10 ml. of nitromethane, yielding 1.6 g. of colorless needles, m. p. 91–114°. Two more recrystallizations from nitromethane gave 0.7 g. (18%) of VIII, colorless needles, m. p. 124–126° (m. p. unchanged after fusion). The compound is very soluble in water, less soluble in alcohol or acetone, and insoluble in benzene.

Anal. Calcd. for $C_9H_{14}O_3N_2$: C, 54.53; H, 7.12; N, 14.14. Found: C, 54.50; H, 7.00; N, 14.04.

2,6-Di-(hydroxymethyl)-4-hydroxy-5-methylpyrimidine Hydrochloride (II).—The pyrimidine-ether VIII (400 mg.) was boiled under reflux for two hours with 2.0 ml. of 8.8 *M* hydrobromic acid. After cooling, the mixture was diluted with 20 ml. of water, filtered, and the filtrate distilled to dryness *in vacuo*. Addition of water and distillation were repeated twice more, to remove excess acid. The residue, a viscous, brown, non-crystallizable oil, was dissolved in 20 ml. of water and the solution boiled one hour. The hot solution was debrominated by stirring a few minutes with 1.3 g. of freshly precipitated and washed silver chloride. The filtrate from the yellow silver halide precipitate was distilled to dryness *in vacuo*, leaving 200 mg. of solid residue, m. p. 152–162°. After two recrystallizations from acetic acid, there was obtained 154 mg. of II, colorless irregular platelets, m. p. 167–169°.

Anal. Calcd. for $C_7H_{11}O_3N_2Cl$: C, 40.68; H, 5.37; N, 13.56. Found: C, 40.31; H, 5.43; N, 13.18.

Summary

The synthesis of 2,6-di-(hydroxymethyl)-4-hydroxy-5-methylpyrimidine hydrochloride, a pyrimidine analog of pyridoxine, has been described. The synthesis of two other 2-hydroxymethylpyrimidines is reported.

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[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Some 4-Aminoquinoline and 9-Aminoacridine Derivatives

BY CHARLES E. KWARTLER AND PHILIP LUCAS[1]

The preparations of some 4-aminoquinoline derivatives[2] in these Laboratories have been described recently. Further work has been carried out on the preparation of 4-amino-7-chloroquinoline and 4-amino-7-chloro-3-methylquinoline derivatives. The necessary 4,7-dichloroquinoline and 4,7-dichloro-3-methylquinoline were prepared as described previously.[2b,2f]

For this study a series of 4-dialkylamino-2-phenylbutylamines (Table II) with substituents on the benzene ring was prepared by catalytic reduction, in the presence of Raney nickel and excess ammonia, of the correspondingly substituted γ-dialkylamino-α-phenylbutyronitriles (Table I). The preparation of γ-diethylamino-α-phenylbutyronitrile by the condensation of β-chloroethyl-

TABLE I

NITRILES

Compd., nitrile	B. p. °C.	Mm.	Formula	Analyses, % Basicity as amino nitrogen Calcd.	Found	Nitrogen Calcd.	Found
γ-Dimethylamino-α-phenylbutyro-[a]	130	4	$C_{12}H_{16}N_2$	..	..	...	...
γ-Diethylamino-α-phenylbutyro-[b]	110	0.5	$C_{14}H_{20}N_2$	6.48	6.49	...	...
α-(*p*-Chlorophenyl)-γ-diethylaminobutyro-	124–126	1	$C_{14}H_{19}ClN_2$	5.59	5.51	11.18	10.94
α-(3,4-Dichlorophenyl)-γ-diethylaminobutyro-	130	0.5	$C_{14}H_{18}Cl_2N_2$	4.92	4.90	9.83	9.55
γ-Diethylamino-α-(*p*-methoxyphenyl)-butyro-	120	0.5	$C_{15}H_{22}N_2O$	5.69	5.74	11.38	11.07
α-(*p*-Chlorophenyl)-δ-diethylaminovalero-	138–139	0.5	$C_{15}H_{21}ClN_2$	5.29	5.32	...	...

[a] Hydrochloric acid salt, m. p. 163–165°; *anal.* Calcd. for $C_{12}H_{16}N_2 \cdot HCl$: N, 12.46. Found: N, 12.40, 12.20. [b] Eisleb, *Ber.*, **74B**, 1433–1450 (1941). Hydrochloric acid salt, m. p. 115–117°; *anal.* Calcd. for $C_{14}H_{20}N_2 \cdot HCl$: N, 11.09. Found: N, 11.02, 11.33.

TABLE II

AMINES

Compd., amine	B. p. °C.	Mm.	Formula	Analyses, % Basicity as amino nitrogen Calcd.	Found	Nitrogen Calcd.	Found
4-Dimethylamino-2-phenylbutyl-	145	13	$C_{12}H_{20}N_2$	14.59	14.10	...	...
4-Diethylamino-2-phenylbutyl-	174–176	27	$C_{14}H_{24}N_2$	12.72	12.42	...	...
2-(*p*-Chlorophenyl)-4-diethylaminobutyl-	113	1	$C_{14}H_{23}ClN_2$	11.00	10.83	11.00	10.72
2-(3,4-Dichlorophenyl)-4-diethylaminobutyl-	125	1	$C_{14}H_{22}Cl_2N_2$	9.77	9.77	9.77	9.90
4-Diethylamino-2-(*p*-methoxyphenyl)-butyl-	133–136	1	$C_{15}H_{26}N_2O$	11.20	11.02	11.20	10.88
2-(*p*-Chlorophenyl)-5-diethylaminopentyl-	123–124	0.5	$C_{15}H_{25}ClN_2$	10.42	9.89	...	...

(1) Present address: Massengill Chemical Co., Bristol, Tennessee.

(2) (a) Huber, Bair and Laskowski, THIS JOURNAL, **67**, 1619 (1945); (b) Surrey and Hammer, *ibid.*, **68**, 113 (1946); (c) Steck, Hallock and Holland, *ibid.*, **68**, 129 (1946); (d) Steck, Hallock and Holland, *ibid.*, **68**, 132 (1946); (e) Huber, Laskowski, Jackman and Clinton, *ibid.*, **68**, 322 (1946); (f) Steck, Hallock and Holland, *ibid.*, **68**, 380 (1946).

TABLE III

7-CHLORO-4-(R-AMINO)-QUINOLINES

SN[a]	R	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
12,029	4-Diethylamino-2-phenylbutyl	124–125	$C_{23}H_{28}ClN_3$	72.35	72.57	7.34	6.98	11.01	11.13
11,800	2-(*p*-Chlorophenyl)-4-diethylamino-butyl	127–129	$C_{23}H_{27}Cl_2N_3$	66.4	66.12	6.50	6.59	10.10	9.79
12,077	2-(3,4-Dichlorophenyl)-4-diethylamino-butyl	111–113	$C_{23}H_{26}Cl_3N_3$	61.3	61.07	5.77	6.06	9.33	9.27
13,149	4-Diethylamino-2-(*p*-methoxyphenyl)-butyl	94–96	$C_{24}H_{30}ClN_3O$	69.99	70.29	7.29	7.56	10.21	9.91
12,704	4-Diethylamino-2-(*p*-hydroxyphenyl)-butyl	163–164	$C_{23}H_{28}ClN_3O$	69.43	69.05	7.04	7.12	10.57	10.57
14,185	2-(*p*-Chlorophenyl)-5-diethylamino-pentyl	119.5–121	$C_{24}H_{29}Cl_2N_3$	66.98	66.98	6.74	7.00	9.77	9.89

[a] The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which Survey Numbers have been assigned will be tabulated in a forthcoming monograph.

TABLE IV

7-CHLORO-3-METHYL-4-(R-AMINO)-QUINOLINES

SN	R	B. p. °C.[a]	B. p. Mm.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
8,411-5[b]	4-Diethylamino-2-phenylbutyl	240	1	$C_{24}H_{30}ClN_3$	72.90	72.86	7.58	7.43	10.62	10.46
11,607	2-(*p*-Chlorophenyl)-4-diethylamino-butyl	212	1	$C_{24}H_{29}Cl_2N_3$	67.00	67.06	6.74	6.83	9.76	10.10
11,434	2-(3,4-Dichlorophenyl)-4-diethyl-aminobutyl	260	0.5	$C_{24}H_{28}Cl_3N_3$	62.00	61.88	6.03	6.09	9.04	8.76
10,753-9995[c]	4-Diethylamino-2-(*p*-methoxy-phenyl)-butyl	260	1.5	$C_{25}H_{32}ClN_3O$	70.50	70.19	7.52	7.76	9.86	9.81

[a] Approximate because distillations were carried out rapidly to minimize decomposition. [b] Phosphoric acid salt. [c] 2-Hydroxy-3-naphthoic acid salt.

TABLE V

ACRIDINES

SN	Acridine di-HCl compound	M. p., °C.	Formula	Analyses, % Nitrogen Calcd.	Nitrogen Found	Chlorine (T, total; I, ionic) Calcd.	Chlorine Found	Moisture Calcd.	Moisture Found
6900-4	6-Chloro-9-(4-dimethylamino-2-phenylbutylamino)-2-methoxy-	120–126	$C_{26}H_{28}ClN_3O\cdot 2HCl\cdot H_2O$	8.02	8.06	T20.29 I13.54	T19.87 I13.68	3.43	3.47
6899-4	6-Chloro-9-(4-diethylamino-2-phenyl-butylamino)-2-methoxy-	196–199	$C_{28}H_{32}ClN_3O\cdot 2HCl\cdot H_2O$			I12.85	I12.57	3.26	3.79
	6-Chloro-2-methoxy-9-(1-methyl-4-phenylpiperidine-4-methylamino)-	215[a]	$C_{27}H_{28}ClN_3O\cdot 2HCl\cdot 2H_2O$	7.58	7.65	I12.80	I12.94	6.50	6.55
5924-4	9-(1-Benzyl-4-phenylpiperidine-4-methylamino)-6-chloro-2-methoxy-	260–262	$C_{33}H_{32}ClN_3O\cdot 2HCl\cdot H_2O$	6.85	6.76	T17.40	T17.06	2.94	3.48
7532-4	9-(4-Diethylamino-2-phenylbutyl-amino)-2,3-dimethoxy-6-nitro-	226–228	$C_{29}H_{34}N_4O_4\cdot 2HCl$	9.74	9.68				

[a] Sintered over wide range beginning at 215°.

diethylamine and benzyl cyanide with sodium amide has been described by Eisleb[3] and the substituted compounds were prepared in the same way. 2-(*p*-Chloro-phenyl)-5-diethylaminopentylamine was synthesized by this method and obviously this is a general method for the preparation of a variety of diamines.

The condensations of these various diamines with 4,7-dichloroquinoline and 4,7-dichloro-3-methylquinoline were accomplished alone or in the presence of phenol. All the bases (Table III) derived from 4,7-dichloroquinoline were crystalline solids. The products (Table IV) prepared from 4,7-dichloro-3-methylquinoline were viscous oils purified by distillation under reduced pressure. Details of the preparation of typical compounds are given in the experimental section.

7-Chloro-4-[4-diethylamino-2-(*p*-methoxyphenyl)-butylamino]-quinoline was demethylated by hydrobromic acid to the corresponding phenolic compound.

Some derivatives of 9-amino-6-chloro-2-methoxyacridine (Table V) were also prepared in the usual manner.[4] The synthesis of 1-benzyl-4-phenyl-4-aminomethylpiperidine has already been described[5] and the 1-methyl compound was prepared in the same way. Physical properties of the latter amine will be reported elsewhere.

(3) Eisleb, *Ber.*, **74B**, 1433 (1941); *C. A.*, **36**, 5466[7] (1942).

(4) Mietzsch and Mauss, U. S. Patent 2,113,357.

(5) Huber, THIS JOURNAL, **66**, 876 (1944).

Experimental

3,4-Dichlorobenzyl Cyanide.—This nitrile was prepared in the usual manner from 3,4-dichlorobenzyl chloride and was obtained as a colorless liquid, b. p. 170° (12 mm.).

Anal. Calcd. for $C_8H_5Cl_2N$: N, 7.50. Found: N, 7.37, 7.51.

2-(3,4-Dichlorophenyl)-4-diethylaminobutylamine.—A solution of 128 g. (0.45 mole) of α-(3,4-dichlorophenyl)-γ-diethylaminobutyronitrile in 600 cc. of 15% methanolic ammonia was reduced in the presence of 30 g. of Raney nickel under fifty atmospheres pressure of hydrogen at 50°. The catalyst was removed by filtration and the residue distilled to give 124 g. (95.5%) of product, b. p. 125° (1 mm.).

Anal. Calcd. for $C_{14}H_{22}Cl_2N_2$: N, 9.77. Found: N (Dumas), 9.90; N (titration), 9.77.

4-[2-(*p*-Chlorophenyl)-4-diethylaminobutylamino]-7-chloroquinoline.—A mixture of 19.8 g. (0.1 mole) of 4,7-dichloroquinoline, 54 g. (0.211 mole) of 2-(*p*-chlorophenyl)-4-diethylaminobutylamine, and a pinch of potassium iodide was heated in a bath kept at 180°. The temperature of the reaction mixture was allowed to rise spontaneously to 198° and then kept at 180° so that the total time of heating at 180° or higher was thirty-five minutes. A solution of the viscous oil in 125 cc. of 40% acetic acid was added to excess, dilute sodium hydroxide and the liberated oil dissolved in ether. The ether solution was dried by shaking with potassium carbonate and set aside to crystallize. The 25.5 g. of white crystalline product, m. p. 122–125°, was recrystallized from Skellysolve C to give 25 g. (60%), m. p. 127–129°.

Anal. Calcd. for $C_{23}H_{27}Cl_2N_3$: C, 66.4; H, 6.50; N, 10.10. Found: C, 66.12; H, 6.59; N, 9.79.

4-[2-(*p*-Chlorophenyl)-5-diethylaminopentylamino]-7-chloroquinoline.—A mixture of 30 g. of phenol, 34 g. (0.126 mole) of 2-(*p*-chlorophenyl)-5-diethylaminopentylamine, 19.8 g. (0.1 mole) of 4,7-dichloroquinoline, and a pinch of potassium iodide was kept at 130–140° for three hours, dissolved in 125 cc. of 40% acetic acid, and added to excess, dilute sodium hydroxide. An ether solution of the liberated oil was washed well with 10% sodium hydroxide and then water, dried by shaking with potassium carbonate, and set aside to crystallize, yielding 29 g. of white crystalline product, m. p. 113–115°. Several recrystallizations from benzene–Skellysolve C gave 24.5 g. (57%), m. p. 119.5–121°.

Anal. Calcd. for $C_{24}H_{29}Cl_2N_3$: C, 66.98; H, 6.74; N, 9.77. Found: C, 66.98; H, 7.00; N, 9.89.

7-Chloro-4-[4-diethylamino-2-(*p*-hydroxyphenyl)-butylamino]-quinoline.—A solution of 30 g. (0.073 mole) of 7-chloro-4-[4-diethylamino-2-(*p*-methoxyphenyl)-butylamino]-quinoline in 450 cc. of 48% hydrobromic acid was refluxed for fifteen minutes and concentrated *in vacuo*. An aqueous solution of the residue was treated with charcoal and filtercel and added to excess ammonium hydroxide to precipitate a white solid weighing 26 g. (89.7%), m. p. 162–164°. Recrystallization from alcohol yielded 20 g., m.p. 163–164°. The product was soluble in dilute sodium hydroxide.

Anal. Calcd. for $C_{23}H_{28}ClN_3O$: C, 69.43; H, 7.04; N, 10.57. Found: C, 69.05; H, 7.12; N, 10.57.

Acknowledgment.—The authors wish to acknowledge, with appreciation, the advice of Drs. C. M. Suter and J. S. Buck. We wish to thank the Misses Bass, Rainey and Curran for the microanalyses recorded.

Summary

The preparation of a series of 4-dialkylaminoalkylnitriles and amines is described in which a phenyl or substituted phenyl group is in the 2-position. These diamines have been condensed with 4,7-dichloroquinoline and 4,7-dichloro-3-methylquinoline to give a series of 7-chloro-4-substituted aminoquinolines and 7-chloro-3-methyl-4-substituted aminoquinolines. The preparation of an analogous series of 9-amino-6-chloro-2-methoxyacridine derivatives is reported.

RENSSELAER, N. Y. RECEIVED JULY 19, 1946

NOTES

The Preparation of β-Aminoethanephosphonic Acid

BY JACOB FINKELSTEIN

During the course of an investigation in this Laboratory it was desirable to prepare β-aminoethanephosphonic acid: $H_2NCH_2CH_2PO(OH)_2$ (I). The only compounds of this type reported are aminomethanephosphonic acid and its N substituted derivatives.[1] These substances were prepared from methylolamides $RCO—NR'CH_2OH$ which when treated with phosphorus trihalide produce intermediate dihalogen phosphorus esters, which rearrange spontaneously into phosphonic acid dihalides, and on hydrolyzing the phosphonic acids are obtained

$$RCONR'CH_2OH + PCl_3 \longrightarrow RCONR'CH_2OPCl_2 \longrightarrow RCONR'CH_2POCl_2 \longrightarrow RCONR'CH_2PO(OH)_2 \longrightarrow HNR'CH_2PO(OH)_2$$

This method is possibly not applicable to the preparation of compounds of the type $=N—(CH_2)_x—P^=$ where $x > 1$.

Nylen[2] has described the preparation of β-phosphonopropionic acid triethyl ester and its C-amide (β-carbamylethanephosphonic acid diethyl ester). This latter substance, when subjected to the Hofmann degradation, yielded the desired substance (I). The corresponding hydrazide was also prepared from the ester but would not undergo the Curtius rearrangement.

Nylen prepared the ester in 35% yield by the reaction of sodiodiethyl phosphite with ethyl β-

(1) U. S. Patent 2,304,156 and 2,328,358.

(2) Nylen, *Ber.*, **59**, 1119 (1926).