solution was dried over potassium carbonate and distilled. The product appeared as 7.5 g. (86% of theoretical) of a pale yellow oil boiling at 174–176° (3 mm.). This diamine is reasonably stable but begins to darken when kept for a few weeks.

Anal. Calcd. for $C_{15}H_{26}ClN_3$: N, 14.80. Found: 14.71.

5-Chloro-1-(1-diethylamino-4-pentyl)-2-*p*-methoxyphenylbenzimidazole (IV).—A. The above diamine (III) (7.5 g., 0.026 mole) was dissolved in 50 cc. of methyl alcohol containing 2.4 cc. of concentrated hydrochloric acid. To this was added a solution of 11.2 g. (0.056 mole) of cupric acetate in 150 cc. of water, followed by a solution of 3.8 g. (0.028 mole) of *p*-anisaldehyde in 50 cc. of methyl alcohol. On warming, the original intense blue color disappeared and a copper-colored precipitate formed. After heating for three hours, the solution was diluted to 750 cc. with water, 6.0 g. of sodium sulfide nonahydrate was added, and a mixture of equal volumes of glacial acetic acid and concentrated hydrochloric acid was added dropwise until the solution was slightly acid (litmus). After filtering and extracting once with ether, the acidic solution was made strongly alkaline (sodium hydroxide), resulting in the separation of a greenish-brown oil. This was taken up in ether, dried over potassium carbonate and distilled. The main fraction boiled at 230–240° (2.5 mm.) and on redistillation, 5.5 g. (53% yield) of a light red-brown oil was obtained, boiling at 236° (2.5 mm.).

B. Seventeen grams (0.06 mole) of the diamine (III) was dissolved in 15 cc. of dry pyridine and 12.2 g. (0.07 mole) of *p*-anisoyl chloride was added with cooling in ice. After standing at room temperature for one hour, the mixture was heated on a steam-bath for twelve hours. Dilute sodium hydroxide was added and the resulting oil extracted with ether (1.5 g. of anisic acid was recovered from the aqueous layer by acidification). The ether layer was dried and distilled as in (A), giving 22.6 g. (94% of the theoretical) of the benzimidazole.

Anal. Calcd. for $C_{23}H_{30}ClN_3O$: N, 10.51. Found: N, 10.22.

5-Chloro-1-(1-diethylamino-4-pentyl)-2-thiomethoxybenzimidazole (VI).—Fifteen grams (0.053 mole) of the diamine (III) was dissolved in a mixture of 20 cc. of carbon disulfide and 20 cc. of 95% ethyl alcohol and refluxed overnight on a steam-bath, after which the excess carbon disulfide and most of the alcohol was distilled. A solution of 4.3 g. (0.11 mole) of sodium hydroxide in 50 cc. of water was added, followed by 5 cc. (0.053 mole) of dimethyl sulfate, the latter in 1-cc. portions, with vigorous shaking. The oil so produced was extracted with a mixture of equal volumes of ether and ethyl acetate, dried over sodium sulfate, and distilled. The product appeared as a light brown viscous oil, boiling at 194–198° (3 mm.). A yield of 12 g. (66% of the theoretical) was obtained.

Anal. Calcd. for $C_{17}H_{26}ClN_3S$: N, 12.36. Found: N, 12.46.

5-Chloro-1-(1-diethylamino-4-pentyl)-benzotriazole (VII).—Twelve grams (0.042 mole) of the diamine (III) was dissolved in 100 cc. of water containing 14 cc. of concentrated hydrochloric acid. After adding about 400 g. of ice, a solution of 3.1 g. (0.045 mole) of sodium nitrite in 50 cc. of water was added dropwise with vigorous stirring. The solution was allowed to stand for twelve hours and then made alkaline (sodium hydroxide). The oil was extracted with ether, dried over potassium carbonate and distilled. The fraction boiling at 162–178° (3 mm.) was redistilled, giving 9.5 g. (76% of the theoretical) of a viscous light brown oil boiling at 177–178° (3 mm.).

Anal. Calcd. for $C_{15}H_{23}ClN_4$: N, 19.00. Found: N, 18.90.

Acknowledgment.—The authors wish to express their appreciation to The Wm. S. Merrell Company through whose generous support this work was carried out.

Summary

3 - Amino - 4 - (1 - diethylamino - 4 - pentylamino)-chlorobenzene has been synthesized and converted into three basically substituted heterocycles.

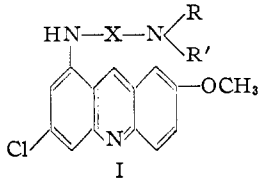
CHAPEL HILL, NORTH CAROLINA RECEIVED MAY 17, 1946

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

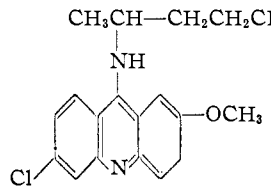
N-Substituted 2-Methoxy-6-chloro-9-aminoacridines Derived from Unsymmetrical Aliphatic Amines[1]

BY JOSEPH CORSE, J. T. BRYANT[2] AND H. A. SHONLE

A number of 2-methoxy-6-chloro-9-(dialkylaminoalkylamino)-acridines (I), related to quinacrine (II), have been made for antimalarial studies.[3] However, although there has been considerable variation in the type of side chain (—X—), there has been but little work reported



I



II

on variations in the dialkylamino part of the molecule.[4] This paper reports a few compounds we have made wherein R and R′ are dissimilar.

The unsymmetrical secondary amines used were obtained from commercial sources or made by known methods, usually by high pressure reduction of mixtures of primary amines and ketones

(1) Reported at the 108th Meeting of the American Chemical Society, September 11 to 15, 1944, New York, N. Y.

(2) Deceased December 30, 1943.

(3) Mietzsch and Mauss, *Angew. Chem.*, **47**, 633 (1934); German Patents 553,072 and 571,449.

(4) Burckhalter, Jones, Holcomb and Sweet, THIS JOURNAL, **65**, 2012 (1943).

TABLE I

DIALKYLAMINOACETONITRILES

Dialkylamino group	Yield, %	B. p., °C.	Mm.	Derivative	M. p., °C.	Formula	Analyses, % N Calcd.	Found
Methyl-*n*-propylamino	75[a]	73–75	35	Picrate	82–83	$C_{13}H_{17}O_7N_5$	19.71	19.44
Cyclopentylmethylamino	69	105–109	32	Flavinate	164–168	$C_{18}H_{20}O_8N_4S$	12.38	12.38
Cyclohexylmethylamino	62[a]	132–134	33	Flavinate	140–150	$C_{19}H_{22}O_4N_8S$	12.01	11.68
Cyclopentylethylamino	57	119–120	29	Flavinate	184–185	$C_{19}H_{22}O_8N_4S$	12.01	11.77
Ethyl-2-pentylamino	50	107–111	29	Flavinate	152–154	$C_{19}H_{24}O_8N_4S$	11.94	11.77
Cyclohexylethylamino	29	128–132	33	Flavinate	140–148	$C_{20}H_{24}O_8N_4S$	11.66	11.58
Ethyl-2-heptylamino	60	128–132	32–33			$C_{11}H_{22}N_2$	15.36	15.85
				Flavinate	125–126	$C_{21}H_{28}O_8N_4S$	11.28	11.13
n-Butylisopropylamino	66	110–115	28			$C_9H_{18}N_2$	17.16	18.10
s-Butylisopropylamino	26[a]	108–115	35	Flavinate	120–125	$C_{19}H_{24}O_8N_4S$	11.94	11.81
n-Amylisopropylamino	52[a]	123–127	37	Flavinate	157–159	$C_{20}H_{26}O_8N_4S$	11.61	11.20
Cyclopentyl-*n*-propylamino	66	130–133	20	Flavinate	150–155	$C_{20}H_{24}O_8N_4S$	11.66	11.65
2-Pentyl-*n*-propylamino	61	111–115	33			$C_{10}H_{20}N_2$	16.65	16.91
3-Pentyl-*n*-propylamino	49	112–116	32			$C_{10}H_{20}N_2$	16.65	16.46
s-Butylisobutylamino	57	108–112	29			$C_{10}H_{20}N_2$	16.65	16.84
s-Butylcyclopentylamino	43	140–143	33	Flavinate	150–158[b]	$C_{21}H_{26}O_8H_4S$	11.33	11.31

[a] "Dreft" was added to the reaction mixture. [b] Sublimes.

TABLE II

3-DIALKYLAMINOPROPIONITRILES

3-Substituent	Yield, %	B. p., °C.	Mm.	Derivative	M. p., °C.	Formula	Analyses, % N Calcd.	Found
Methyl-*n*-propylamino	93[b]	102–106	26			$C_7H_{14}N_2$	22.20	22.10
				Picrate	82–83	$C_{13}H_{17}O_7N_5$	19.71	19.44
Methylisopropylamino	76[a]	94–96	32			$C_7H_{14}N_2$	22.20	21.64
n-Butylmethylamino	83[a]	108–112	40			$C_8H_{16}N_2$	19.98	20.15
s-Butylmethylamino	87[a]	111–112	32			$C_8H_{16}N_2$	19.98	20.07
Isobutylmethylamino	78[a]	103–105	33			$C_8H_{16}N_2$	19.98	19.44
Methyl-2-pentylamino	89[a]	101–103	18			$C_9H_{18}N_2$	18.16	17.64
Methyl-3-pentylamino	81[a]	111–114	17			$C_9H_{18}N_2$	18.16	18.37
Cyclopentylmethylamino	96[a]	134–135	33			$C_9H_{16}N_2$	18.40	18.21
Methyl-3-methyl-2-butylamino	66[a]	118–123	40			$C_9H_{18}N_2$	18.16	17.82
Methyl-2-methyl-4-pentylamino	92[a]	131–134	40			$C_{10}H_{20}N_2$	16.65	16.54
Cyclohexylmethylamino	61[a]	145–148	40	Flavinate	157–160	$C_{20}H_{24}O_8N_4S$	11.66	11.36
4-Heptylmethylamino	65[a]	152–153	38			$C_{11}H_{22}N_2$	15.36	15.99
Ethylisopropylamino	31[b]	98–101	29			$C_8H_{16}N_2$	19.98	20.36
Ethylisobutylamino	56[a]	114–115	35	Flavinate	164–168	$C_{19}H_{24}O_8N_4S$	11.94	11.51
Cyclopentylethylamino	48[b]	130–133	20			$C_{10}H_{18}N_2$	16.85	17.05
Isopropyl-*n*-propylamino	80[a]	110–113	31–32	Flavinate	160–161	$C_{19}H_{24}O_8N_4S$	11.94	12.22
n-Butyl-*n*-propylamino	61[a]	128–129	35	Flavinate	124–127	$C_{20}H_{26}O_8N_4S$	11.61	11.66
s-Butyl-*n*-propylamino	34[b]	105–111	22–25			$C_{10}H_{20}N_2$	16.65	16.88
Isobutyl-*n*-propylamino	49[a]	105–110	21			$C_{10}H_{20}N_2$	16.65	17.00
				Flavinate	156–158	$C_{20}H_{26}O_8N_4S$	11.61	11.94
n-Butyl-*s*-butylamino	42[b]	135–138	28			$C_{11}H_{22}N_2$	15.36	15.83
Cyclopentyl-*n*-butylamino	68[a]	142–143	17			$C_{12}H_{22}N_2$	14.41	14.38

[a] "Triton B" used as catalyst; heated at 95° overnight. [b] No catalyst; reaction mixture heated at 95° overnight.

or aldehydes.[5] Those amines which are new will be reported elsewhere.[6]

The necessary side chains, dialkylaminoalkylamines, were made by standard reactions coupling the unsymmetrical secondary amine at the proper place. 2-Dialkylaminoethylamines were obtained by reduction of dialkylaminoacetonitriles.[7] The dialkylaminoacetonitriles were readily prepared by the method of Knoevenagel and Mercklin,[8] using a secondary amine, formaldehyde solution, sodium bisulfite and potassium cyanide. This reaction proceeded moderately well except with hindered amines. The yields were almost negligible with these unless "Dreft" or a similar dispersing agent was added and vigorous stirring was instituted. As other workers have reported,[9] the catalytic reduction of aminoalkylnitriles is facilitated by the use of liquid ammonia.

(5) (a) Henze and Humphreys, THIS JOURNAL, **64**, 2878 (1942); (b) Campbell, Sommers and Campbell, *ibid.*, **66**, 82 (1944).

(6) Shonle, Rohrmann and Corse, to be published.

(7) Baltzly, Buck and Ide, *ibid.*, **64**, 2232 (1942).

(8) (a) Knoevenagel and Mercklin, *Ber.*, **37**, 4089 (1904); (b) Luten, *J. Org. Chem.*, **3**, 588 (1939).

(9) Whitmore, Mosher, Adams, Taylor, Chapin, Weisel and Yanko, THIS JOURNAL, **66**, 725 (1944).

TABLE III

2-DIALKYLAMINOETHYLAMINES

2-Substituent	Yield, %	B. p., °C.	Mm.	Derivative	M. p., °C.	Formula	Analyses, % N Calcd.	Found
Methyl-*n*-propylamino	88[b]	63–68	42	Picrate	193	$C_{18}H_{22}O_{14}N_8$	19.5	19.4
Methyl-2-pentylamino	66[b]	93–95	40	Picrate	168–170	$C_{20}H_{26}O_{14}N_8$	18.60	18.82
Cyclopentylmethylamino	75[b]	106–108	37	Picrate	106–110	$C_{20}H_{24}O_{14}N_8$	18.66	18.49
Cyclohexylmethylamino	54[b]	126–129	43	Picrate	199–200	$C_{21}H_{26}O_{14}N_8$	18.23	18.5
Cyclopentylethylamino	42[a]	112–113	33	Picrate	183	$C_{21}H_{26}O_{14}N_8$	18.23	18.2
Ethyl-2-pentylamino	57[b]	98–103	37–38	Picrate	148	$C_{21}H_{28}O_{14}N_8$	18.18	18.2
Ethyl-2-heptylamino	71[b]	127–132	38	Picrate	165–166	$C_{23}H_{32}O_{14}N_8$	17.4	17.6
s-Butyl-*n*-propylamino	66[b]	103–106	43	Picrate	176–178	$C_{21}H_{28}O_{14}N_8$	18.18	18.2
n-Butylisopropylamino	41[b]	88–90	24	Picrate	124–126	$C_{21}H_{28}O_{14}N_8$	18.18	17.70
n-Amylisopropylamino	60[b]	101–105	20	Picrate	169–171	$C_{22}H_{30}O_{14}N_8$	17.77	18.06
Cyclopentyl-*n*-propylamino	61[a]	121–123	28	Picrate	183	$C_{22}H_{28}O_{14}N_8$	17.85	17.86
2-Pentyl-*n*-propylamino	34[b]	108–112	37–38	Picrate	175	$C_{22}H_{30}O_{14}N_8$	17.77	18.0
3-Pentyl-*n*-propylamino	75[b]	113–116	35	Picrate	147–149	$C_{22}H_{30}O_{14}N_8$	17.77	17.78
s-Butylcyclopentylamino	45[b]	120–145	37	Picrate	127–135	$C_{23}H_{30}O_{14}N_8$	17.46	17.53

[a] Sodium and alcohol reduction. [b] Catalytic reduction in bomb in ether and liquid ammonia at 125°.

TABLE IV

3-DIALKYLAMINOPROPYLAMINES

3-Substituent	Yield, %	B. p., °C.	Mm.	Derivative	M. p., °C.	Formula	Analyses, % N Calcd.	Found
Methyl-*n*-propylamino	33[b]	164–168	755	Picrate	169–170	$C_{19}H_{24}O_{14}N_8$	19.04	19.01
Methylisopropylamino	92[a]	72–74	33	Picrate	206–207	$C_{19}H_{24}O_{14}N_8$	19.04	18.9
n-Butylmethylamino	78[a]	94–98	47	Picrate	160–163	$C_{20}H_{26}O_{14}N_8$	18.60	18.13
s-Butylmethylamino	83[a]	88–91	33–34	Picrate	176–180	$C_{20}H_{26}O_{14}N_8$	18.60	18.58
Isobutylmethylamino	92[a]	83–86	37	Picrate	180–181	$C_{20}H_{26}O_{14}N_8$	18.60	18.68
				Phenyl thiourea	85	$C_{15}H_{25}N_3S$	15.06	14.95
n-Amylmethylamino	73[a]	104–106	30	Picrate	165–168	$C_{21}H_{28}O_{14}N_8$	18.18	18.15
Methyl-2-pentylamino	66[a]	112–113	40	Picrate	145	$C_{21}H_{28}O_{14}N_8$	18.18	18.4
Cyclopentylmethylamino	79[a]	126–127	43	Picrate	164–171	$C_{21}H_{26}O_{14}N_8$	18.23	18.5
Methyl-3-methyl-2-butylamino				Picrate	152–153	$C_{21}H_{28}O_{14}N_8$	18.18	17.78
Methyl-2-methyl-4-pentylamino	71[a]	109–114	30	Picrate	156–158	$C_{22}H_{30}O_{14}N_8$	17.83	17.65
Cyclohexylmethylamino	70[a]	122–124	24	Picrate	192–193	$C_{22}H_{28}O_{14}N_8$	17.83	18.52
				Flavinate	210–213	$C_{30}H_{34}O_{16}N_6S_2$	10.52	10.13
4-Heptylmethylamino	51[a]	113–116	20	Picrate	190–192	$C_{23}H_{32}O_{14}N_8$	17.38	17.61
Ethylisobutylamino	58[a]	99–100	36	Picrate	192–195	$C_{21}H_{28}O_{14}N_8$	18.18	17.8
Ethylisopropylamino	75[c]	81–84	33–34	Phenyl thiourea	87	$C_{15}H_{25}N_3S$	15.06	15.3
Cyclohexylethylamino	65[b]	135–141	32	Picrate	200–202	$C_{23}H_{30}O_{14}N_8$	17.13	17.35
Cyclopentylethylamino	70[b]	122–126	28	Phenyl thiourea	78	$C_{17}H_{27}N_3S$	13.77	14.0
Isopropyl-*n*-propylamino	39[b]	101–103	37	Picrate	194–195	$C_{21}H_{28}O_{14}N_8$	18.18	18.08
n-Butyl-*n*-propylamino	56[a]	118–119	38	Picrate	178–180	$C_{22}H_{30}O_{14}N_8$	17.83	17.8
s-Butyl-*n*-propylamino	49[b]	110–114	32	Picrate	185–188	$C_{22}H_{30}O_{14}N_8$	17.83	17.6
n-Butyl-*s*-butylamino	59[b]	124–128	29	Picrate	144 d.	$C_{23}H_{32}O_{14}N_8$	17.38	17.1
n-Butylcyclopentylamino	62[a]	145–148	24	Picrate	195–196	$C_{24}H_{32}O_{14}N_8$	17.60	17.49

[a] Catalytically reduced in bomb; liquid ammonia added. [b] Sodium and alcohol reduction. [c] Catalytically reduced in bomb; no liquid ammonia.

3-Dialkylaminopropylamines were prepared by the reduction of 3-dialkylaminopropionitriles. These were made by the condensation of amines with acrylonitrile.[4,9,10] Various catalysts named in the patents mentioned were unsatisfactory. However, "Triton B"[11] proved generally as efficient in effecting this condensation as it is in catalyzing ketone–acrylonitrile reactions.[12]

4-Dialkylaminobutylamines were prepared by reduction of 4-dialkylaminobutyronitriles, which in turn were formed by the reaction of secondary amines with 4-chlorobutyronitrile.[13]

The Mannich reaction was used to prepare 4-dialkylamino-2-butanones[14] which were converted to 4-dialkylamino-2-butylamines. The Mannich reaction[15] was likewise used to prepare 3-dialkylamino-2,2-dimethylpropionaldehydes which were used to make 3-dialkylamino-2,2-di-

(10) British Patents 404,744 and 457,621.

(11) "Triton B" is a 37% solution of benzyltrimethylammonium hydroxide and may be obtained from Röhm and Haas Co., Philadelphia.

(12) Bruson, THIS JOURNAL, **64**, 2457 (1942).

(13) Strukov, *Khim. Farm. Prom.*, 332 (1933); *C. A.*, **28**, 3714 (1934).

(14) (a) Mannich, *Arch. Pharm.*, **255**, 261 (1917); (b) Tsuda, Fukushima and Oguri, *J. Pharm. Soc. Japan*, **61**, 31 (1941).

(15) Mannich, Lesser and Silten, *Ber.*, **65**, 378 (1932).

TABLE V

MISCELLANEOUS DERIVATIVES[a]

Compound	Yield, %	B. p., °C.	Mm.	Derivative	M. p., °C.	Formula	Analyses, % N Calcd.	Found
4-Ethylmethylaminobutyronitrile	21[b]	95–96	33	Picrate	155–156	$C_{13}H_{17}O_7N_7$	19.71	19.17
				Flavinate	139–140	$C_{17}H_{20}O_8N_4S$	12.72	12.55
4-Methyl-*n*-propylaminobutyronitrile	68[b]	110–115	35	Picrate	75–77	$C_{14}H_{19}O_7N_7$	18.96	19.0
				Flavinate	167–169	$C_{18}H_{22}O_8N_4S$	12.33	12.12
3-Methyl-*n*-propylaminobutyronitrile	33	96–99	17	Picrate	94–95	$C_{14}H_{19}O_7N_7$	18.96	18.98
4-Ethylmethylaminobutylamine	82[c]	88–91	42	Picrate	155–156	$C_{19}H_{24}O_{14}N_8$	19.04	19.17
4-Methyl-*n*-propylaminobutylamine	76[c]	94–96	35	Picrate	121	$C_{20}H_{26}O_{14}N_8$	18.60	18.60
4-Methyl-*n*-propylamino-2-butanone oxime	79	144–144	35			$C_8H_{18}ON_2$	17.70	17.3
4-Methyl-*n*-propylamino-2-butylamine	92[d]	88–91	44	Picrate	125–126	$C_{20}H_{26}O_{14}N_8$	18.6	18.9
4-*n*-Butylisobutylamino-2-butylamine	25[d,e]	120–122	29	Picrate	153–155	$C_{24}H_{34}O_{14}N_8$	17.0	16.9
3-Methyl-*n*-propylamino-2,2-dimethylpropylamine	28[e]	90–94	35	Picrate	148 dec.	$C_{21}H_{28}O_{14}N_8$	18.2	18.6
5-Ethylmethylamino-2-pentanone[f]	52	64–67	9			$C_8H_{17}ON_2$	7.79	7.8
5-Methyl-*n*-propylamino-2-pentanone	55	81–83	6			$C_9H_{19}ON_2$	8.9	8.1
5-*n*-Butylmethylamino-2-pentanone[f]	55	81–83	5-6			$C_{10}H_{21}ON_2$	8.18	8.02
5-*n*-Butylethylamino-2-pentanone[f]	60	83–85	3			$C_{11}H_{23}ON_2$	7.57	7.4
5-Isobutylisopropylamino-2-pentanone	46	97	2			$C_{12}H_{25}ON_2$	7.03	6.4
5-Ethylmethylamino-2-pentanone oxime	70	100–102	2			$C_8H_{18}ON_2$	17.70	17.9
5-Ethyl-*n*-propylamino-2-pentanone oxime	80	161–163	32			$C_{10}H_{22}ON_2$	15.04	14.72
5-Isopropyl-*n*-propylamino-2-pentanone oxime	80	150–155	30			$C_{11}H_{24}ON_2$	13.99	14.69
5-Isobutylisopropylamino-2-pentanone oxime	81	106–110	2			$C_{12}H_{26}ON_2$	13.07	12.78
5-Methyl-*n*-propylamino-2-aminopentane	81	98–101	35	Flavinate	243–246 dec.	$C_{29}H_{34}O_{16}N_8S_2$	11.86	11.85
5-Ethyl-*n*-propylamino-2-aminopentane	78[e]	115–118	37	Flavinate	255 dec.	$C_{30}H_{36}O_{16}N_8S_2$	11.51	11.32
5-Isopropyl-*n*-propylamino-2-aminopentane	51[g]	118–120	33	Flavinate	255–256	$C_{31}H_{38}O_{16}N_8S_2$	11.2	11.1

[a] "Triton B" used as catalyst. [b] Based on 4-chlorobutyronitrile. [c] Catalytic reduction in bomb in ether and liquid ammonia at 125°. [d] Catalytic reduction in bomb at 80–85°. [e] Based on ketone. [f] Prepared by Dr. Wm. J. Haines. [g] Sodium and alcohol reduction.

methylpropylamines. The yields in the several steps in these preparations were low.

5-Dialkylamino-2-aminopentanes were made by condensation of a secondary amine with 3-acetylpropyl bromide[16] or 3-acetylpropyl chloride. It was found necessary to use a sealed tube in reactions with the latter halide. The oximes of the amino ketones were then made and reduced to the diamines either catalytically or with sodium and alcohol.

5-Methyl-*n*-propylaminopentylamine was made in the same manner that Magidson and Grigorowsky made 5-diethylaminopentylamine,[17] using 5-benzoylaminopentyl chloride.

3-Methyl-*n*-propylamino-1-butylamine was made by the addition of methyl-*n*-propylamine to either crotononitrile of vinylacetonitrile, with "Triton B" as a catalyst, and subsequent reduction of the substituted butyronitrile formed.

The reaction of 2-methoxy-6,9-dichloroacridine with the diamine was carried out in phenol and worked up according to the method of Knunyantz, *et al.*,[16] with slight modifications where needed. The dihydrochlorides were made of all compounds and in general were recrystallized from ethanol–ether mixtures.

A number of intermediates were used without purification. In other instances sufficiently large samples were not saved for characterization. Because of the urgency of the problem and Mr. Bryant's untimely death, their preparation was not repeated and their conversion products or the final acridine derivatives must serve as identification agents.

(16) Knunyantz, Chelintzev, Benevolenska, Osetrova and Kursonova, *Bull. acad. sci. U. R. S. S.*, 165 (1934).

(17) Magidson and Grigorowsky, *Ber.*, **69B**, 396 (1936).

The pharmacological study of these compounds was made by Mr. C. L. Rose and Dr. K. K. Chen of these laboratories. Their report will be published elsewhere.

Experimental[18]

General directions or a single instance will be given of the type reactions.

Dialkylaminoacetonitriles.[8]—A mixture of 30.3 g. (0.3 mole) of cyclopentylmethylamine, 31.2 g. of sodium bisulfite, 27 ml. of 37% formaldehyde solution and 60 ml. of water was heated on a steam-bath and stirred vigorously. A solution of 19.8 g. of potassium cyanide in 30 ml. of water was then added dropwise and the heating and stirring was maintained for an additional six and one-half hours after the addition was complete. The reaction mixture was cooled and the resulting oil was extracted with ether and dried over anhydrous magnesium sulfate. The product, cyclopentylmethylaminoacetonitrile (28.5 g.) was isolated by distillation *in vacuo*, b. p. 105–109° (32 mm.).

2-Dialkylaminoethylamines.—The nitrile to be reduced was dissolved in its own weight of ether and placed in a small bomb precooled with Dry Ice. Then about a half volume of liquid ammonia and 5–10 g. of Raney nickel catalyst was added and reduction carried out at 125° in the usual manner at 1400 to 1800 p.s.i.

When sodium–alcohol reductions were run, 0.1 mole of nitrile was dissolved in 200 ml. of hot absolute alcohol and 18 g. of sodium was added as rapidly as possible. After the sodium had all dissolved, the alcohol was removed by steam distillation and the residual oil was separated and dried over potassium hydroxide. The diamine was purified by distillation.

3-Dialkylaminopropionitriles.—The secondary amine was added cautiously to an excess of acrylonitrile. With some amines, a vigorous reaction ensued; with most, however, there was at best only a slight warming. Then 3–5 drops of "Triton B,"[11] was added and the mixture was heated on a steam-bath overnight. The reaction product was decanted from a small amount of gum which usually formed and was distilled *in vacuo*.

(18) The melting points herein reported were taken by slowly heating on a Fisher–Johns block. They are reproducible but vary considerably from those taken by the melting point tube method.

TABLE VI

2-METHOXY-6-CHLORO-9-AMINOACRIDINE DIHYDROCHLORIDES

9-Substituent	M. p., °C.[a]	Formula	Analyses, % N Calcd.	Found
2-Methyl-*n*-propylaminoethylamino	215–217	$C_{20}H_{26}ON_3Cl_3$	9.75	9.52
2-Methyl-2′-pentylaminoethylamino	213–215	$C_{22}H_{30}ON_3Cl_3$	9.14	9.12
2-Cyclopentylmethylaminoethylamino	227–229	$C_{22}H_{28}ON_3Cl_3$	9.19	9.00
2-Cyclohexylmethylaminoethylamino	238–240	$C_{23}H_{30}ON_3Cl_3$	8.92	8.72
2-Cyclopentylethylaminoethylamino	227–229	$C_{23}H_{30}ON_3Cl_3$	8.92	8.66
2-Ethyl-2′-pentylaminoethylamino	225–227	$C_{23}H_{32}ON_3Cl_3$	8.89	8.91
2-Cyclohexylethylaminoethylamino	215–228	$C_{24}H_{32}ON_3Cl_3$	8.67	8.89
2-Ethyl-2′-heptylaminoethylamino	135–137	$C_{25}H_{36}ON_3Cl_3$	8.39	8.04
2-Isopropyl-*n*-propylaminoethylamino	233–236	$C_{22}H_{30}ON_3Cl_3$	9.14	9.43
2-*s*-Butyl-*n*-propylaminoethylamino	228–230	$C_{23}H_{32}ON_3Cl_3$	8.89	8.84
2-*n*-Butylisopropylaminoethylamino	214–216	$C_{23}H_{32}ON_3Cl_3$	8.89	8.70
2-*s*-Butylisopropylaminoethylamino	219–221	$C_{23}H_{32}ON_3Cl_3$	8.89	8.73
2-*n*-Amylisopropylaminoethylamino	187–189	$C_{24}H_{34}ON_3Cl_3$	8.63	8.51
2-Cyclopentyl-*n*-propylaminoethylamino	230–233	$C_{24}H_{32}ON_3Cl_3$	8.67	8.63
2,2′-Pentyl-*n*-propylaminoethylamino	191–193	$C_{24}H_{34}ON_3Cl_3$	8.63	8.42
2,3′-Pentyl-*n*-propylaminoethylamino	219–221	$C_{24}H_{34}ON_3Cl_3$	8.63	8.47
2-*s*-Butylisobutylaminoethylamino	163–165	$C_{24}H_{34}ON_3Cl_3$	8.63	8.60
2-*s*-Butylcyclopentylaminoethylamino	210–212	$C_{25}H_{34}ON_3Cl_3$	8.42	8.51
3-Methyl-*n*-propylaminopropylamino	204–208	$C_{21}H_{28}ON_3Cl_3$	9.45	9.42
3-Isopropylmethylaminopropylamino	237–240	$C_{21}H_{28}ON_3Cl_3$	9.45	9.39
3-*n*-Butylmethylaminopropylamino	237–240	$C_{22}H_{30}ON_3Cl_3$	9.14	9.30
3-*s*-Butylmethylaminopropylamino	198–199	$C_{22}H_{30}ON_3Cl_3$	9.14	9.08
3-Isobutylmethylaminopropylamino	205–208	$C_{22}H_{30}ON_3Cl_3$	9.14	9.11
3-*n*-Amylmethylaminopropylamino	230–232	$C_{23}H_{32}ON_3Cl_3$	8.89	9.06
3-Methyl-2′-pentylaminopropylamino	162–164	$C_{23}H_{32}ON_3Cl_3$	8.89	8.79
3-Methyl-3′-pentylaminopropylamino	175–177	$C_{23}H_{32}ON_3Cl_3$	8.89	8.88
3-Cyclopentylmethylaminopropylamino	220–222	$C_{23}H_{30}ON_3Cl_3$	8.92	8.77
3-Methyl-3′-methyl-2′-butylaminopropylamino	215–220	$C_{23}H_{32}ON_3Cl_3$	8.89	8.7
3-Methyl-2′-methyl-4′-pentylaminopropylamino	197–199	$C_{24}H_{34}ON_3Cl_3$	8.63	8.80
3-Cyclohexylmethylaminopropylamino	216–218	$C_{24}H_{32}ON_3Cl_3$	8.67	8.80
3,4′-Heptylmethylaminopropylamino	217–219	$C_{25}H_{36}ON_3Cl_3$	8.39[b]	7.64 7.68
3-Ethylisopropylaminopropylamino	238–240	$C_{22}H_{30}ON_3Cl_3$	9.14	9.13
3-Ethylisobutylaminopropylamino	225–228	$C_{23}H_{32}ON_3Cl_3$	8.89	8.97
3-Cyclopentylethylaminopropylamino	215–217 d.	$C_{24}H_{32}ON_3Cl_3$	8.67	8.52
3-Cyclohexylethylaminopropylamino	253–255	$C_{25}H_{34}ON_3Cl_3$	8.42	8.53
3-Isopropyl-*n*-propylaminopropylamino	215–218	$C_{23}H_{32}ON_3Cl_3$	8.89	8.7
3-*n*-Butyl-*n*-propylaminopropylamino	172–174	$C_{24}H_{34}ON_3Cl_3$	8.63	8.81
3-*s*-Butyl-*n*-propylaminopropylamino	157–160	$C_{24}H_{34}ON_3Cl_3$	8.63	8.68
3-Isobutyl-*n*-propylaminopropylamino	210–212	$C_{24}H_{34}ON_3Cl_3$	8.63	8.74
3-*n*-Butyl-*s*-butylaminopropylamino	196–198	$C_{25}H_{36}ON_3Cl_3$	8.39	8.57
3-*n*-Butylcyclopentylaminopropylamino	221–223	$C_{26}H_{36}ON_3Cl_3$	8.19	8.32
4-Ethylmethylaminobutylamino	247–249	$C_{21}H_{28}ON_3Cl_3$	9.45	9.34
4-Methyl-*n*-propylaminobutylamino	236–238	$C_{22}H_{30}ON_3Cl_3$	9.14	9.23
4-Methyl-*n*-propylamino-2-butylamino	170–173	$C_{22}H_{30}ON_3Cl_3$	9.14	9.26
4-*n*-Butylisobutylamino-2-butylamino	164–167	$C_{26}H_{38}ON_3Cl_3$	8.15	8.00
3-Methyl-*n*-propylamino-1-butylamino	209–212	$C_{22}H_{30}ON_3Cl_3$	9.14	8.77[c]
5-Ethylmethylamino-2-pentylamino	249–251	$C_{22}H_{30}ON_3Cl_3$	9.14	9.23
5-Methyl-*n*-propylamino-2-pentylamino	179–181	$C_{23}H_{32}ON_3Cl_3$	8.89	8.86
5-*n*-Butylmethylamino-2-pentylamino	160–162	$C_{24}H_{34}ON_3Cl_3$	8.63	8.57
5-Ethyl-*n*-propylamino-2-pentylamino	162–165	$C_{24}H_{34}ON_3Cl_3$	8.63	8.43
5-Ethylisopropylamino-2-pentylamino	160–162	$C_{24}H_{34}ON_3Cl_3$	8.63	8.56
5-*n*-Butylethylamino-2-pentylamino	182–183	$C_{25}H_{36}ON_3Cl_3$	8.39	8.26
5-Isopropyl-*n*-propylamino-2-pentylamino	165–168	$C_{25}H_{36}ON_3Cl_3$	8.39	8.19
5-Isobutylisopropylamino-2-pentylamino	161–163	$C_{26}H_{38}ON_3Cl_3$	8.15	7.85
5-Methyl-*n*-propylaminopentylamino	218–220	$C_{23}H_{32}ON_3Cl_3$	8.89	8.97
3-Methyl-*n*-propylamino-2,2-dimethylpropylamino	226–229	$C_{23}H_{32}ON_3Cl_3$	8.89	8.71
3-Isopropyl-*n*-propylamino-2,2-dimethylpropylamino	233–237	$C_{25}H_{36}ON_3Cl_3$	8.39	9.14

[a] The melting points recorded were taken on a micro-block. [b] For the monohydrate, % N calcd. is 7.78. [c] For the monohydrate, % N calcd. is 8.81.

3-Dialkylaminopropylamines.—These were prepared by reduction in exactly the same manner as 2-dialkylaminoethylamines.

5-Dialkylamino-2-aminopentanones.—The secondary amine (1.2 moles) was cooled to 0°; then 0.6 mole of 3-acetylpropyl bromide was added dropwise with stirring and cooling in an ice-bath. The reaction mixture was allowed to come to room temperature and to stand for fourteen to twenty hours. After refluxing several hours the dark mixture was cooled, acidified, extracted with ether, made alkaline and the resulting organic layer was separated and dried. Distillation gave unreacted amine and the desired 5-dialkylamino-2-pentanone.

The alternative method was to add two molecular equivalents of amine to one of 3-acetylpropyl chloride[19] and heat the resulting solution in a sealed tube at 125–150° for from twelve to forty-eight hours. The reaction product was worked up as for the bromo compound.

5-Dialkylamino-2-pentanone Oximes.—The aminoketone was added to 10% excess of hydroxylammonium chloride in water. Then a quantity of sodium carbonate sufficient to neutralize the hydroxylammonium chloride was added and the mixture was heated on a steam-bath for four to five hours. The oxime separated as an oily layer and was extracted with ether, dried over magnesium sulfate and then distilled *in vacuo*.

5-Dialkylamino-2-aminopentanes.—The oximes when reduced with sodium and alcohol were treated similarly to the nitriles, except for 0.1 mole of oxime, 450 ml. of alcohol was used and 45 g. of sodium was added slowly.

If reduced catalytically, the oxime was dissolved in ethanol and reduced at 80° in the presence of Raney nickel catalyst and hydrogen at 1400 to 1800 p.s.i.

4-Dialkylaminobutyronitriles.—A mixture of 0.65 mole of 4-chlorobutyronitrile, 1.1 moles of secondary amine and 5 g. of potassium iodide was heated in an oil-bath at 110° for twenty-four to forty-eight hours. Dilute hydrochloric acid was added, neutral material was removed with ether and then the cooled reaction mixture was made alkaline with 12.5 *N* sodium hydroxide solution. The resulting 4-dialkylaminobutyronitrile was extracted with ether, dried over magnesium sulfate and distilled *in vacuo*.

4-Dialkylaminobutylamines.—The 4-dialkylaminobutyronitriles were reduced catalytically the same as the dialkylaminoacetonitriles.

4-Dialkylamino-2-butanones.—A solution of 0.5 mole of amine hydrochloride, 145 g. of acetone, 45 ml. of formalin and 80 ml. of water was refluxed overnight.[14b] The excess acetone was removed by distillation; water and ether were then added and the ether layer was discarded. On making the aqueous portion alkaline, the expected aminoketone separated; it was dried and distilled *in vacuo*.

4-Dialkylamino-2-butanone Oximes.—These were made in the same manner as the homologous 5-dialkylamino-2-pentanone oximes.

4-Dialkylamino-2-butylamines.—The reductions of the oximes were done catalytically in a bomb at 80–85° with Raney nickel catalyst at 1400 to 1800 p.s.i.

3-Methyl-*n*-propylamino-2,2-dimethylpropylamine.—A mixture of 30 g. of isobutyraldehyde, 37.6 g. of methyl-*n*-propylamine hydrochloride, 25 g. of absolute alcohol and 15.8 g. of paraformaldehyde was heated on a steam-bath and stirred vigorously for one hour. Then an additional 15.8 g. of paraformaldehyde was added and the heating and stirring was maintained for an additional three hours. Dilute hydrochloric acid was then added, the mixture was cooled and extracted with ether. An excess of strong caustic was added and the organic layer, 3-methyl-*n*-propylamino-2,2-dimethylpropionaldehyde, was separated with ether, dried and distilled *in vacuo;* 9 g. of product b. p. 84–86° (33 mm.) was obtained. The aldoxime was made in the usual manner and reduced catalytically without purification. A yield of 3.7 g. of 3-methyl-*n*-propylamino-2,2-dimethylpropylamine, b. p. 90–94° (35 mm.), was obtained.

2-Methoxy-6-chloro-9-(dialkylaminoalkylamino)-acridine Dihydrochlorides.—Five-hundredths mole of dialkylaminoalkylamine, 50 ml. of phenol and 14 g. of 2-methoxy-6,9-dichloroacridine were mixed and heated on a steam-bath for one to two hours with occasional stirring. The hot reaction product was then poured into cold dilute sodium hydroxide and extracted with ether. The ether extract was washed with water and extracted with cold dilute acetic acid. The acetic acid portion was washed with ether and made alkaline with ammonia. An oil separated which was extracted with ether and washed thoroughly with water and dried over magnesium sulfate. Dry hydrogen chloride was added and the resulting 2-methoxy-6-chloro-9-(dialkylaminoalkylamino)-acridine dihydrochloride was recrystallized from ethanol–ether.

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Summary

A number of unsymmetrical secondary amines have been used in the preparation of dialkylaminoalkylamines which were intermediates in the preparation of the corresponding 2-methoxy-6-chloro-9-(dialkylaminoalkylamino)-acridines.

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(19) Obtained from The Carbide and Carbon Chemicals Corporation.