2 mole) of 2-bromoethylbenzene and 100 mg. of potassium iodide was heated in an oil-bath maintained at 140° for 0.5 hr. When cool, the crystalline mass was dissolved in 100 ml. of water, the solution made alkaline with 6 *N* sodium hydroxide and extracted with three 100-ml. portions of ether. The combined ether extracts were dried (magnesium sulfate), filtered, the ether removed and the residue distilled. The product, 8.3 g. (35%), boiled at 122–128° (0.1–0.2 mm.).

Anal. Calcd. for $C_{17}H_{21}N$: C, 85.3; H, 8.8; N, 5.9. Found: C, 85.1; H, 8.9; N, 5.8.

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YONKERS, NEW YORK

[CONTRIBUTION FROM THE KETTERING-MEYER LABORATORY,[1] SOUTHERN RESEARCH INSTITUTE]

Synthesis of Potential Anticancer Agents. XIV. Ribosides of 2,6-Disubstituted Purines

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The syntheses of several new 2-substituted-6-methoxy- and 2-substituted-6-aminopurine ribosides have been accomplished.

In an earlier paper of this series,[1] we discussed the reasons for our interest in the area of purine ribosides as potential anticancer agents, with special reference to certain 6-substituted purine ribosides. In a continuation of our studies, we have now prepared a representative number of 2,6-disubstituted purine ribosides for biological evaluation.

Because of the recently demonstrated[2] differences in the reactivity of the chlorine atoms in 2,6-dichloropurine, we selected 2,6-dichloro-9-β-D-ribofuranosylpurine (IIIc) as the key intermediate for the syntheses of some 2,6-disubstituted purine ribosides. Since the 6-chlorine atom is much more reactive than the 2-chlorine atom in the free purine, it is logical to assume that the chlorine atoms of the corresponding riboside (IIIc) would show a similar difference in reactivity. Thus, monosubstitution of 2,6-dichloropurine riboside by a nucleophilic reagent should yield a 6-substituted product which, after isolation, should be capable of undergoing further substitution of the 2-position with a variety of nucleophilic reagents. In this way, a useful method for the preparation of a wide variety of 2,6-disubstituted purine ribosides would be available.

Condensation of bis-(2,6-dichloropurinyl)-mercury (I) with 2,3,5-tri-*O*-benzoylribofuranosyl chloride (IIa)[3] proceeded in high yield, and the blocked nucleoside IIIa, which was isolated as a glass, was shown to be fairly pure by its elemental analysis. The proof of structure of the crude nucleoside IIIa will be described later in the paper. The next step in our synthetic scheme was the removal of the *O*-benzoyl blocking groups from the crude nucleoside IIIa. In an earlier paper of this series,[4] it was demonstrated that *O*-benzoyl blocking groups may be removed from several 6-chloropurine blocked nucleosides with methanolic ammonia at 0° in 24 hours without concomitant replacement of the 6-chloro group. However, when we allowed IIIa to react with methanolic ammonia at 0° for 18 hours a complex reaction mixture resulted which was shown by paper chromatography to contain at least four materials. Elution of the spot having an R_{ad} 1.00[5] from the chromatogram and determination of its ultraviolet spectrum indicated by comparative studies with an authentic sample[6] that the material was 6-amino-2-chloropurine-9-β-D-ribofuranosylpurine.[7a,b] Since it is known[8] that the removal of the acetyl blocking group proceeds at a much faster rate than the removal of the benzoyl blocking group, we attempted to prepare IIIc by a procedure which employs the more easily removed acetyl blocking group. Condensation of bis-(2,6-dichloropurinyl)-mercury (I) with 2,3,5-tri-*O*-acetylribofuranosyl chloride (IIb)[9a,b,10] proceeded smoothly; the blocked nucleoside IIIb was allowed to react with excess

(1) Affiliated with Sloan-Kettering Institute. This work was supported by funds from the C. F. Kettering Foundation and the National Institutes of Health, Grant Number CY-2942. Part XIII. J. A. Johnson, Jr., H. J. Thomas and H. J. Schaeffer, THIS JOURNAL, **80**, 699 (1958).

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(5) Paper chromatograms were developed with butanol saturated with water by the descending technique on Whatman No. 1 paper. Adenine was employed as a standard and was assigned R_{ad} 1.00.

(6) This sample of IVa was furnished by Dr. G. B. Brown of the Sloan-Kettering Institute; see also *J. Org. Chem.*, **23**, 125 (1958).

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